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## Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: analysis from the phase 2 TRITON2 study

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## Abstract

**Purpose:** Genomic alterations in DNA damage repair (DDR) genes other than *BRCA* may confer synthetic lethality with PARP inhibition in metastatic castration-resistant prostate cancer (mCRPC). To test this hypothesis, the phase 2 TRITON2 study of rucaparib included patients with mCRPC and deleterious non-*BRCA* DDR gene alterations.

**Patients and Methods:** TRITON2 enrolled patients who had progressed on 1 to 2 lines of next-generation androgen receptor (AR)-directed therapy and 1 taxane-based chemotherapy for mCRPC. Key endpoints were investigator-assessed radiographic response per modified RECIST/PCWG3 and prostate-specific antigen (PSA) response ( 50% decrease from baseline).

**Results:** TRITON2 enrolled 78 patients with a non-*BRCA* DDR gene alteration (*ATM* [ $n = 49$ ], *CDK12* [ $n = 15$ ], *CHEK2* [ $n = 12$ ], and other DDR genes [ $n = 14$ ]). Among patients evaluable for each endpoint, radiographic and PSA responses were observed in a limited number of patients with an alteration in *ATM* (2/19 [10.5%] and 2/49 [4.1%], respectively), *CDK12* (0/10 [0%] and 1/15 [6.7%], respectively), or *CHEK2* (1/9 [11.1%] and 2/12 [16.7%], respectively), including no radiographic or PSA responses in 11 patients with confirmed biallelic *ATM* loss or 11 patients with *ATM* germline mutations. Responses were observed in patients with alterations in the DDR genes *PALB2*, *FANCA*, *BRIP1*, and *RAD51B*.

**Conclusions:** In this prospective, genomics-driven study of rucaparib in mCRPC, we found limited radiographic/PSA responses to PARP inhibition in men with alterations in *ATM*, *CDK12*, or *CHEK2*. However, patients with alterations in other DDR-associated genes (eg, *PALB2*) may benefit from PARP inhibition.

### Keywords

DNA damage repair genes; metastatic castration-resistant prostate cancer; rucaparib

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## INTRODUCTION

Poly(ADP-ribose) polymerase (PARP) inhibitors are approved for use in *BRCA1* and *BRCA2* (*BRCA*)-mutant breast and ovarian cancers (1, 2), and have also shown evidence of activity in patients with *BRCA*-mutant metastatic castration-resistant prostate cancer (mCRPC), based on a well-described synthetically lethal effect (3). Confirmed radiographic and prostate-specific antigen (PSA) responses were observed in 25 (43.9%) of 57 and 51 (52.0%) of 98 patients with a deleterious *BRCA* alteration, respectively, in the phase 2 TRITON2 study (CO-338-052; [NCT02952534](#)) evaluating the PARP inhibitor rucaparib in men who progressed on an androgen receptor (AR)-directed therapy and chemotherapy (4). Olaparib and niraparib also have reported activity in patients with *BRCA*-mutant mCRPC (5–8). Rucaparib, olaparib, and niraparib have received Breakthrough Therapy designations from the U.S. Food and Drug Administration for the treatment of patients with *BRCA*-mutant mCRPC (9–11).

Beyond *BRCA*, deleterious alterations in other genes may also lead to DNA damage repair (DDR) deficiency and are hypothesized to render tumor cells sensitive to PARP inhibition. For example, *ATM* and *CHEK2* are sensors of DNA damage, *CDK12* is a positive regulator of *BRCA* genes, and *PALB2* and *FANCA* interact with *BRCA1* and/or *BRCA2* during DNA repair (12–16). Clinical responses, defined variably as a radiographic response, or a decline in PSA or circulating tumor cell count, have been reported in mCRPC patients with alterations in *ATM*, *CHEK2*, *FANCA*, *PALB2*, or other non-*BRCA* DDR genes in studies evaluating olaparib (TOPARP-A [[NCT01682772](#)], TOPARP-B [[NCT01682772](#)] and niraparib (GALAHAD [[NCT02854436](#)]), and patients with alterations in these genes were included in a randomized study comparing olaparib to physician's choice of abiraterone or enzalutamide (PROfound [[NCT02987543](#)]) (5, 6, 8, 17). Notably, the co-occurrence of alterations in different non-*BRCA* DDR genes, as seen in the TOPARP and PROfound studies (5, 6, 18), makes it difficult to attribute PARP inhibitor sensitivity to a given gene.

