original reports abstract

Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer

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PURPOSE Metastatic castration-resistant prostate cancer (mCRPC) remains a lethal disease with current standard-of-care therapies. Homologous recombination repair (HRR) gene alterations, including *BRCA1/2* alterations, can sensitize cancer cells to poly (ADP-ribose) polymerase inhibition, which may improve outcomes in treatment-naïve mCRPC when combined with androgen receptor signaling inhibition.

METHODS MAGNITUDE (ClinicalTrials.gov identifier: NCT03748641) is a phase III, randomized, double-blinded study that evaluates niraparib and abiraterone acetate plus prednisone (niraparib + AAP) in patients with (HRR+, n = 423) or without (HRR−, n = 247) HRR-associated gene alterations, as prospectively determined by tissue/plasma-based assays. Patients were assigned 1:1 to receive niraparib + AAP or placebo + AAP. The primary end point, radiographic progression-free survival (rPFS) assessed by central review, was evaluated first in the *BRCA1/2* subgroup and then in the full HRR+ cohort, with secondary end points analyzed for the full HRR+ cohort if rPFS was statistically significant. A futility analysis was preplanned in the HRR− cohort.

RESULTS Median rPFS in the *BRCA1/2* subgroup was significantly longer in the niraparib + AAP group compared with the placebo + AAP group (16.6 *v* 10.9 months; hazard ratio [HR], 0.53; 95% CI, 0.36 to 0.79; $P = .001$). In the overall HRR+ cohort, rPFS was significantly longer in the niraparib + AAP group compared with the placebo + AAP group (16.5 *v* 13.7 months; HR, 0.73; 95% CI, 0.56 to 0.96; $P = .022$). These findings were supported by improvement in the secondary end points of time to symptomatic progression and time to initiation of cytotoxic chemotherapy. In the HRR− cohort, futility was declared per the prespecified criteria. Treatment with niraparib + AAP was tolerable, with anemia and hypertension as the most reported grade ≥ 3 adverse events.

CONCLUSION Combination treatment with niraparib + AAP significantly lengthened rPFS in patients with HRR+ mCRPC compared with standard-of-care AAP.

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INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) remains a lethal disease, highlighting a need for new therapies.[1-3] Alterations in homologous recombination repair (HRR)–associated genes, present in up to approximately 30% of mCRPC, have been associated with poor prognosis and resistance to current systemic therapies.[4-8] Deleterious gene alterations, particularly in *BRCA1/2*, can sensitize prostate cancer cells to inhibition of poly (ADP-ribose) polymerase (PARP) through a mechanism of synthetic lethality.[4,9] Inhibition of androgen receptor signaling can also result in downregulated expression of DNA repair genes and sensitize prostate cancer cells to PARP inhibition.[10,11] Therefore, we hypothesized that targeting both oncogenic pathways concurrently may improve outcomes in patients with and without HRR alterations.[10,12]

Niraparib, a potent and highly selective inhibitor of PARP-1 and PARP-2, is approved in the United States, Canada, Europe, and China in select patients for several indications, including ovarian, fallopian tube, and primary peritoneal cancers.[13-17] In the phase II GALAHAD trial (ClinicalTrials.gov identifier: NCT02854436), an objective response rate (ORR) of 34.2% with niraparib monotherapy as third-line or higher therapy was achieved in patients with mCRPC, measurable metastases, and *BRCA1/2* pathogenic alterations.[18] Abiraterone acetate (AA) plus prednisone (AAP) is a standard first-line therapy that improves progression-free survival (PFS) and overall survival (OS) in patients with mCRPC.[1] The daily combination dose of niraparib in combination with AA was established as 200/1,000 mg, respectively, plus prednisone on the basis of achieving maximum concentration and area under the curve values within the

ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Metastatic castration-resistant prostate cancer (mCRPC) with alterations in homologous recombination repair (HRR)–associated genes has been associated with poor prognosis and resistance to current systemic therapies. The phase III MAGNITUDE study prospectively enrolled patients into two cohorts on the basis of HRR biomarker status and compared the efficacy and safety of niraparib and abiraterone acetate plus prednisone (niraparib + AAP) versus placebo + AAP as first-line treatment for patients with mCRPC.

Knowledge Generated

Patients with mCRPC and HRR alterations experienced substantial and clinically meaningful benefit from the combination of niraparib + AAP, with no new safety signals that affected the benefit-risk profile. Such results underscore the need for HRR gene testing for metastatic prostate cancer and support the use of niraparib + AAP as first-line combination therapy for these patients with particularly poor prognoses.

Relevance *(M.A. Carducci)*

These results underscore the need for HRR gene testing for metastatic prostate cancer and support the use of niraparib + AAP as first-line combination therapy for these patients with particularly poor prognoses.*

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

efficacious target combination ranges, with no dose-limiting toxicities (DLTs) observed in the phase Ib BEDIVERE study. When the 300-mg dose of niraparib was combined with AAP, three of eight patients experienced DLT. Given the pharmacokinetic results and safety profile, 200-mg niraparib was chosen to be combined with AAP for future studies.[19]

The phase III MAGNITUDE study was designed to compare the efficacy and safety of niraparib + AAP versus placebo + AAP for first-line mCRPC. Clinical data have shown the efficacy of combining androgen receptor–targeted therapy and a PARP inhibitor in metastatic prostate cancer, but the patient population who could have an optimal benefit with this combination was not yet defined at study initiation. Hence, patients in MAGNITUDE were prospectively enrolled into two cohorts on the basis of HRR biomarker status.

METHODS

Patients

Patients ≥18 years of age with mCRPC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 were eligible for prescreening to determine HRR biomarker status using a required assay on tissue and/or blood samples (FoundationOne tissue test [FoundationOneCDx], Resolution Bioscience homologous recombination deficiency plasma test, AmoyDx blood and tissue assays, or accredited local laboratory biomarker tests with central review demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel). Patients must have been tested by both tissue and plasma to be randomly assigned in the HRR− cohort. Patients had to have a gene alteration detected by ≥1 assay to be eligible for the HRR+ cohort.

Patients could not have received prior PARP inhibitors. Systemic therapy (eg, apalutamide, enzalutamide, darolutamide, and docetaxel) for mCRPC was exclusionary; systemic therapies for metastatic castration-sensitive prostate cancer (mCSPC) or nonmetastatic castration-resistant prostate cancer (nmCRPC) were allowed. Up to 4 months of AAP for first-line mCRPC before random assignment was allowed while completing HRR testing. Patients who received >2 months of AAP underwent prostate-specific antigen (PSA) testing to document a lack of PSA progression before random assignment. Full eligibility criteria are described in the trial protocol. The study protocol and amendments were reviewed by an independent ethics committee or institutional review board; the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written informed consent.

Trial Design and Interventions

This is a phase III, randomized, double-blind, placebo-controlled, multicenter study. The HRR+ cohort consisted of patients with either monoallelic or biallelic pathogenic gene alterations in ≥1 of the following: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2*, or *PALB2*; the HRR− cohort included patients who had no detectable alterations in any of these genes. This nine-gene panel was chosen on the basis of previous clinical data of PARP inhibitor activity in this disease setting.[20-22] A third, open-label cohort to evaluate a dual-action tablet of niraparib + AA (given with prednisone) was enrolled; the results will be reported later.

