EUROPEAN UROLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Rucaparib for the Treatment of Metastatic Castration-resistant Prostate Cancer Associated with a DNA Damage Repair Gene Alteration: Final Results from the Phase 2 TRITON2 Study

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Article info

Article history:
Accepted May 17, 2023

Associate Editor:
Todd M. Morgan

Statistical Editor:
Andrew Vickers

Keywords:
Poly(ADP-ribose) polymerase inhibitor
Metastatic castration-resistant

Abstract

Background: Initial TRITON2 (NCT02952534) results demonstrated the efficacy of rucaparib 600 mg BID in patients with metastatic castration-resistant prostate cancer (mCRPC) associated with a *BRCA1* or *BRCA2* (BRCA) or other DNA damage repair (DDR) gene alteration.
Objective: To present the final data from TRITON2.
Design, setting, and participants: TRITON2 enrolled patients with mCRPC who had progressed on one or two lines of next-generation androgen receptor–directed therapy and one taxane-based chemotherapy.
Outcome measurements and statistical analysis: The primary endpoint was objective response rate (ORR; as per the modified Response Evaluation Criteria in Solid Tumor Version 1.1/Prostate Cancer Clinical Trials Working Group 3 criteria in patients with measurable disease by independent radiology review [IRR]); prostate-specific antigen (PSA) response rate (≥50% decrease from baseline [PSA50]) was a key secondary endpoint.

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https://doi.org/10.1016/j.eururo.2023.05.021

Please cite this article as: W. Abida, D. Campbell, A. Patnaik et al., Rucaparib for the Treatment of Metastatic Castration-resistant Prostate Cancer Associated with a DNA Damage Repair Gene Alteration: Final Results from the Phase 2 TRITON2 Study, Eur Urol (2023), https://doi.org/10.1016/j.eururo.2023.05.021

prostate cancer
DNA damage repair gene alteration

Results and limitations: As of July 27, 2021 (study closure), TRITON2 had enrolled 277 patients, grouped by mutated gene: BRCA (n = 172), *ATM* (n = 59), *CDK12* (n = 15), *CHEK2* (n = 7), *PALB2* (n = 11), or other DDR gene (Other; n = 13). ORR by IRR was 46% (37/81) in the BRCA subgroup (95% confidence interval [CI], 35–57%), 100% (4/4) in the *PALB2* subgroup (95% CI, 40–100%), and 25% (3/12) in the Other subgroup (95% CI, 5.5–57%). No patients within the *ATM*, *CDK12*, or *CHEK2* subgroups had an objective response by IRR. PSA50 response rates (95% CI) in the BRCA, *PALB2*, *ATM*, *CDK12*, *CHEK2*, and Other subgroups were 53% (46–61%), 55% (23–83%), 3.4% (0.4–12), 6.7% (0.2–32%), 14% (0.4–58%), and 23% (5.0–54%), respectively.

Conclusions: The final TRITON2 results confirm the clinical benefit and manageable safety profile of rucaparib in patients with mCRPC, including those with an alteration in BRCA or select non-BRCA DDR gene.

Patient summary: Almost half of TRITON2 patients with BRCA-mutated metastatic castration-resistant prostate cancer had a complete or partial tumor size reduction with rucaparib; clinical benefits were also observed with other DNA damage repair gene alterations.

1. Introduction

Inhibition of poly(ADP-ribose) polymerase (PARP) proteins has emerged as an attractive treatment strategy for patients with metastatic castration-resistant prostate cancer (mCRPC) associated with a DNA damage repair (DDR) gene defect [1–3]. The PARP inhibitor rucaparib received accelerated approval from the US Food and Drug Administration for the treatment of patients with *BRCA1* or *BRCA2* (BRCA) mutation-associated mCRPC who were previously treated with androgen receptor–directed therapy and taxane-based chemotherapy [2,4].

This approval was based on the initial results from the TRITON2 open-label, international, phase 2 study investigating rucaparib in patients with mCRPC associated with DDR deficiency [2,4]. Rucaparib demonstrated meaningful activity in patients with a BRCA alteration, with an objective response rate (ORR) of 44% (95% confidence interval [CI], 31–57%; 27/62 patients) assessed by independent radiology review (IRR), and a prostate-specific antigen (PSA) response rate of 55% (95% CI, 45–64%; 63/115 patients) [2]. Among TRITON2 patients with a non-BRCA DDR gene alteration (n = 78), tumor responses were observed in patients with a *FANCA*, *PALB2*, *BRIP1*, or *RAD51B* gene alteration [5]. Here, we present the final data from the TRITON2 study of patients with mCRPC associated with a deleterious alteration in BRCA or other DDR gene.

2. Patients and methods

2.1. Study design

TRITON2 (ClinicalTrials.gov identifier: NCT02952534) was an international, open-label, phase 2 study evaluating rucaparib in patients with mCRPC associated with DDR deficiency. Enrollment criteria have previously been reported [2] and are included in the Supplementary material.

This study was approved by local or national review boards and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Council for Harmonization. All patients provided written informed consent.

2.2. Procedures

Patients had a deleterious germline or somatic alteration in one or more genes: *BRCA1*, *BRCA2*, *ATM*, *CDK12*, *CHEK2*, *PALB2*, or other DDR genes (*FANCA*, *BARD1*, *BRIP1*, *NBN*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L* [Other]), which was determined by central tissue or plasma testing by Foundation Medicine, Inc. [6,7] or through local testing. Designated germline testing was performed by Color Health, Inc. [8,9].

Patients initiated treatment with 600 mg oral rucaparib twice daily. Additional procedural details have been reported previously [2] and are included in the Supplementary material.