The available data provide a compelling rationale to explore PARP inhibition in men with mCRPC and a DDR gene alteration, and to define the set of DDR gene deficiencies that confer a synthetically lethal effect with PARP inhibitors. The TRITON2 study is investigating the PARP inhibitor rucaparib in patients with mCRPC associated with alterations in 15 DDR genes. Here, we report an ad hoc analysis of patients with deleterious alterations in non-*BRCA* DDR genes, including *ATM*, *CDK12*, *CHEK2*, *FANCA*, and *PALB2*.

## METHODS

### Study Design

TRITON2 is an open-label, phase 2 study evaluating the safety and efficacy of rucaparib in men with mCRPC associated with DDR deficiency. This trial is being conducted at 144 centers in 12 countries. Eligible patients at least 18 years old had histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma of the prostate that was metastatic and that had progressed on second-generation, AR-directed therapy (e.g., abiraterone acetate, enzalutamide, or apalutamide) for prostate cancer and 1 prior line of taxane-based chemotherapy for mCRPC. Disease progression on prior therapy was based on any of the following criteria: rise in prostate-specific antigen (PSA; minimum of 2 consecutive rising levels, with an interval of 1 week or more between each determination; the most recent screening measurement must have been greater than or equal to 2 ng/mL); transaxial imaging with new or progressive soft tissue masses on computed tomography (CT) or magnetic resonance imaging (MRI) as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST); or radionuclide bone scan with at least 2 new metastatic lesions. Patients were surgically or medically castrated, with serum testosterone levels of 50 ng/dL or less.

Patients with and without measurable visceral or nodal disease per RECIST criteria were eligible for the study; patients without measurable disease were required to have PSA levels of greater than 2 ng/mL on the most recent measurement. Patients had an Eastern Cooperative Oncology Group Performance Status of 0 or 1 and adequate organ function. Patients who had prior treatment with any PARP inhibitor, mitoxantrone, cyclophosphamide, or any platinum-based chemotherapy were excluded.

The study was approved by national or local institutional review boards and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Patients provided written informed consent before participation.

### Procedures

Patients were screened for the presence of a deleterious somatic or germline alteration in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L* through central genomic testing of plasma or tumor tissue (archival or contemporaneous), or through local testing. Central testing was performed by Foundation Medicine, Inc (19, 20). To classify alterations as somatic or germline, whole blood samples were tested by Color Genomics using an assay validated to detect germline alterations (21, 22).

Patients received oral rucaparib 600 mg twice daily until confirmed radiographic disease progression as assessed by investigator based on modified RECIST and/or Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria, unequivocal clinical disease progression, death, or other reason for discontinuation. Dose reductions were permitted if a patient had a grade 3 or greater or a persistent grade 2 adverse event (AE).

Tumor assessments (computed tomography/magnetic resonance imaging and bone scans) were performed every 8 weeks for 24 weeks, then every 12 weeks, and at treatment discontinuation. PSA was evaluated at baseline and every 4 weeks thereafter.

After discontinuation, all patients had a 28-day follow-up visit, and subsequent treatment and survival information was collected every 12 weeks from the last dose of rucaparib until death, loss to follow-up, or withdrawal of consent from study. For patients who discontinued for a reason other than disease progression, tumor assessments continued as above.

## Outcomes

The proportion of patients achieving a confirmed complete or partial response per modified RECIST/PCWG3 as assessed by the investigator is reported for patients with measurable disease at baseline (hereafter, “evaluable patients”). The proportion of patients with a confirmed PSA response (50% or greater decrease from baseline confirmed by a second consecutive measurement at least 3 weeks later) is reported for patients with or without measurable disease at baseline. Additional outcomes reported here include clinical benefit rate (proportion of patients without radiographic progression per RECIST/PCWG3 criteria who were receiving treatment at a given time point [e.g., at 6 or 12 months]) and time to PSA progression.

The tumor responses were assessed by investigators per modified RECIST/PCWG3. Modified RECIST allows up to 10 target lesions, with a maximum of 5 per site, not including prostatic bed or bone lesions; MRI is allowed. For PSA response (50% decrease from baseline confirmed by a second consecutive measurement at least 3 weeks later), measurements were performed by local laboratories. Early rises in PSA (before 12 weeks following the first dose of study drug) were not considered in determining PSA progression.

The clinical benefit rate was calculated as the number of patients without radiographic progression who were on study through the given time interval divided by the number of patients who had the given amount of follow-up time. Time to PSA progression was defined as the time from the first dose of rucaparib to the date that a 25% or greater increase and absolute increase of at least 2 ng/mL above the nadir (or baseline if there was no PSA decline after baseline) in PSA was measured, plus 1 day.