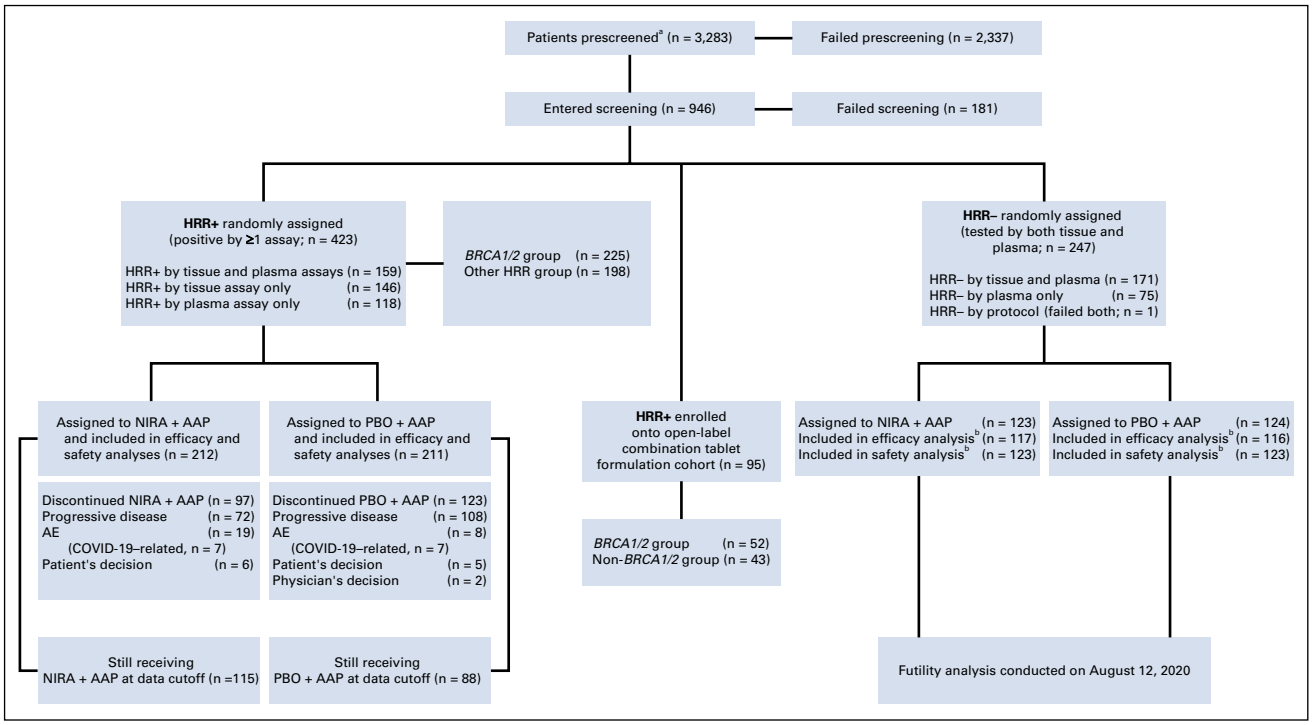

FIG 1. CONSORT diagram. [a]3,283 includes those 2,984 patients who entered prescreening de novo (did not have known HRR status from local testing or from the local vendor in China, AmoyDx). [b]Fourteen patients with *CDK12* alterations were prospectively included in the HRR− cohort before amendment 4. Reasons for failed screening include AE, death, progressive disease, screen failure, withdrawal by patient, and others. HRR biomarker status was determined using the required assay on tissue and/or blood samples (FoundationOne tissue test [FoundationOneCDx], Resolution Bioscience HRD plasma test, AmoyDx blood and tissue assays, or accredited local laboratory biomarker tests with central review demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel). AAP, abiraterone acetate plus prednisone; AE, adverse event; HRD, homologous recombination deficiency; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo.

Patients in the HRR+ and HRR− cohorts were randomly assigned in a 1:1 ratio to receive either niraparib 200 mg once daily with AA 1,000 mg once daily plus prednisone 5 mg twice daily (niraparib + AAP group) or placebo + AAP. Treatment was continuous in 28-day cycles until unequivocal clinical progression, unacceptable toxicity, or death. Patients with radiographic progression could continue study treatment at the investigator's discretion but had to be discontinued after unequivocal clinical progression.

Study Assessments and End Points

The primary end point was radiographic PFS (rPFS), defined as the time from random assignment to the first occurrence of radiographic progression assessed by blinded independent central review or death due to any cause. rPFS was determined by first observation of progression by bone scan (per Prostate Cancer Working Group 3) or progression of soft-tissue lesions by CT or MRI (per RECIST 1.1), with imaging done every 8 weeks for the first 6 months and every 12 weeks after.[23,24] Secondary end points were time to initiation of cytotoxic chemotherapy (TCC), time to symptomatic progression (TSP), and OS (Data Supplement [online only]). Other end points included time to PSA progression, ORR, and patient-reported outcomes (Data Supplement). Treatment-emergent adverse events (AEs) were defined as AEs occurring after the first dose of study drug to 30 days after the last dose and summarized by category and preferred term. Detailed biomarker analyses were planned and will be reported in the future.

A futility analysis for the HRR− cohort was preplanned when approximately 200 patients had been enrolled and approximately 125 composite end point events (the first of either PSA progression, radiographic progression, or death; Data Supplement) had been observed.

Statistical Analysis

The primary and secondary end points in the HRR+ cohort were tested using a graphical testing approach to control the family-wise type I error rate at a two-sided level of 0.05. rPFS was tested first in the *BRCA1/2* subgroup and then the HRR+ cohort. Secondary end points were analyzed for the full HRR+ cohort if rPFS was statistically significant. Two interim analyses and a final analysis were planned for the secondary end points. Approximately 220 radiographic progression events were required to provide 87% power in detecting a hazard ratio (HR) of 0.65 at a two-tailed significance level of .05. Approximately 102 radiographic progression events were to be observed to provide 93% power to detect an HR