2.3. Patient populations

Patients were grouped by mutated gene: BRCA, *ATM*, *CDK12*, *CHEK2*, *PALB2*, or Other. Patients with co-occurring DDR gene alterations were allocated into a subgroup as per the hierarchy above. Zygosity was evaluated only in patients whose tissue was tested and had sufficiently high quality. The PSA response rate was assessed in all evaluable patients (overall efficacy population), and ORR was assessed in the subset of patients who had measurable disease at baseline as per the blinded central IRR assessment (IRR-evaluable population). Efficacy evaluations based on parameters assessed by IRR were undertaken in patients with IRR-evaluable disease only. Efficacy evaluations based on investigator assessment were undertaken in all randomized patients. The safety population included all patients who received one or more doses of rucaparib 600 mg.

This study is complete, and the analyses presented herein are based on the data collected as of the study closure on July 27, 2021. IRR-assessed radiographic progression-free survival (rPFS) events occurred in 55% of patients; overall survival (OS) events occurred in 66%.

2.4. Outcomes

The primary endpoint for patients with measurable disease was confirmed ORR by IRR (complete or partial response) as per the modified Response Evaluation Criteria in Solid Tumors version 1.1/Prostate Cancer Working Group Guidelines version 3 criteria in the IRR-evaluable population. Patients without measurable disease were assessed for a confirmed PSA response ($\geq$50% decrease from baseline confirmed by a consecutive measurement $\geq$3 wk later [PSA50]), which was measured in the overall efficacy population.

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The secondary efficacy endpoints in the overall efficacy population included a confirmed PSA response rate of ≥90% decrease (PSA90), time to PSA progression, clinical benefit rate, and OS; the IRR-evaluable population endpoints included rPFS, duration of radiographic response (DOR), and safety. The definitions of secondary endpoints are included in the Supplementary material.

Exploratory endpoints included an examination of ORR and PSA response rates in patients with BRCA alterations with co-occurring alterations in *TP53*, *PTEN*, or *RB1*.

2.5. Statistical analysis

Confirmed ORR and PSA responses were summarized descriptively with frequencies and 95% CIs (Clopper-Pearson). Time-to-event variables were summarized using the Kaplan-Meier methodology. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patients and genomic characteristics

A total of 277 patients were enrolled in the TRITON2 study, with 187 selected based on eligible alterations detected from central screening of tissue and/or plasma samples. Additionally, 90 patients were enrolled based on the results from local genomic testing. Of enrolled patients, 133 were IRR evaluable for ORR, and rPFS, and all 277 were evaluable for PSA response, clinical benefit rate, OS, and safety (Fig. 1). Baseline characteristics are shown in Supplementary Table 1 for the BRCA (n = 172), *ATM* (n = 59), *CDK12* (n = 15), *CHEK2* (n = 7), *PALB2* (n = 11), and Other (n = 13) subgroups. The Other subgroup included patients with an alteration in *BARD1* (n = 1), *FANCA* (n = 5), *NBN* (n = 3), *RAD51* (n = 1), *RAD51B* (n = 1), and *BRIP1* (n = 2).

This patient population was heavily pretreated, with 136 (49%) patients having received three or more prior CRPC therapies. The median long-term follow-ups obtained using the reverse Kaplan-Meier method for patients in the BRCA and non-BRCA groups were 23.7 and 25.8 mo, respectively.

3.2. Efficacy

3.2.1. BRCA subgroup

A confirmed objective response was observed in 37/81 (46%; 95% CI, 35–57%) patients with IRR-evaluable disease associated with a BRCA alteration (Table 1 and Fig. 2). Among patients in this subgroup, 67% demonstrated a single best reduction in the sum of target lesions of ≥30% from baseline (Fig. 3A). The DOR by IRR was 15.5 mo (95% CI, 6.4–not reached [NR]), although heavily censored (Supplementary Fig. 1A). DOR by investigator and median rPFS by IRR in the BRCA subgroup are presented in Supplementary Figure 1B and Figure 4A. PSA50, best PSA reduction ≥50% from baseline, clinical benefit rate, PSA90 response, time to PSA progression, and median OS are presented in Table 1; Figures 2, 3B, and 4B; Supplementary Table 2; and Supplementary Figure 2. For time-to-event analyses, median follow up time for patients without the event is provided in Supplementary Table 3.

Zygosity was available in 31/81 (38%) patients with a *BRCA* alteration and measurable disease. Responses are as follows: 14/25 (56%) in patients with biallelic alterations, 2/6 (33%) in those with monoallelic alterations, and 21/50 (42%) in those with unknown zygosity. The biallelic population was heavily skewed by patients with homozygous deletions (11/14 responders).

The confirmed ORR as per the IRR was 48% among patients with a *BRCA2* alteration and 30% among those with a *BRCA1* alteration (Fig. 2). ORR was similar between patients with a germline or somatic BRCA alteration and between those with or without co-occurring *TP53*, *PTEN*, or *RB1* alterations, except that ORR was numerically lower for patients in the BRCA subgroup with a co-occurring *RB1* alteration (3/13, 23%, 95% CI 5.0–54, Fig. 2). PSA50 response rates were 59% for patients with a *BRCA2* alteration and 18% for those with a *BRCA1* alteration (Fig. 2); however, we did not observe a difference in response rates among patients with co-occurring mutations in *TP53*, *RB1*, or *PTEN*.