Safety was assessed by monitoring AEs and vital signs, laboratory testing, and physical examination.

## Statistical Analysis

For this ad hoc analysis, data are reported for patients with a non-*BRCA* DDR gene alteration enrolled in TRITON2 as of Jan 4, 2019, using a visit cutoff date of April 29, 2019; therefore, patients in this analysis had a minimum of 16 weeks of follow-up, allowing for at least 2 radiographic tumor assessments and for confirmation of response. The safety population included all patients who received at least 1 dose of study treatment.

Time to PSA progression was summarized using Kaplan-Meier methodology. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

### Patients and Genomic Characteristics

Between Feb 15, 2017, and Jan 4, 2019, 78 patients were enrolled based on a non-*BRCA* DDR gene alteration identified during screening. Patients were allowed to submit multiple tissue and plasma samples for genomic testing. The majority of patients had results from 1 genomic test (44 [56.4%] patients), with the remainder having results from 2 (31 [39.7%] patients) or 3 (3 [3.8%] patients; Supplementary Table). Patients were grouped by gene alteration (*ATM*, *CDK12*, *CHEK2*, and other DDR gene), and patients with co-occurring alterations were included in multiple gene groups. For example, a patient with co-occurring *CDK12* and *CHEK2* alterations was included in both the *CDK12* and *CHEK2* groups.

Including cases of co-occurring alterations identified prior to enrolment or in samples tested after enrolment, 49 patients had an *ATM* alteration, 15 patients had a *CDK12* alteration, and 12 patients had a *CHEK2* alteration (Fig. 1; Supplementary Table). Among 14 patients with other DDR gene alterations, 4 had a *FANCA* alteration, 4 had an *NBN* alteration, 2 had a *BRIP1* alteration, 2 had a *PALB2* alteration, and 1 each had a *RAD51*, *RAD51B*, or *RAD54L* alteration (Fig. 1). Among 49 patients with an *ATM* alteration, 11 (22.4%) had a germline alteration; the most frequent type of *ATM* alteration was a frameshift mutation (36.1% of alterations; Supplementary Table and Supplementary Figs. S1 and S2). Zygosity could be determined for 17 (34.7%) patients with an *ATM* alteration, 11 of whom had a biallelic alteration and 6 had a monoallelic alteration. Among the 15 patients with *CDK12* alterations, 7 (47%) had 2 distinct *CDK12* alterations presumed to result in biallelic inactivation, and an additional 2 (13%) had loss of heterozygosity of the other allele. We could not confirm that these alterations were somatic due to the absence of *CDK12* from our germline panel, but *CDK12* alterations have not been reported to occur in the germline (16). Of the 12 patients with *CHEK2* alterations, 4 were germline and 8 somatic, and biallelic inactivation was identified in 3 of 4 evaluable cases, 2 of which were germline (Figure 2, Supplementary Table).

Patients with an *ATM* alteration generally had lower Gleason scores at diagnosis and less measurable disease at study entry than those in the other groups (Table 1). At the visit cutoff date, patients still receiving treatment included 13 (26.5%) with an *ATM* alteration, 6 (50.0%) with a *CHEK2* alteration, and 7 (50.0%) with another DDR gene alteration.

### Efficacy Outcomes

**ATM Cohort**—Among 19 evaluable patients with an *ATM* alteration, 2 (10.5%) had confirmed partial radiographic responses, including 1 with a co-occurring *CHEK2* alteration (Table 2, Fig. 2A). Both patients had ongoing responses (1.8+ and 2.0+ months from the date of radiographic response) at the time of the visit cutoff (Fig. 3A). A confirmed PSA response was observed in 2 (4.1%) of 49 overall patients with an *ATM* alteration (Table 2 and Supplementary Fig. S3A), occurring in the same 2 patients who achieved a radiographic response. The 6- and 12-month clinical benefit rate for patients with an *ATM* alteration with or without measurable disease was 28.6% (12 of 42 patients) and 16.7% (3 of 18 patients) (Table 2).



The 2 patients who had radiographic and PSA responses had somatic *ATM* alterations detected through cell-free DNA (cfDNA) screening, so the possibility of homozygous loss of another DDR gene (e.g., *BRCA2* or *PALB2*) cannot be ruled out. Archival tissue was not available for these patients to assess *ATM* alteration zygosity. However, none of the 11 patients with known biallelic alterations in *ATM* or 11 patients with germline alterations in *ATM* had a radiographic or PSA response.