TABLE 1. Baseline Characteristics of HRR+ Patients

Characteristic	NIRA + AAP (n = 212)	PBO + AAP (n = 211)	Total (N = 423)
Median age (range), years	69 (45-100)	69 (43-88)	69.0 (43-100)
Mean body weight (SD), kg[a]	84.4 (17.3)	85.2 (17.9)	84.8 (17.6)
Race, No. (%)			
White	160 (75.5)	153 (72.5)	313 (74.0)
Asian	29 (13.7)	41 (19.4)	70 (16.5)
Black or African American	5 (2.4)	0	5 (1.2)
American Indian or Alaska Native	1 (0.5)	1 (0.5)	2 (0.5)
Unknown	17 (8.0)	16 (7.6)	33 (7.8)
Ethnicity, No. (%)			
Hispanic or Latino	26 (12.3)	25 (11.8)	51 (12.1)
Not Hispanic or Latino	166 (78.3)	169 (80.1)	335 (79.2)
Not reported	20 (9.4)	17 (8.1)	37 (8.7)
Median hemoglobin at baseline (range), g/L[b]	129.0 (64.0-172.0)	131.0 (75.0-161.0)	130.0 (64.0-172.0)
Median lactate dehydrogenase at baseline (range), enzyme U/L[c]	199.0 (87.0-2,959.0)	200.5 (77.0-1,530.0)	200.0 (77.0-2,959.0)
Median PSA at baseline (range), μg/L[c]	21.4 (0-4,826.5)	17.4 (0.1-4,400.0)	19.8 (0-4,826.5)
Patients with alterations in a single gene, No. (%)			
ATM	43 (20.3)	42 (19.9)	85 (20.1)
BRCA1	12 (5.7)	4 (1.9)	16 (3.8)
BRCA2	86 (40.6)	88 (41.7)	174 (41.1)
BRIP1	4 (1.9)	4 (1.9)	8 (1.9)
CDK12	5 (2.4)	8 (3.8)	13 (3.1)
CHEK2	18 (8.5)	20 (9.5)	38 (9.0)
FANCA	5 (2.4)	6 (2.8)	11 (2.6)
HDAC2	2 (0.9)	3 (1.4)	5 (1.2)
PALB2	8 (3.8)	4 (1.9)	12 (2.8)
ECOG performance status, No. (%)			
0	130 (61.3)	146 (69.2)	276 (65.2)
1	82 (38.7)	65 (30.8)	147 (34.8)
Metastatic site involvement at study entry, No. (%)			
Bone	183 (86.3)	170 (80.6)	353 (83.5)
Lymph node	113 (53.3)	95 (45.0)	208 (49.2)
Visceral	51 (24.1)	39 (18.5)	90 (21.3)
Adrenal gland	3 (1.4)	7 (3.3)	10 (2.4)
Liver	18 (8.5)	13 (6.2)	31 (7.3)
Lung	27 (12.7)	18 (8.5)	45 (10.6)
Other soft tissue	6 (2.8)	15 (7.1)	21 (5.0)
Metastasis stage at diagnosis, No. (%)			
M0	76 (35.8)	97 (46.0)	173 (40.9)
M1	127 (59.9)	106 (50.2)	233 (55.1)
Unknown	9 (4.2)	8 (3.8)	17 (4.0)
Gleason score at diagnosis, No. (%)[d]			
<8	57 (27.0)	62 (29.5)	119 (28.3)
≥8	144 (68.2)	142 (67.6)	286 (67.9)
Unknown	10 (4.7)	6 (2.9)	16 (3.8)

(continued on following page)

TABLE 1. Baseline Characteristics of HRR+ Patients (continued)

Characteristic	NIRA + AAP (n = 212)	PBO + AAP (n = 211)	Total (N = 423)
Mean BPI-SF pain score, Item 3 (SD)[d]	1.13 (1.66)	1.25 (1.71)	1.19 (1.68)
Prior therapies for prostate cancer, No. (%)			
ADT[e]	204 (96.2)	201 (95.3)	405 (95.7)
Radiotherapy	90 (42.5)	91 (43.1)	181 (42.8)
Prostatectomy	133 (62.7)	138 (65.4)	271 (64.1)
AR-targeted therapy for nmCRPC or mCSPC	8 (3.8)	5 (2.4)	13 (3.1)
Taxane chemotherapy for mCSPC	41 (19.3)	44 (20.9)	85 (20.1)
AAP (≤4 months) for mCRPC	50 (23.6)	48 (22.7)	98 (23.2)
Others[f]	52 (24.5)	58 (27.5)	110 (26.0)

NOTE. Percentages may not add up to 100% because of rounding.

Abbreviations: AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; AR, androgen receptor; BPI-SF, Brief Pain Inventory–Short Form; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; NIRA, niraparib; nmCRPC, nonmetastatic castration-resistant prostate cancer; PBO, placebo; PSA, prostate-specific antigen; SD, standard deviation.

[a]N = 422 for the total population.

[b]All patients met screening criteria for hemoglobin (hemoglobin level >90 g/L). Baseline hemoglobin values were based on cycle 1 day 1 measurements.

[c]N = 419 for the total population.

[d]N = 421 for the total population.

[e]Patients were permitted to undergo a bilateral orchiectomy instead of ADT, with a gonadotropin-releasing hormone agonist, during the study.

[f]Other therapies included steroids (dexamethasone, prednisone, prednisolone), immunotherapy (ipilimumab, sipuleucel-T), investigational drugs, and nontaxane chemotherapy (estramustine).

of 0.5 in the *BRCA1/2* subgroup. For rPFS and OS, multivariate analyses were preplanned, adjusting for selected baseline prognostic factors. Additional details are provided in the Data Supplement.

RESULTS

Screening and Random Assignment

A total of 2,984 patients were prescreened for HRR status across the three cohorts using tissue and plasma tests. Of them, 742 (24.9%) tested positive for ≥1 of the nine genes (Fig 1).

Patient Characteristics

Between May 2019 and March 2021, 423 patients were enrolled, with 212 randomly assigned to the niraparib + AAP group and 211 to the placebo + AAP group. Although baseline characteristics were broadly comparable between treatment arms, rates of visceral metastases, bone metastases, and ECOG performance status of one were higher in the niraparib + AAP group (Table 1). Three percent of patients had prior exposure to novel hormonal agents in mCSPC or nmCRPC and 23% had <4 months of AAP for mCRPC before study treatment. In the HRR− cohort, between March 2019 and March 2020, 123 patients were randomly assigned to the niraparib + AAP group and 124 to the placebo + AAP group. Baseline characteristics were generally comparable; rates of lung metastases and ECOG performance status of one were higher in the niraparib + AAP group (Data Supplement).

Efficacy

HRR+ cohort. At clinical cutoff (October 8, 2021), the median duration of follow-up in the HRR+ cohort was 18.6 months (range, 0.3-29.0 months). In the *BRCA1/2* subgroup, median rPFS by central review was significantly longer in the niraparib + AAP group than in the placebo + AAP group (16.6 *v* 10.9 months; HR, 0.53; 95% CI, 0.36 to 0.79; *P* = .001; Fig 2A). Similarly, HRR+ patients in the niraparib + AAP group experienced a significantly longer rPFS (16.5 *v* 13.7 months; HR, 0.73; 95% CI, 0.56 to 0.96; *P* = .022; Fig 2B). Findings were consistent in the prespecified sensitivity analyses of investigator-assessed rPFS (Figs 2C and 2D). An HR of 0.99 (95% CI, 0.68 to 1.44) was observed for rPFS in the subgroup of patients with HRR alterations other than *BRCA1/2*; in a preplanned sensitivity analysis of patients with HRR alterations excluding *BRCA1/2*, single *ATM* or *CDK12* alterations and co-occurring *ATM/CDK12* alterations, a trend toward benefit was observed (HR, 0.87; 95% CI, 0.51 to 1.49). Additional gene-by-gene analysis showed that when combined into functional groups, patients with an alteration in the HRR-Fanconi pathway (*BRIP1*, *FANCA*, and *PALB2*) or an HRR-associated alteration (*CHEK2* or *HDAC2*) showed improvement in all end points.