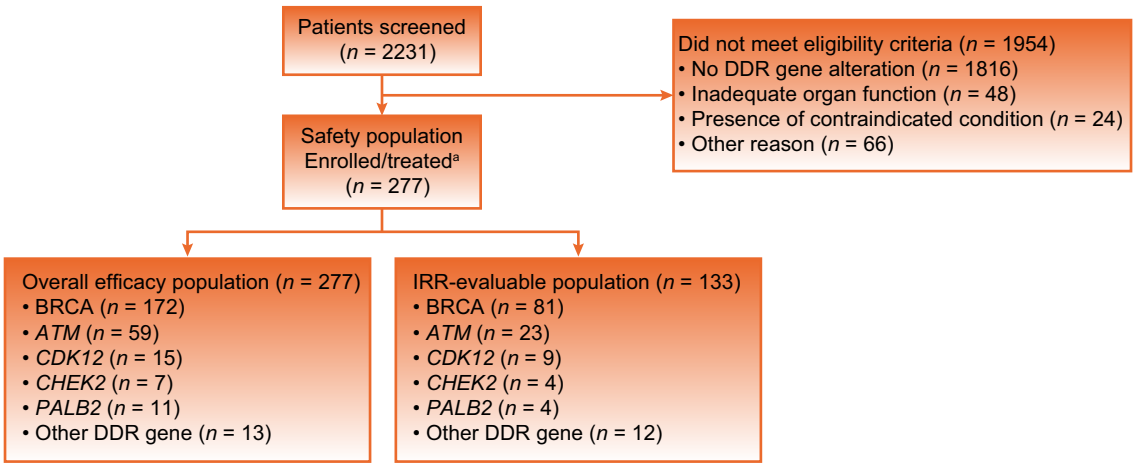

Fig. 1 – Patient flow diagram. DDR = DNA damage repair; IRR = independent radiology review. [a] A total of 187 patients were enrolled based on eligible alterations detected from central screening of tissue and/or plasma samples; 90 patients were enrolled based on the results from local genomic testing. The study closed on July 27, 2021; 23 patients continued to receive rucaparib outside of the study after study closure (BRCA [*n* = 19], *CHEK2* [*n* = 1], and other DDR gene [*n* = 3]).

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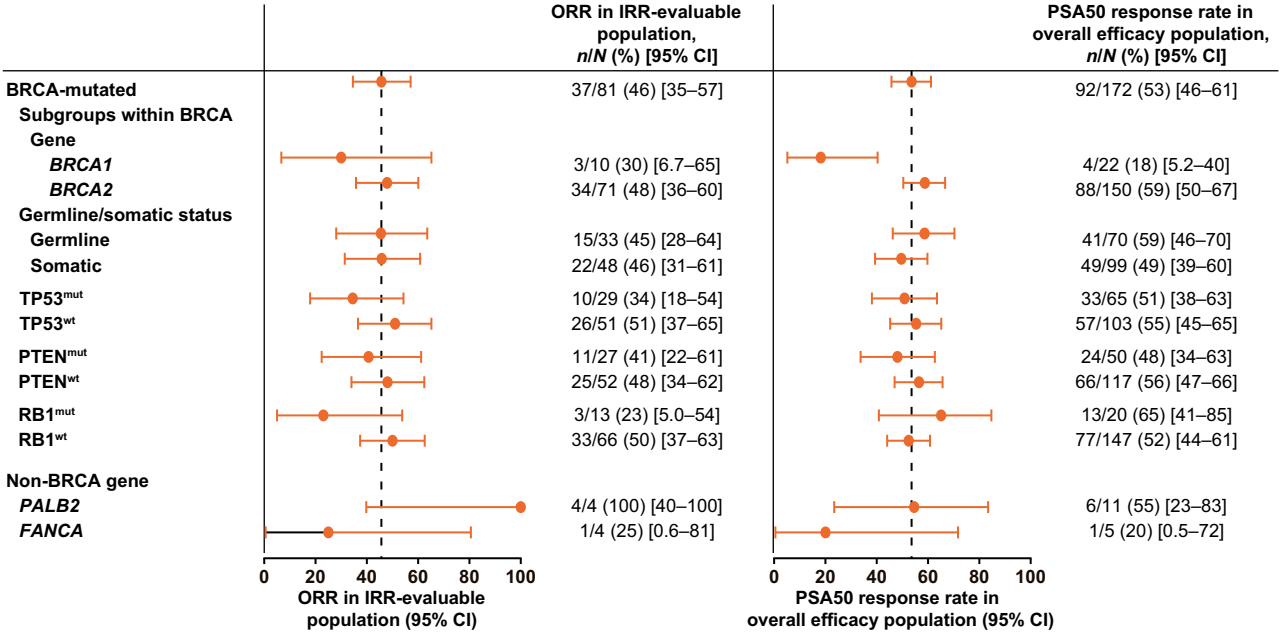

Fig. 2 – FOREST PLOTS OF ORR AND PSA50 RESPONSE RATE BY SUBGROUP. The vertical dotted line corresponds to the ORR or PSA50 response in the BRCA-mutated group. CI = confidence interval; IRR = independent radiology review; ORR = objective response rate; PSA50 = prostate-specific antigen ≥50% decrease from baseline.

Table 1 – Confirmed ORR and PSA50 response by gene in the IRR-evaluable population

	BRCA (n = 81)	*PALB2* (n = 4)	*ATM* (n = 23)	*CDK12* (n = 9)	*CHEK2* (n = 4)	Other (n = 12)
Confirmed ORR as per IRR [a], n (%; 95% CI)	37 (46; 35–57)	4 (100; 40–100)	0 (0; 0–15)	0 (0; 0–34)	0 (0; 0–60)	3 (25; 5.5–57)
Best overall confirmed response, n (%)						
CR	8 (9.9)	0	0	0	0	2 (17) [b]
PR	29 (36)	4 (100)	0	0	0	1 (8.3) [c]
SD	34 (42)	0	17 (74)	6 (67)	3 (75)	6 (50)
PD	8 (9.9)	0	5 (22)	2 (22)	1 (25)	2 (17)
NE	2 (2.5)	0	1 (4.3)	1 (11)	0	1 (8.3)
PSA50 response rate in the overall efficacy population, n/N (%; 95% CI)	92/172 (53; 46–61)	6/11 (55; 23–83)	2/59 (3.4; 0.4–12)	1/15 (6.7; 0.2–32)	1/7 (14; 0.4–58)	3/13 (23; 5.0–54)

BRCA = *BRCA1*, or *BRCA2*; CI = confidence interval; CR = complete response; IRR = independent radiology review; NE = not evaluable; ORR = objective response rate; PCWG3 = Prostate Cancer Working Group Guidelines version 3; PD = progressive disease; PR = partial response; PSA50 = confirmed prostate-specific antigen response of ≥50% decrease from baseline; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease.