**CDK12 Cohort**—No confirmed radiographic responses were observed among the 10 evaluable patients with a *CDK12* alteration (Table 2). Among 15 overall patients with a *CDK12* alteration, 1 (6.7%) had a confirmed PSA response lasting 1.8 months (Table 2, Fig. 3B, and Supplementary Fig. S3B). The 6- and 12-month clinical benefit rate in the *CDK12* cohort was 20.0% (3 of 15 patients) and 7.1% (1 of 14 patients) (Table 2).

The patient with a PSA response had 2 distinct *CDK12* alterations that are presumed to be biallelic and were identified in both cfDNA and tissue (Supplementary Table and Supplementary Fig. S2B).

**CHEK2 Cohort**—Among 9 evaluable patients with a *CHEK2* alteration, 1 (11.1%) with a co-occurring *ATM* alteration had a confirmed partial radiographic response, as previously described (Table 2). A confirmed PSA response was observed in 2 (16.7%) of 12 overall patients with a *CHEK2* alteration, 1 of whom was the patient with a radiographic response. Both were still on study as of the visit cutoff date and had ongoing PSA responses (3.7+ and 0.9+ months; Fig. 3C and Supplementary Fig. S3C). The 6-month clinical benefit rate for patients with a *CHEK2* alteration was 37.5% (3 of 8 patients); no patients with a *CHEK2* alteration were still receiving treatment at 12 months (Table 2).

*CHEK2* alterations for both patients with PSA responses were identified through cfDNA screening; 1 was somatic and the other was germline. The PSA responder with a germline *CHEK2* alteration (patient 68) was found to have a somatic *BRCA2* alteration through tissue analysis conducted after study enrolment (Supplementary Table).

**Other DDR Gene Cohort**—Of the 14 evaluable patients with other DDR gene alterations, 4 (28.6%) had a confirmed radiographic response and 5 (35.7%) had a PSA response (Table 2, Fig. 3D). Both patients with a *PALB2* alteration had PSA responses, and 1 patient also had a partial radiographic response that was ongoing for 3.9+ months as of the visit cutoff; the other patient had a 47% reduction in tumor volume but had not undergone a follow-up scan for confirmation of the response as of the visit cutoff. Of 4 patients with a *FANCA* alteration, 1 patient with a monoallelic truncating alteration had complete radiographic and PSA responses that were ongoing at the time of the visit cutoff. One of 2 patients with a *BRIP1* alteration had a partial radiographic and a PSA response, both ongoing.

The patient with a *RAD51B* alteration had a partial radiographic and a PSA response, both ongoing.

## Safety

The safety population included 78 patients with a non-*BRCA* DDR gene alteration who received at least 1 dose of rucaparib. At the visit cutoff date, the median (range) treatment duration was 4.3 (0.7–22.1) months.

A treatment-emergent AE (TEAE) of any grade occurred in 76 (97.4%) patients, the most frequent (reported in at least 20% of patients) were asthenia or fatigue, nausea, decreased appetite, anemia, constipation, vomiting, and diarrhea (Table 3). Among all 39 (50.0%) patients with grade 3 or higher TEAEs, anemia, asthenia or fatigue, and thrombocytopenia were the most frequent (Table 3). No TEAEs of myelodysplastic syndrome or acute myeloid leukemia were reported.

Treatment interruption due to a TEAE occurred in 34 (43.6%) patients, most commonly due to asthenia or fatigue (10 [12.8%] patients) and anemia (8 [10.3%]). Dose reduction due to a TEAE occurred in 21 (26.9%) patients, most commonly due to asthenia or fatigue (6 [7.7%] patients), anemia (3 [3.8%]), and thrombocytopenia (3 [3.8%]).

Four (5.1%) patients discontinued because of a TEAE (excluding disease progression), 1 each due to asthenia or fatigue, decreased appetite, hematuria, and postoperative respiratory failure. One (1.5%) death due to intestinal ischemia was reported and was considered unrelated to rucaparib by the investigator.

## DISCUSSION

PARP inhibitors have shown dramatic responses in heavily pretreated mCRPC patients with *BRCA* gene alterations; however, the utility of alterations in non-*BRCA* DDR genes as biomarkers for PARP inhibitor sensitivity is not well established. This report describes 78 patients with mCRPC and prospectively identified non-*BRCA* DDR gene alterations treated with the PARP inhibitor rucaparib. The safety profile of rucaparib in these patients was consistent with that in patients with ovarian cancer and other solid tumors (23, 24). A limited number of radiographic and PSA responses was observed in patients with *ATM*, *CDK12*, or *CHEK2* gene alterations, whereas responses were observed in patients with alterations in other DDR genes less frequently altered in mCRPC such as *PALB2*, *BRIP1*, *FANCA*, and *RAD51B*. These results suggest there are non-*BRCA* biomarkers associated with PARP inhibitor activity in mCRPC that warrant further investigation.