rPFS in prespecified subgroups defined by baseline characteristics showed no heterogeneity of effect across subgroups (Fig 3). Adjustment for imbalances in baseline characteristics (PSA value, lactate dehydrogenase, alkaline

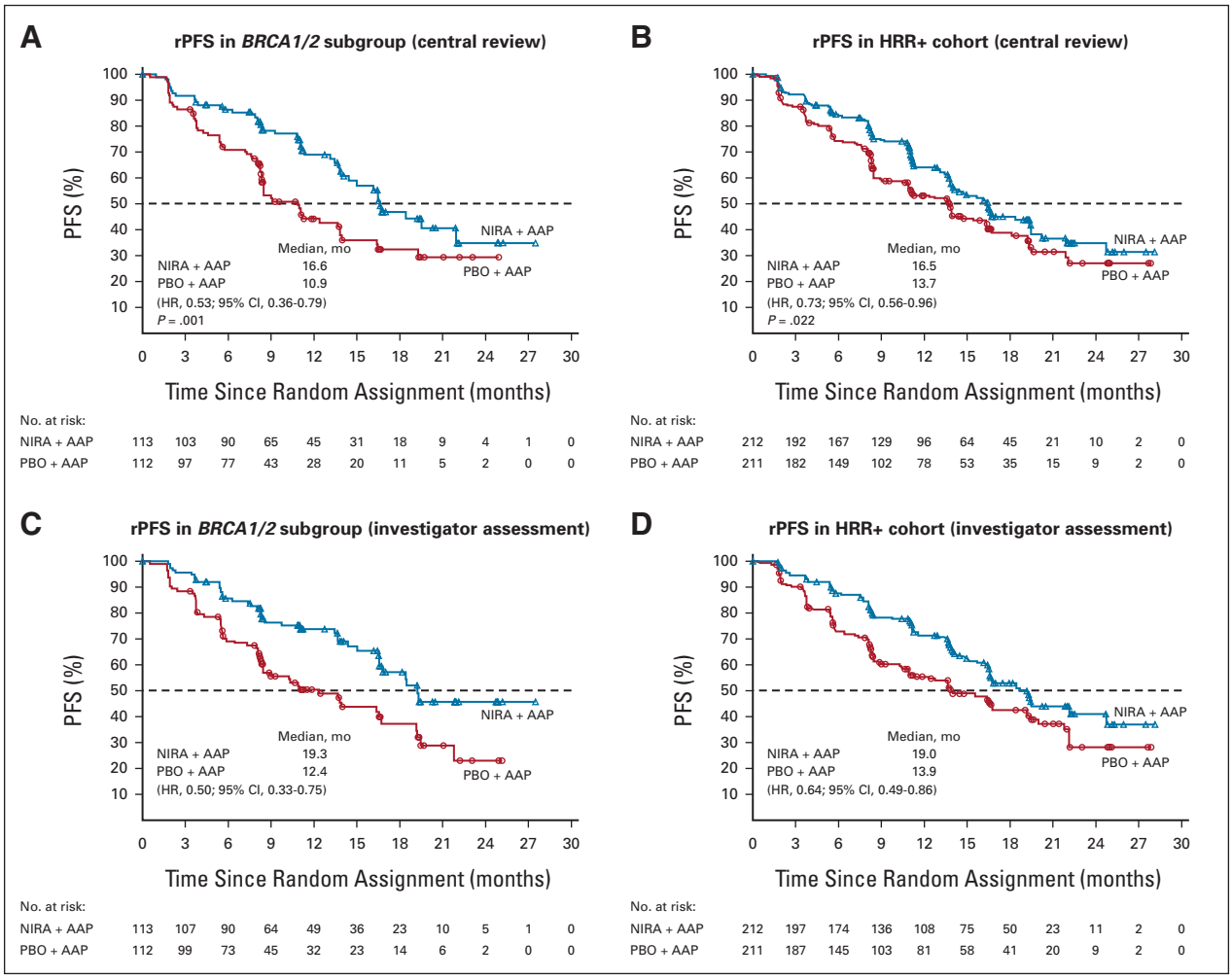

FIG 2. Kaplan-Meier estimates of rPFS. (A) rPFS of the subgroup of patients with *BRCA1/2* alterations as assessed by blinded independent central review. (B) rPFS of the overall HRR+ cohort as assessed by blinded independent central review. (C) Prespecified sensitivity analysis of rPFS of patients with *BRCA1/2* alterations by investigator assessment. (D) rPFS of the overall HRR+ cohort by investigator assessment. AAP, abiraterone acetate plus prednisone; HR, hazard ratio; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; PFS, progression-free survival; rPFS, radiographic progression-free survival.

phosphatase, and presence of visceral disease at baseline) in the multivariate model underscores the benefit of niraparib + AAP (Data Supplement).

Niraparib + AAP showed consistent benefits in the patient-relevant secondary and exploratory end points across HRR alterations. In the HRR+ cohort, niraparib + AAP delayed TCC (HR, 0.59; 95% CI, 0.39 to 0.89; $P = .011$; Fig 4A) and TSP (HR, 0.69; 95% CI, 0.47 to 0.99; $P = .04$; Fig 4B), which was also observed in the *BRCA1/2* subgroup (Figs 4C and 4D). At this preplanned interim analysis, the significance boundary of .0001 (O'Brien-Fleming method) was not met by either end point. OS data are immature at this first interim analysis, with 46.3% of the required events for final analysis (Fig 4E; Data Supplement). The prespecified multivariate analysis of OS, adjusting for baseline variables, favored the niraparib + AAP arm in the HRR+ cohort (0.77; 95% CI, 0.53 to 1.12; Data Supplement). Additionally, niraparib + AAP prolonged time to PSA progression and led to higher ORR in the HRR+ and *BRCA1/2* groups (Fig 5). Time to PSA progression and rPFS were strongly correlated, with an overall r = 0.67 (95% CI, 0.56 to 0.75). In the HRR+ cohort, patient-reported quality of life (QoL) changes over time between treatment arms were similar as determined by FACT-P total score (Data Supplement).

HRR− cohort. In the futility analysis, 233 HRR− patients (niraparib + AAP, n = 117; placebo + AAP, n = 116) were evaluated for the composite end point of time to PSA progression and/or rPFS (HR, 1.09; 95% CI, 0.75 to 1.57; $P = .66$; Data Supplement) and the individual end points of rPFS and time to PSA progression (Data Supplement). On the basis of the prespecified criteria, futility was declared for the HRR− cohort in August 2020, which was closed to further enrollment on the basis of Independent Data Monitoring Committee recommendations. All patients in the HRR− cohort were unblinded, and patients randomly