[a] AS per the modified RECIST/PCWG3 criteria.

[b] One patient with a *FANCA* alteration and one with a *BRIP1* alteration (subsequently found to have a co-occurring homozygous *BRCA2* deletion).

[c] The patient had a *RAD51B* alteration.

3.2.2. Patients with PALB2, ATM, CDK12, CHEK2, or other DDR gene alterations

All four patients with measurable disease by IRR and a *PALB2* alteration had a confirmed objective response (100%, 95% CI 40–100%; Table 1 and Fig. 2), with a median DOR of 10.1 mo (95% CI, NR–NR; Supplementary Fig. 1). Of 11 patients with a *PALB2* alteration, six (55%; 95% CI, 23–83%) had a PSA50 response (Table 1 and Fig. 2); PSA90 response rates, median rPFS, OS, clinical benefit rate, and time to PSA progression are presented in Figure 4A, Supplementary Table 2, and Supplementary Figure 2.

For the 11 patients with *PALB2* alterations, zygosity could be determined only for three patients, two of whom responded (one with a monoallelic and one with a biallelic alteration).

Among patients with IRR-evaluable disease in the Other subgroup, a confirmed objective response was observed in 3/12 (25%) patients (95% CI, 5.5–57%). The three patients had alterations in *FANCA*, *RAD51B*, and *BRIP1* (Table 1 and Fig. 3A), although the responder with a *BRIP1* alteration was later found to have had a co-occurring homozygous *BRCA2* deletion at the time of enrollment. No patients

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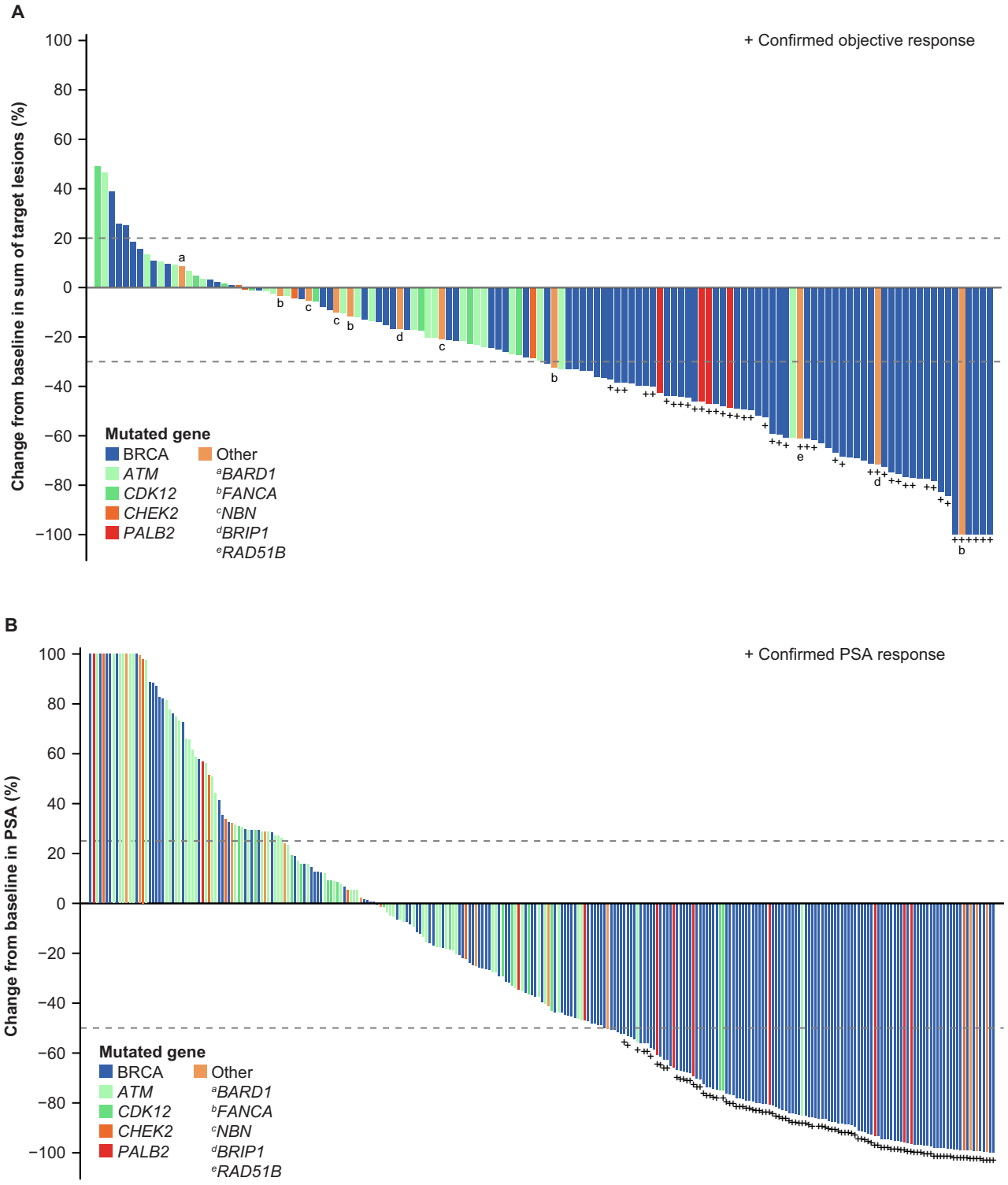

Fig. 3 – Best change from baseline in (A) sum of target lesion(s) in the IRR-evaluable population and (B) PSA in the overall efficacy population. In Figure 3A, the upper dotted line indicates the threshold for progressive disease, a 20% increase in the sum of the longest diameter of the target lesions; the lower dotted line indicates the threshold for partial response, a 30% decrease in the sum of the longest diameter of the target lesions. In Figure 3B), the upper dotted line indicates the threshold for PSA progression, a 25% increase from baseline (accompanied by an absolute increase of ≥2 ng/ml above the nadir); the lower dotted line indicates the threshold for PSA response, a 50% decrease from baseline. Bars were capped at 100% for visual clarity. PSA increases for the 15 leftmost patients were 689%, 373%, 319%, 231%, 220%, 183%, 146%, 142%, 133%, 132%, 126%, 125%, 109%, 106%, and 101%. In both panels, patients with 0% change from baseline are shown as 0.5% for visual clarity. IRR = independent radiology review; PSA50 = prostate-specific antigen ≥50% decrease from baseline.

within the *ATM*, *CDK12*, or *CHEK2* subgroups had an objective response by IRR (Table 1 and Fig. 3A).

A PSA50 response was observed in 2/59 (3.4%) patients in the *ATM* subgroup (95% CI, 0.4–12%), 1/15 (6.7%) patients in the *CDK12* subgroup (95% CI, 0.2–32%), 1/7 (14%) patients in the *CHEK2* subgroup (95% CI, 0.4–58%), and 3/13 (23%) patients in the Other subgroup (95% CI, 5.0–54%; Table 1 and Fig. 3B). The PSA90 response rates were 14% and 23%

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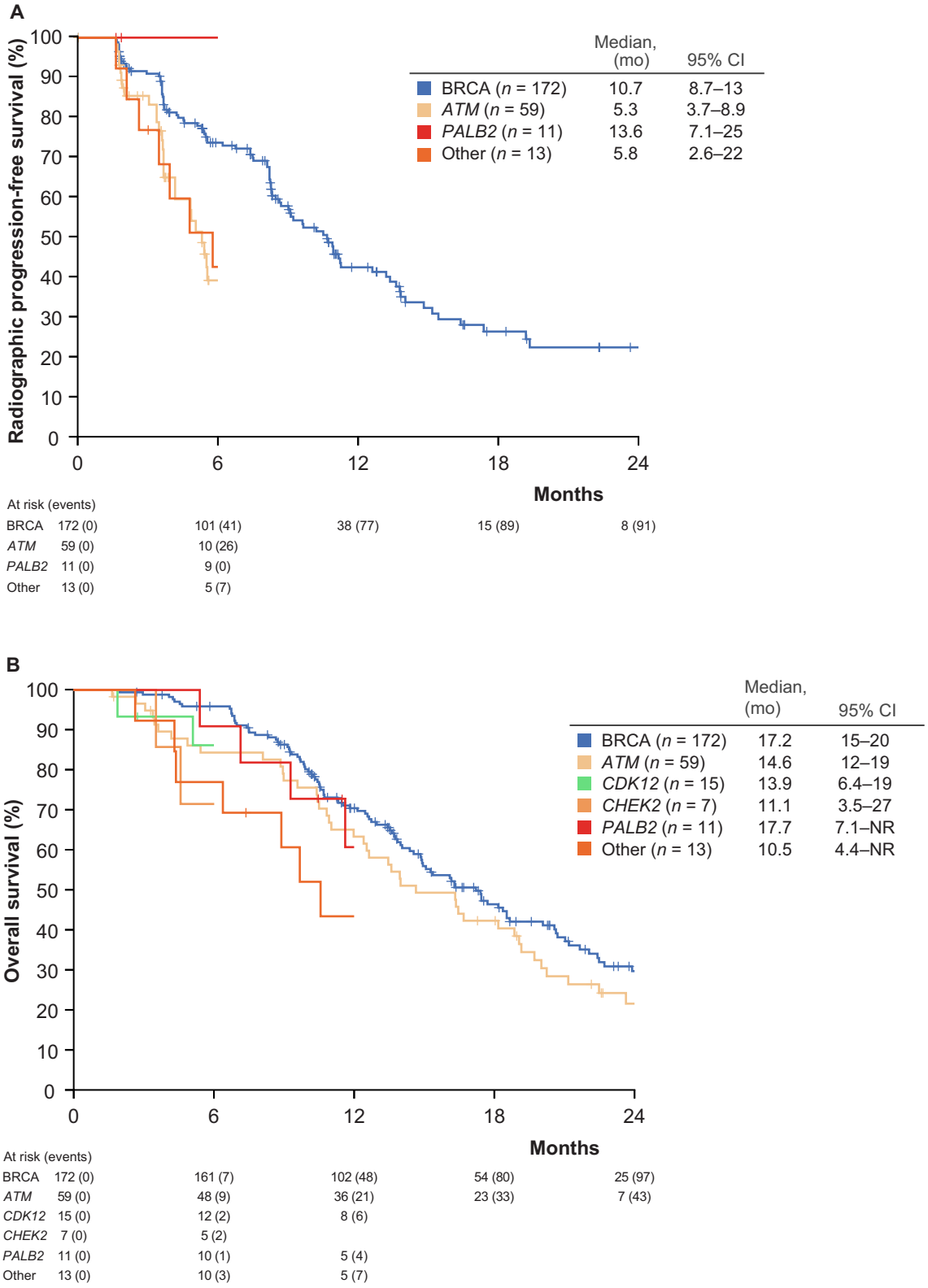

Fig. 4 – Kaplan-Meier curves for (A) IRR-assessed rPFS and (B) OS. CI = confidence interval; IRR = independent radiology review; NR = not reached; OS = overall survival; rPFS = radiographic progression-free survival.

in the *CHEK2* and Other subgroups, respectively; a PSA90 response was not observed in the *ATM* or *CDK12* subgroup (Supplementary Table 2). The median time to PSA progression ranged from 3.1 to 7.5 mo across the *PALB2*, *ATM*, *CDK12*, *CHEK2*, and Other subgroups (Supplementary Fig. 2), and the clinical benefit rate ranged from 13% to 82% at 6 mo and from 0% to 27% at 12 mo across these subgroups (Supplementary Table 2).