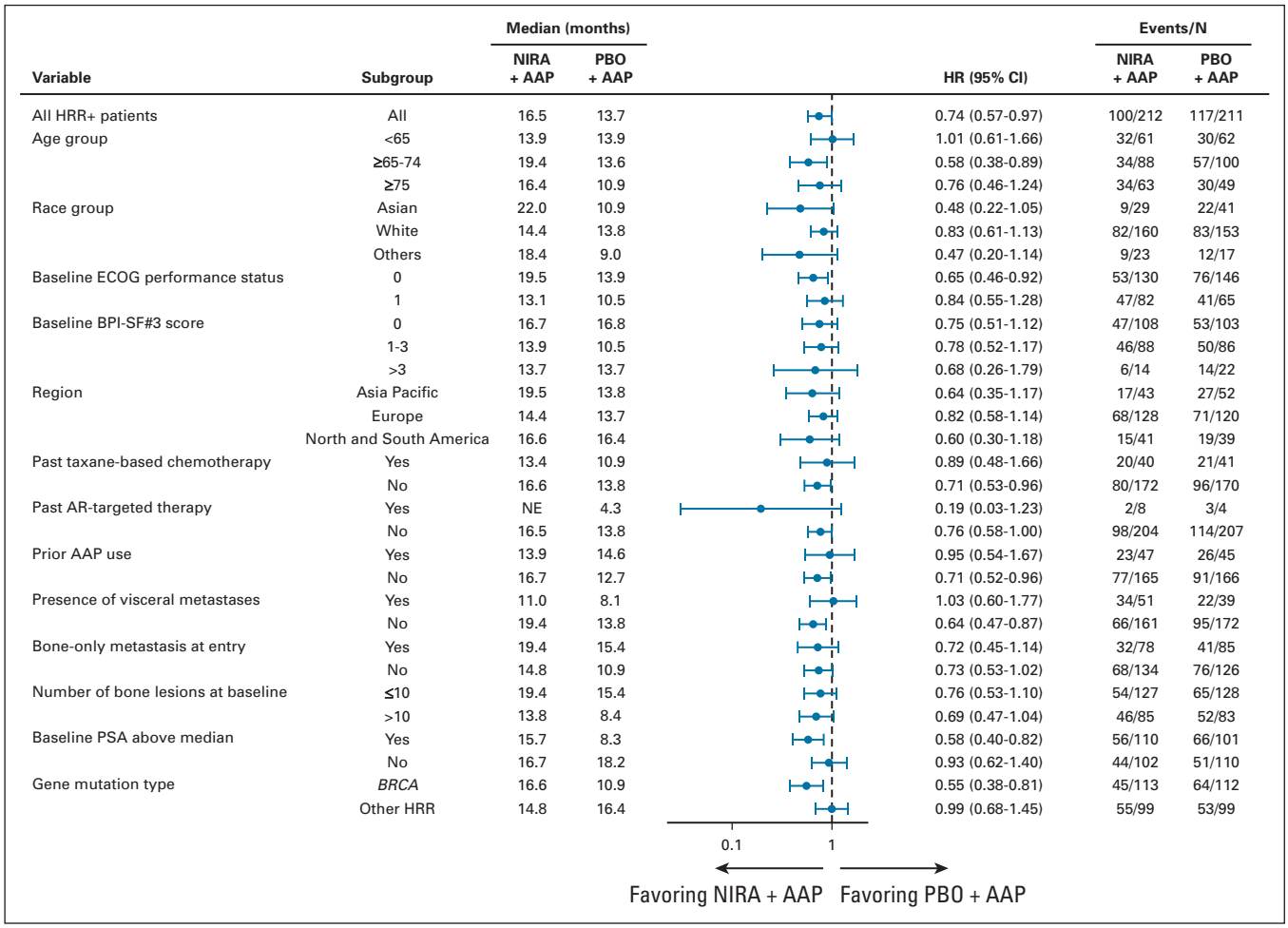

FIG 3. Forest plot of rPFS for subgroups defined by baseline clinical disease characteristics in the HRR+ cohort. AAP, abiraterone acetate plus prednisone; AR, androgen receptor; BPI-SF#3, Brief Pain Inventory–Short Form, Item 3; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HRR, homologous recombination repair; NE, not evaluable; NIRA, niraparib; PBO, placebo; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

assigned to niraparib + AAP were allowed to continue niraparib + AAP or AAP alone per the investigator's discretion. Additional efficacy assessments were not performed once patients entered a safety data collection phase.

Safety

The median total duration of assigned treatment for the HRR+ cohort was 13.8 months (range, 0-29.0) in the niraparib + AAP group and 12.1 months (range, 0-29.0) in the placebo + AAP group. The estimated relative dose intensity was generally high and comparable in the groups (Data Supplement). The incidence of grade ≥ 3 AEs was 67.0% with niraparib + AAP and 46.4% with placebo + AAP. The most common grade 3 AEs were anemia (28.3% *v* 7.6%) and hypertension (14.6% *v* 12.3%) with niraparib + AAP versus placebo + AAP, respectively. Other grade 3/4 AEs of note include thrombocytopenia (6.6% *v* 2.4%) and neutropenia (6.6% *v* 1.4%) with niraparib + AAP versus placebo + AAP, respectively (Table 2). AEs leading to dose reductions and treatment discontinuations are presented in the Data Supplement. A total of 38 patients died during study treatment, with 19 in each group (Data Supplement). In patients who died due to AEs, infections (eg, COVID-19 and pneumonia) were the leading cause of death in the niraparib + AAP group; cardiac disorders were the leading cause of death in the placebo + AAP group. Patients with niraparib drug interruptions or dose reductions had comparable rPFS benefit from niraparib + AAP compared with the observed benefit in the overall HRR+ population (HR, 0.72; 95% CI, 0.53 to 0.97 and HR, 0.70; 95% CI, 0.46 to 1.08, respectively). In the HRR− cohort, the median duration of assigned treatment was 16.8 months (range, 0-29.0); AEs were similar to those in the HRR+ cohort (Data Supplement).

DISCUSSION

Prior studies have demonstrated that niraparib and other PARP inhibitors have clinical benefit as monotherapy in HRR+ mCRPC after progression on androgen receptor pathway inhibitors and chemotherapy.[18,25,26] In the phase III MAGNITUDE study, rPFS was significantly longer in the niraparib + AAP group versus placebo + AAP in the