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Table 2 – Most commonly reported TEAEs in the safety population

TEAEs, *n* (%)	Overall safety population (*N* = 277)	
	Any grade	Grade ≥3
Number of patients with ≥1 TEAE	274 (99)	178 (64)
Asthenia or fatigue	164 (59)	31 (11)
Nausea	140 (51)	7 (2.5)
Anemia or decreased hemoglobin	133 (48)	80 (29)
Decreased appetite	96 (35)	5 (1.8)
ALT or AST increased	82 (30)	16 (5.8)
Constipation	76 (27)	2 (0.72)
Vomiting	70 (25)	5 (1.8)
Diarrhea	66 (24)	3 (1.1)
Rash	64 (23)	4 (1.4)
Thrombocytopenia or decreased platelet count	61 (22)	22 (7.9)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event.
MedDRA preferred terms are combined for the following adverse events: asthenia or fatigue, anemia or decreased hemoglobin, ALT or AST increased, rash, and thrombocytopenia or decreased platelet count.
Any-grade TEAEs were reported in ≥20% of patients, as well as corresponding grade ≥≥3 TEAEs.

Among patients in the non-BRCA subgroups, the median rPFS by IRR ranged from 5.1 to 13.6 mo (Fig. 4A), and the median OS ranged from 10.5 to 17.7 mo (Fig. 4B).

3.3. *Safety*

The safety population included 277 patients who received one or more doses of rucaparib. The median treatment duration was 7.1 mo (interquartile range, 3.6–11.2) for all patients and 8.2 mo (interquartile range, 5.0–12.0) in the BRCA subgroup. Most patients (98.9%) experienced any-grade treatment-emergent adverse events (TEAEs), with 178 patients (64%) reporting grade ≥3 TEAEs. The most common any-grade TEAEs were asthenia/fatigue (59%), nausea (51%), and anemia/decreased hemoglobin (48%; Table 2). The most common grade ≥3 TEAEs were anemia/decreased hemoglobin (29%) and asthenia/fatigue (11%). TEAEs led to treatment interruption in 160 (58%) patients, dose reduction in 106 (38%) patients, and treatment discontinuation in 32 (12%) patients. The most common TEAEs leading to treatment discontinuation were decreased anemia/hemoglobin (3%) and asthenia/fatigue (2%).

Excluding disease progression, the following TEAEs led to death in seven (3%) patients (*n* = 1 each): acute respiratory distress syndrome, cerebral hemorrhage, intestinal ischemia, lung infection (pneumonia), pneumonia legionella, pulmonary embolism, and Torsades de Pointes. Of these, acute respiratory distress syndrome and Torsades de Pointes were considered related to rucaparib by the study investigator. No myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) events were reported during treatment or long-term follow-up. In the safety population, 92 (33%) patients had at least one transfusion and 19 (7%) patients received concomitant antianemic medications.

4. Discussion

PARP inhibitors are an important targeted treatment option for patients with mCRPC and certain DDR gene alterations, as observed in phase 2 (eg, GALAHAD, TALAPRO-1, and TRITON2) and phase 3 (eg, PROfound, MAGNITUDE, and PROpel) studies [2,5,10–14]. The TRITON2 study investigated rucaparib treatment in patients with mCRPC and a deleterious germline or somatic alteration in one of 15 DDR genes. The final results from TRITON2 shown here confirm the previously reported interim efficacy and safety profile of rucaparib in patients with mCRPC.

Patients with a germline or somatic BRCA alteration showed improved clinical outcomes with rucaparib, confirming the robust benefit demonstrated previously in patients with a BRCA alteration. *BRCA1* and *BRCA2* are central mediators of homologous recombination repair (HRR), and deficiencies in this repair pathway result in synthetic lethality with PARP inhibition [15]. Targeting BRCA-mutated mCRPC tumors with rucaparib demonstrated meaningful radiographic and PSA response rates of 46% (37 of 81) and 53% (92 of 172), respectively, and 6- and 12-mo clinical benefit rates of 58% and 21%, respectively. Co-occurring alterations in the tumor suppressor genes *TP53*, *RB1*, or *PTEN*, which are associated with poor prognosis in prostate cancer [16–19], did not appear to affect radiographic and PSA response rates in our study, although the number of patients with an *RB1* alteration was limited.

Notably, patients with a *PALB2* alteration had the highest ORR and PSA response rate, and the longest rPFS, median time to PSA progression, and OS among all genomic groups investigated. Maintenance treatment with rucaparib has also demonstrated activity in patients with pancreatic cancer and a germline *PALB2* mutation [20], and talazoparib has demonstrated efficacy in patients with advanced breast cancer and a germline *PALB2* mutation [21]. *PALB2* acts as a bridging protein between *BRCA1* and *BRCA2*; thus, these results are consistent with its central role in HRR. Although the number of patients in each subgroup was small, this analysis included the largest group of patients with mCRPC and *PALB2*-mutated tumors treated with a PARP inhibitor to date.

Beyond BRCA and *PALB2*, radiographic responses were observed in patients with rare alterations in other DDR genes, specifically *RAD51B* [22], *FANCA*, and *BRIP1*; however, we hypothesize that the response in one of two patients with *BRIP1*-mutated tumors was likely driven by a co-occurring homozygous *BRCA2* loss identified after enrollment.

Although two patients in the *ATM* subgroup had investigator-assessed partial responses in the interim TRITON2 analysis [5], no objective IRR-assessed responses were observed in patients with an *ATM* alteration, including those with germline alterations or homozygous gene deletions. Similarly, no radiographic responses were observed in patients with *CDK12, CHEK2, BARD1,* or *NBN* alterations; these genes all play an auxiliary role in HRR. Objective responses were observed in a small proportion of patients with *ATM* or *CDK12* mutations in PROfound [23].

These results from TRITON2 align with the results of other trials of PARP inhibitors in mCRPC. In TRITON2, the ORRs in patients with a *BRCA2* and a *BRCA1* mutation were 48% and 30%, respectively. In the phase 3 PROfound study of olaparib in patients with mCRPC, which included those with and without prior taxane treatment, the ORR was 56% in

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patients with a *BRCA2* mutation; there were no radiographic responses in patients with a *BRCA1* mutation [23]. In the phase 2 GALAHAD study, niraparib demonstrated antitumor activity in BRCA-mutated mCRPC [12], with an ORR by investigator of 34%. Among patients in the phase 2 TALAPRO-1 [11] study evaluating talazoparib in mCRPC, the ORR by IRR was 46%.

In a retrospective study of patients with taxane-refractory mCRPC treated with platinum-based chemotherapy (one or more cycles of carboplatin or cisplatin as monotherapy or in combination with a taxane or etoposide), a PSA50 response was more likely in patients with a DDR alteration than in those without [24]. These findings further highlight the potential of DDR mutation status as a biomarker for patient selection.

Radiographic responses were not observed in TRITON2 patients with a *CHEK2* or *BRIP1* alteration; partial responses were observed in the *PALB2* group. In the TALAPRO-1 study, among patients with a non-BRCA DDR gene alteration, no responses were observed in the *CHEK2* subgroup, while the ORR in the small *PALB2* subgroup was somewhat lower than that of the BRCA group [11].

The rucaparib safety profile in patients with mCRPC was consistent with that observed in patients with ovarian cancer or other solid tumor types treated with rucaparib [20,25,26], and in studies of patients with mCRPC who received other PARP inhibitors; asthenia/fatigue, gastrointestinal adverse effects, and myelosuppression were among the most common TEAEs reported [10,11]. Transient elevations in liver enzymes and creatinine were reported, consistent with studies of PARP inhibitors in ovarian cancer; these elevations were not associated with liver or kidney toxicity [4,23,27–29].

No MDS or AML events were reported in TRITON2, consistent with previous reports of PARP inhibitor treatment in patients with mCRPC [10,11]. Despite reports of fatal pneumonitis with other PARP inhibitors [23], interstitial lung disease has not been identified as a potential risk from rucaparib treatment across multiple tumor types; alternative etiologies were identified in the majority of cases, and most resolved with continued rucaparib treatment or after dose treatment interruption, with a negative rechallenge.

Strengths of this study are the large number of patients included in the BRCA and *ATM* subgroups, and the description of responses in rare subgroups, including *PALB2* and *RAD51B*, which support the use of PARP inhibition, especially in patients with a *PALB2* alteration. Limitations include the small sample size of several genomic subgroups, which limited power to compare outcomes among them, and the lack of a control arm in this phase 2 study.

5. Conclusions

In conclusion, the final results from TRITON2 demonstrate the efficacy of rucaparib in patients with BRCA-altered mCRPC, with signs of activity in patients with less common alterations such as *PALB2*. The rucaparib safety profile is consistent with prior TRITON2 data [2,5]. Primary results from the open-label, randomized, international, phase 3 TRITON3 study (NCT02975934) have confirmed the rPFS benefit of rucaparib versus physician's choice of therapy in patients with *BRCA1/2*-mutated mCRPC in the pretaxane chemotherapy setting [30].

***Author contributions*:** Wassim Abida had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept design: Abida, Campbell, Patnaik, Bryce, Zhang, Sautois, Piulats, Merseburger, Daugaard, Heidenreich, Fizazi, Despain, Watkins, Chowdhury.
Acquisition of data: Abida, Campbell, Patnaik, Bryce, Shapiro, Bambury, Zhang, Burke, Castellano, Font, Ganju, Hardy-Bessard, McDermott, Sautois, Spaeth, Voog, Piulats, Pintus, Merseburger, Heidenreich, Dowson, Go, Chowdhury.
Analysis and interpretation of data: Abida, Campbell, Patnaik, Bryce, Shapiro, Bambury, Zhang, Burke, Castellano, Font, Ganju, Hardy-Bessard, McDermott, Sautois, Spaeth, Voog, Piulats, Pintus, Ryan, Merseburger, Daugaard, Heidenreich, Fizazi, Loehr, Despain, Simmons, Watkins, Chowdhury.
Drafting of the manuscript: Loehr, Despain, Simmons, Dowson, JG, Watkins.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Despain.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: All authors.
Other: None.