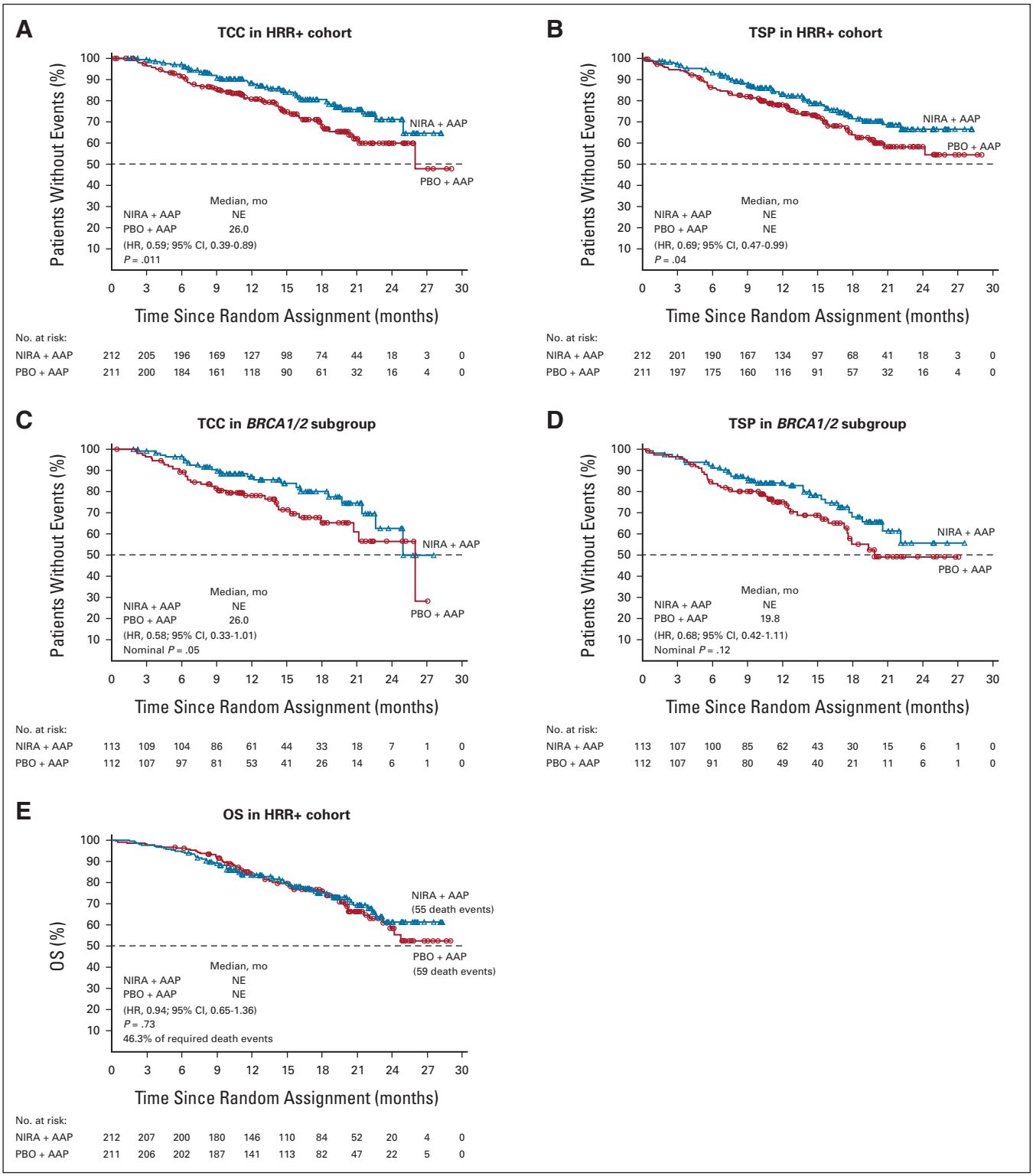

FIG 4. Kaplan-Meier estimates of secondary end points. (A and B) Kaplan-Meier estimates of TCC and TSP in the HRR+ cohort, respectively. (C and D) Kaplan-Meier estimates of TCC and TSP in the *BRCA1/2* subgroup, respectively. (E) Kaplan-Meier estimate of OS in the HRR+ cohort. AAP, abiraterone acetate plus prednisone; HR, hazard ratio; HRR, homologous recombination repair; NE, not evaluable; NIRA, niraparib; OS, overall survival; PBO, placebo; TCC, time to initiation of cytotoxic chemotherapy; TSP, time to symptomatic progression.

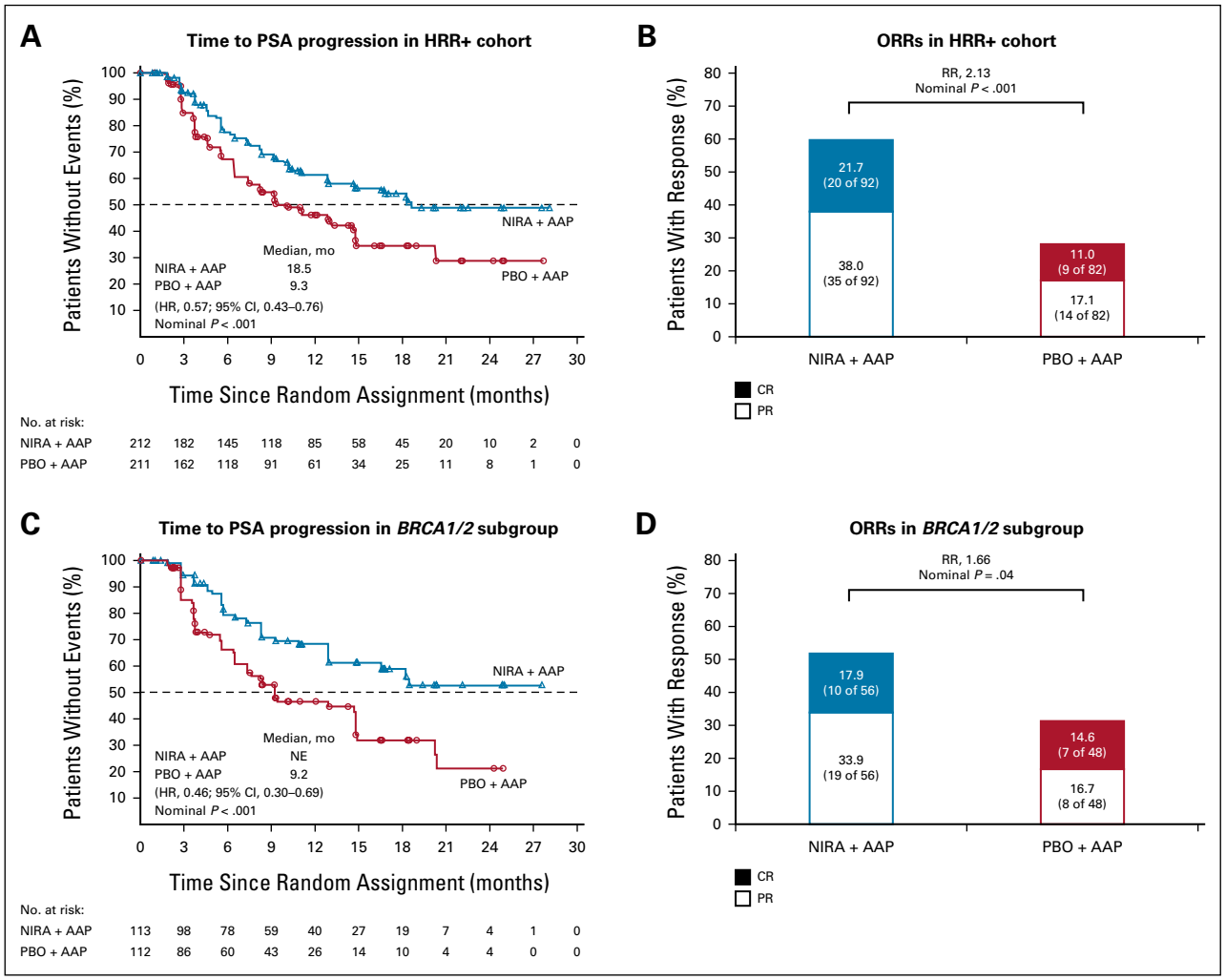

FIG 5. Kaplan-Meier estimates of time to PSA progression and ORRs. (A and B) Kaplan-Meier estimates of time to PSA progression and ORRs in the HRR+ cohort, respectively. (C and D) Kaplan-Meier estimates of time to PSA progression and ORRs in the *BRCA1/2* subgroup, respectively. AAP, abiraterone acetate plus prednisone; CR, complete response; HR, hazard ratio; HRR, homologous recombination repair; NE, not evaluable; NIRA, niraparib; ORR, objective response rate; PBO, placebo; PR, partial response; PSA, prostate-specific antigen; RR, relative risk.