Financial disclosures: Wassim Abida certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Dr. Wassim Abida reports receiving grants or contracts from AstraZeneca, Epizyme, ORIC, Prostate Cancer Foundation, and Zenith Epigenetics; consulting fees from AstraZeneca, Daiichi Sankyo, Janssen Pharma UK, and ORIC Pharmaceuticals; speaking honoraria from Aptitude Health, Medscape, OncLive/MJH Health, Roche, and TouchIME; and publication royalties. Dr. David Campbell has nothing to disclose. Dr. Akash Patnaik has served in a consulting or advisory role for Exelixis, Janssen, and Jounce Therapeutics; has received honoraria from Clovis Oncology, Merck, Prime Inc., and Roche; has received research funding from Clovis Oncology, Bristol Myers Squibb, GlaxoSmithKline, and Progenics; and has received clinical trial support from AstraZeneca and Laekna. Dr. Alan H. Bryce reports receiving institutional funding from Astra Zeneca, Gilead, and Janssen; payment or honoraria from Elsevier, Fallon Medica, Horizon CME, MJH Life Sciences, PRIME Education, and Research to Practice; travel support from Prostate Cancer Foundation; holding a patent on Therapeutic Targeting of Cancer Patients with NRG1 Rearrangements (15/735,289); and receiving data safety monitoring board or advisory board fees, paid to Mayo Clinic, from Bayer and Janssen, and from Carden Jennings, Foundation Medicine, Merck, Myovant, and Novartis AG. Dr. Jeremy Shapiro has no disclosures or conflicts. Dr. Richard M. Bambury reports receiving travel support from Bayer, Ipsen, and Pfizer; data safety monitoring or advisory board fees from BMS, Janssen, and Pfizer; and other financial or nonfinancial interests from ONCOassist (Portable Medical Technology). Dr. Jingsong Zhang has received consulting fees from AstraZeneca, Bayer, Dendreon, Myovant

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Sciences, and Pfizer; and speaker fees from AstraZeneca, Dendreon, and Sanofi. Dr. Daniel Castellano has consulting and advisory roles for Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Ipsen, Janssen, Lilly, MSD Oncology, Novartis, Pfizer, Pierre-Fabre, Roche, and Sanofi; received research funding from Janssen; and received travel support from AstraZeneca, Bristol Myers Squibb, Roche, and Pfizer. Dr. Albert Font has consulting and advisory roles for Astellas, Eusa, Janssen, and Sanofi; and has received research funding from AstraZeneca. Dr. Ray McDermott has served in a consulting or advisory role for Bayer, Janssen, and Pfizer; has received support for travel and/or accommodation from Celgene, Janssen, and Pfizer; and has received research funding related to clinical trials from Clovis Oncology, Amgen, Bayer, Bristol-Myers Squibb, and Merck. Dr. Brieuc Sautois reports receiving consulting fees from Clovis Oncology, Astellas Pharma, BMS Belgium, and Janssen, and payment or honoraria from Janssen and MSD. Dr. Josep M. Piulats reports receiving grant support for investigator-sponsored trial from Beigene, Mirati, MSD, and Pfizer, and for preclinical proposal from Janssen; consulting fees from MSD and Novartis; payments for medical writing from Immunocore, MSD, and Pfizer; travel support from AstraZeneca; advisory board fees from Immunocore and Lilly; and other services from Clovis, BeiGene, BMS, Jansen, and Lilly. Dr. Elias Pintus reports receiving consulting fees from Janssen and Merck Sharp & Dohme, financial support from Bayer, and nonfinancial support from Amgen. Dr. Charles J. Ryan has received research support from Clovis Oncology and has served as a consultant for AstraZeneca and Bayer. Professor Axel S. Merseburger has served as a principal investigator or subinvestigator for clinical studies by Clovis Oncology, Astellas, Bayer, GlaxoSmithKline, Ipsen, Janssen, Novartis, Pfizer, Teva, and Wyeth; served as a speaker for Astellas, Bayer, GlaxoSmithKline, Hexal, Ipsen, Janssen, Novartis, Sanofi Aventis, and Teva; served on an advisory board for Clovis Oncology, Astellas, Bayer, Ipsen, Janssen, Novartis, Pfizer, and Teva; and received research grants from Wyeth. Professor Gedske Daugaard reports receiving consulting fees from Astellas, Bayer, Enterome, Janssen, MSD, and Pfizer, and data safety monitoring or advisory board fees from Astellas, Bayer, MSD, and Pfizer. Professor Karim Fizazi has received personal fees from Clovis Oncology, Amgen, Astellas, AstraZeneca, Bayer, CureVac, ESSA, Janssen, Orion Pharma, Roche-Genentech, and Sanofi. Dr. Andrea Loehr, Darrin Despain, Dr. Andrew D. Simmons, Melanie Dowson, Jowell Go, and Dr. Simon P. Watkins report being employed by and owning stock in Clovis Oncology. Dr. Simon Chowdhury reports receiving consulting fees for serving on advisory boards and speakers' bureaus from Clovis Oncology, AstraZeneca, Athenex, Bayer, Beigene, Janssen Oncology, and Novartis; honoraria from Beigene, Huma, Janssen, Remedy Bio, and Telix; owning stock in Curve.Life and Huma Remedy Bio; and receiving research funding from Clovis Oncology. No potential conflicts of interest were disclosed by these authors: Dr. John M. Burke, Professor Vinod Ganju, Dr. Anne-Claire Hardy-Bessard, Dr. Dominique Spaeth, Dr. Eric Voog, and Professor Axel Heidenreich.

***Funding/Support and role of the sponsor*:** This work was supported by Clovis Oncology Inc; supported in part by the National Cancer Institute (NCI) Cancer Center Support (grant number P30-CA008748), NCI Prostate Specialized Program of Research Excellence (SPORE; grant number P50-CA092629-16), Department of Defense Prostate Cancer Research Program (grant number W81XWH-17-1-0124), and a Prostate Cancer Foundation Young Investigator Award (to Wassim Abida); and supported in part by a Prostate Cancer Foundation Challenge Award and NCI Prostate SPORE grant (no. P50-CA180995; to Akash Patnaik).

***Acknowledgments*:** The authors thank Dr. Nicholas J. Vogelzang for his valuable contributions to this study, including the provision of study materials and data collection/assembly. This study was funded by Clovis Oncology, Inc. Medical writing and editorial support were funded by Clovis Oncology, Inc., and were provided by Sachi Yim, PhD, and Kathleen Blake, PhD, of Ashfield MedComms, an Inizio company.

Peer Review Summary and Supplementary data

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2023.05.021.

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