HRR+ cohort, with the greatest benefit in the *BRCA1/2* subgroup. The median rPFS was 10.9 months in the *BRCA1/2* subgroup that received AAP alone compared with the historical rPFS of approximately 16 months in unselected patients.[6,27-29] These findings are consistent with prior reports of patients with *BRCA1/2* gene alterations having poor prognosis and worse treatment outcomes with standard therapies. In MAGNITUDE, treatment effect for niraparib + AAP was generally consistent across gene alteration groups, possibly mitigating the negative prognostic impact of HRR alterations. The study design allowed for a definitive evaluation of niraparib + AAP in patients with *BRCA1/2* alterations; however, the rarity of some other HRR alterations precluded statistical significance testing in these individual genes. A preplanned sensitivity analysis showed the increase in HR for other HRR alterations were driven by *ATM* or *CDK12* alterations. Additionally, the previously reported gene-by-gene analysis demonstrated that patients with alterations in the HRR-Fanconi pathway and HRR-associated alterations showed improvement in all end points, supporting the benefit of niraparib + AAP in HRR alterations beyond *BRCA1/2*.[30]

The benefit in rPFS in the current study was also supported by clinically meaningful improvements in TCC and TSP. Although the *P* value for both end points was <.05, the conservative boundary for statistical significance (.0001; O'Brien-Fleming method) was not crossed. These end points will be further tested at the prespecified second interim and final analysis. Both of these secondary end points are well established in mCRPC as clinically meaningful measures of patient outcome.[31-33] In contrast to radiographic progression, which can have limited clinical impact on worsening of symptoms in some patients, the events that constitute symptomatic progression are significant drivers of morbidity.

TABLE 2. TEAEs in HRR+ Patients (occurring in >10% of patients)

	NIRA + AAP (n = 212)			PBO + AAP (n = 211)		
Event	**All Grades, No. (%)**	**Grade 3, No. (%)**	**Grade 4, No. (%)**	**All Grades, No. (%)**	**Grade 3, No. (%)**	**Grade 4, No. (%)**
Patients with ≥1 SAE	76 (35.8)			52 (24.6)		
Any TEAEs	210 (99.1)	119 (56.1)	23 (10.8)	199 (94.3)	90 (42.7)	8 (3.8)
Anemia	98 (46.2)	60 (28.3)	3 (1.4)	43 (20.4)	16 (7.6)	0
Hypertension	66 (31.1)	31 (14.6)	0	44 (20.9)	26 (12.3)	0
Constipation	65 (30.7)	0	0	29 (13.7)	0	0
Fatigue	56 (26.4)	7 (3.3)	0	35 (16.6)	9 (4.3)	0
Nausea	50 (23.6)	1 (0.5)	0	29 (13.7)	0	0
Thrombocytopenia	45 (21.2)	6 (2.8)	8 (3.8)	18 (8.5)	5 (2.4)	0
Dyspnea	34 (16.0)	4 (1.9)	0	12 (5.7)	2 (0.9)	0
Asthenia	33 (15.6)	1 (0.5)	1 (0.5)	19 (9.0)	1 (0.5)	0
Back pain	31 (14.6)	5 (2.4)	0	44 (20.9)	2 (0.9)	0
Decreased appetite	30 (14.2)	1 (0.5)	0	13 (6.2)	1 (0.5)	0
Hypokalemia	29 (13.7)	6 (2.8)	0	20 (9.5)	6 (2.8)	0
Neutropenia	29 (13.7)	11 (5.2)	3 (1.4)	12 (5.7)	3 (1.4)	0
Vomiting	28 (13.2)	1 (0.5)	0	14 (6.6)	1 (0.5)	0
Arthralgia	28 (13.2)	1 (0.5)	0	20 (9.5)	1 (0.5)	0
Dizziness	24 (11.3)	1 (0.5)	0	12 (5.7)	0	0
Insomnia	22 (10.4)	0	0	8 (3.8)	0	0
Leukopenia	22 (10.4)	4 (1.9)	0	5 (2.4)	1 (0.5)	0
Bone pain	21 (9.9)	3 (1.4)	0	24 (11.4)	1 (0.5)	0
Fall	11 (5.2)	2 (0.9)	0	26 (12.3)	6 (2.8)	0

NOTE. Grade 5 TEAEs in the NIRA + AAP, group, No. (%): dyspnea, 1 (0.5).

Abbreviations: AAP, abiraterone acetate with prednisone; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

OS data were immature at this first interim analysis, although results from the OS multivariate analysis favor the niraparib + AAP group. As noted, the conservative boundary for statistical significance at this first interim analysis for all secondary end points was not crossed. Follow-up of patients with HRR+ mCRPC enrolled in MAGNITUDE is ongoing. Other limitations of the MAGNITUDE study include the limited diversity in patient race and demographics. Furthermore, although the nine-gene panel selection was based on previous clinical data, comprehensive assessment of other genes implicated in HRR was not undertaken.

The incidence of grade 3/4 AEs was higher with niraparib + AAP, with approximately a 4-fold increase of grade ≥ 3 anemia with niraparib + AAP compared with 7% with placebo + AAP, similar to previously reported data for AAP.[34] The safety profile of niraparib + AAP was manageable and consistent with prior studies of each therapy in prostate cancer, with no new safety signals that affected the benefit-risk profile. Outcomes for patients with dose interruptions/reductions support its use in patient management without concerns of negatively affecting outcomes. QoL was also maintained with the addition of niraparib to AAP. Additional analyses that included patient-reported outcomes have been presented, and further in-depth analyses will be reported.[30,35]

MAGNITUDE was designed intentionally to determine which group of patients would derive the greatest benefit from a PARP inhibitor with standard-of-care AAP therapy while limiting undue risks associated with combination therapy. HRR status was prospectively and comprehensively determined by plasma- and tissue-based assays. The study was practically designed with prior chemotherapy and use of novel hormonal agents allowed in the mCSPC or nmCRPC settings. Patients were allowed to receive up to 4 months of prior AAP for mCRPC, and approximately one-fourth of patients in the HRR+ cohort had received prior AAP treatment (median duration [range], 1.9 [0.3-4.1] months), which may have affected the disease characteristics and outcomes. As HRR alterations testing is not yet routine practice in early prostate cancer, allowing a short course of AAP before random assignment acknowledged the need to initiate therapy for advancing prostate cancer while HRR alteration status was determined. These features of a pragmatic trial design were implemented to suit the

evolving standard of care in advanced prostate cancer while informing a key practice pattern.

Futility was declared, and no benefit was observed in patients without HRR alterations (HRR– cohort), who were prospectively identified before random assignment. As time to PSA progression and rPFS have demonstrated a strong correlation in prior trials and that correlation was also observed in the HRR+ cohort in MAGNITUDE, the composite end point allowed for a rapid assessment of possible futility.[36] Although the more limited sample size of the HRR− cohort potentially precludes detection of a modest benefit, the individual components of rPFS and PSA progression each had an HR > 1.0, and demonstration of benefit-risk ratio in this subset would be challenging. Nevertheless, results from MAGNITUDE highlight the importance of testing for HRR status before initiating niraparib + AAP to identify who will gain the most benefit from combination therapy balanced with additional toxicity.

In the recently published phase III PROpel study, which assessed olaparib + AAP versus placebo + AAP for first-line mCRPC in patients who were unselected for HRR alterations, the primary end point of rPFS was met (24.8 *v* 16.6 months; HR, 0.66; 95% CI, 0.54 to 0.81; $P < .0001$). A retrospective analysis demonstrated rPFS improvement with olaparib + AAP in both HRR+ and HRR− populations, with lesser benefit in the latter.[37] Differences, including study design, gene testing strategies, prior exposure to novel hormonal agents, and patient population, limit the comparability between PROpel and MAGNITUDE; however, together they confirm the substantial benefit of PARP inhibition with AAP for patients with HRR+ mCRPC and the need for continued development of predictive biomarkers.[38]

In summary, HRR+ patients with mCRPC derived significant and clinically meaningful benefit from niraparib + AAP. The safety profile of this combination was manageable, with no new safety signals that affected the benefit-risk profile. These data underscore the need to test for HRR gene alterations for metastatic prostate cancer and support the use of niraparib + AAP as first-line combination therapy for these patients with particularly poor prognoses.

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The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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List of MAGNITUDE principal investigators are listed in Appendix Table A1 (online only).

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Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer

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Uncompensated Relationships: AAA/Endocyte/Novartis (Inst)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of MAGNITUDE Principal Investigators

Country	Principal Investigator
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Australia	Tom Ferguson, Howard Gurney, Elizabeth Hovey, Anthony Joshua, Matos Marco, Gavin Marx, Michelle Morris, Siobhan Ng, David Pook, Shahneen Sandhu, Ali Tafreshi, Thean Hsiang Tan
Belgium	Tsvetanka Tosheva
Brazil	Livia Andrade, Felipe Cruz, Luiza Faria, Jose Figueiredo, Fabio Franke, Andrea Juliana Gomes, Ariel Kann, Celio Kussumoto, Suelen Martins, Andre Murad, Helio Pinczowski, Giovani Pioner, Luis Pires, Daniel Preto, Gisele Santos, Eduardo Silva, Jamile Silva, Luciano Viana, Karina Vianna, Adriano Paula
Canada	Zhiwen Chen, Kim Chi, Urban Emmenegger, Neil Fleshner, Sunil Parimi, Fred Saad, Francisco Vera-Badillo
China	Hongqian Guo, Hong Luo, Lulin Ma, Mingxing Qui, Wei Xue, Guo Yonglian, Lei Li, Jinxian Pu, Song Zheng, Qing Zou
Czech Republic	Milos Brodak, Milan Hora, Vladimir Samal, Vladimir Student, Jaroslav Vanasek
France	Emmanuelle Bompas, Philippe Barthelemy, Delphine Borchiellini, Aude Flechon, Hakim Mahammedi, Guilhem Roubaud, Antoine Thiery-Vuillemin, Diego Tosi, Spaeth Dominique, Carole Helissey
Germany	Martin Boegemann, Susan Feyerabend, Eva Hellmis, Martin Schostak
Great Britain	Gerhardt Attard, Anna Lydon, Ian Sayers, Omi Parikh, Duncan Wheatley
Hungary	Peter Arkosy, Jozsef Erfan, Lajos Geczi, Peter Nyirady, Judit Olah, Istvan Papos, Bela Piko
Israel	Raanan Berger, Avivit Peer
Italy	Umberto Basso, Sergio Bracarda, Orazio Caffo, Francesco Carrozza, Gianluca Del Conte, Luca Galli, Donatello Gasparro, Sandro Pignata, Riccardo Ricotta, Daniele Santini, Giampaolo Tortora
Korea	Seoksoo Byun, SeolHo Choo, ByungHa Chung, Jaeyoung Joung, Wonho Jung, Taek Won Kang, Cheol Kwak, TaeGyun Kwon, Hyo Jin Lee, Ji Youl Lee, SeongIl Seo, YoungDeuk Choi, HongKoo Ha, ChoungSoo Kim
Malaysia	Flora Li Tze Chong, Chun Sen Lim, Vijayan Manogran, Hwoei Fen Soo Hoo, Guan Chou Teh, Marniza Saad
Mexico	David Calvo Dominguez, Abraham Cardenas, Julia Saenz
The Netherlands	Andre Bergman, Helgi Helgason, C.B. Hunting, Rik Somford
Poland	Tomasz Byrski, Tomasz Drewa, Dorota Filarska, Jolanta LuniewskaBury, Adam Marcheluk, Konrad Talasiewicz, Krzysztof Tupikowski, Renata Zaucha, Bogdan Zurawski
Portugal	Pedro Madeira, Andre Mansinho, Nuno Vau
Russia	Anna Alyasova, Victoria Chistyakova, Denis Khvorostenko, Dmitry Kirtbaya, Gennady Kolesnikov, Evgeny Kopyltsov, Igor Lifirenko, Alexander Lykov, Konstantin Penkov, Andrey Semenov, Mikhail Shkolnik, Pavel Skopin, Roman Smirnov, Evgeny Usynin, Sergey Varlamov, Vladimir Vladimirov
Spain	Teresa Alonso, Sara Breijo, Elena Castro, Enrique Gallardo, Jose Gutierrez Banos, Alvaro Juarez, Rebeca Lozano, Pablo Maroto, Javier Puente, Alejo Rodriguez-Vida, Regina Girones, Begona Mellado
Sweden	Enrique Castellanos, Chunde Li
Taiwan	Chao-Hsiang Chang, Hsiao-Jen Chung, Kuan-Hua Huang, Yen-Chuan Ou, Yu-Chieh Tsai, Shian-Shiang Wang, Wen-Jeng Wu, See-Tong Pang
Turkey	Cagatay Arslan, Devrim Cabuk, Hasan Coskun, Mahmut Gumus, Mustafa Ozguroglu, Berna Oksuzoglu, Berksoy Sahin, Deniz Tural, Bulent Yalcin, Irfan Cicin
Ukraine	Igor Bondarenko, Yaroslav Gotsuliak, Yevhen Hotko, Gennadii Khareba, Oleksandr Lychkovskyy, Iryna Lytvyn, Taron Nalbandyan, Viktor Paramonov, Valerii Sakalo, Eduard Stakhovsky, Viktor Stus
USA	Sunil Babu, Alan Bryce, David Cahn, Herta Chao, Franklin Chu, Curtis Dunshee, Oscar Goodman, Michael Grable, Jason Hafron, Joelle Hamilton, Ralph Hauke, Joseph Maly, David Morris, Gregg Newman, Patrick Pilie, Neal Shore, Paul Sieber, Matthew Smith, Andrew Trainer, Ronald Tutrone