Radiographic and PSA responses in the *ATM* cohort of this study were observed in 10.5% and 4.1% of patients evaluable for each endpoint, respectively. The *ATM* cohort included patients with frameshift mutations, truncating mutations, homozygous deletions, and rearrangements (Supplementary Figs. S1 and S2A) expected to result in complete loss of function of that allele, whereas few patients (11.5%) had missense alterations predicted to be oncogenic. The *ATM* cohort also included patients with confirmed germline *ATM* alterations and patients with biallelic loss of *ATM* (Fig. 2A). Despite the various types and locations of *ATM* alterations observed, there was no clear association between response and the characteristics of the genomic alterations. These results suggest that *ATM* deficiency alone is not sufficient to result in synthetic lethality with PARP inhibition in mCRPC. In the



TOPARP-A study, which did not enroll patients based on biomarker selection, although PSA and/or circulating tumor cell responses were observed in 4 patients with an *ATM* alteration, none of these patients had a radiographic response. In TOPARP-B, RECIST and PSA responses were observed in 8.3% and 5.3% of patients with an *ATM* alteration (6). Similarly, among 23 men with mCRPC who received olaparib, no PSA responses were observed in 6 patients with an *ATM* alteration, compared to 13 (76.4%) of 17 patients with a *BRCA* alteration (25). In PROfound, median radiographic PFS was similar in patients with an *ATM* alteration who received olaparib and those who received enzalutamide or abiraterone (8). In our study, although only a limited number of patients with an *ATM* alteration had a radiographic or PSA response, most patients had a best response of stable disease. These data, as well as the 6- and 12-month clinical benefit rates, suggest that rucaparib may provide, at best, disease stabilization in patients with an *ATM* alteration, although it should be noted that TRITON2 was not designed to assess this outcome. Detailed results from randomized studies such as PROfound or the phase 3 TRITON3 study of rucaparib (NCT02975934) are needed to more fully evaluate the effect of PARP inhibition in this patient subgroup while controlling for a potential prognostic effect of *ATM* alterations. The apparent lower sensitivity to PARP inhibitors of tumors harboring an *ATM* alteration may be due to *ATM*'s role as a sensor of DNA damage rather than a mediator of homologous recombination repair (15).

Most patients with *CDK12* alterations enrolled in TRITON2 had a best response of stable disease and only 1 patient had a PSA response; as a result, enrolment of patients with a *CDK12* alteration into TRITON2 was halted per protocol. *CDK12* plays a role in the elongation phase of transcription, and studies suggest that inactivation of *CDK12* can reduce DDR gene expression and sensitize tumor cells to PARP inhibition (26–28). However, a recent study reported that tumors with biallelic inactivation of *CDK12* have distinct genomic and transcriptional profiles compared with DDR-deficient tumors (16). In TOPARP-B, no radiographic or PSA responses were observed in the 20 patients with a *CDK12* alteration (6). Similarly, in a recent retrospective study, none of 11 men with *CDK12*-altered advanced prostate cancer had a radiographic or PSA response to PARP inhibitor treatment (29). In PROfound, median radiographic PFS in patients with a *CDK12* alteration was longer with olaparib than with enzalutamide or abiraterone, although the statistical significance of this finding is unclear (8). Together, the genomics and clinical data suggest that *CDK12* deficiency does not reliably predict response to PARP inhibitors.

We identified 1 confirmed radiographic response in the *CHEK2* cohort, and 2 patients had a PSA response. However, *CHEK2* alterations alone do not appear sufficient to render tumor cells responsive to PARP inhibitor treatment as co-occurring alterations in other DDR genes were often observed in TRITON2 patients with a *CHEK2* alteration. In particular, both patients with *CHEK2* alterations that responded were enrolled from plasma testing, and subsequent tissue testing in 1 patient revealed the presence of a somatic *BRCA2* alteration.

Among patients with alterations in other DDR genes, patients with alterations in *PALB2*, *FANCA*, *BRIP1*, and *RAD51B* had both confirmed radiographic and PSA responses. The duration of response was up to a year in some of these patients, highlighting the durability of the responses. These data are consistent with reports of PARP inhibitor activity in patients

with mCRPC (5, 6, 30, 31). For example, radiographic and/or PSA responses were observed in 57% of patients (4 of 7) with *PALB2* alterations in TOPARP-B (6). Additionally, reversion mutations in *PALB2* have been detected in a patient with mCRPC who progressed on olaparib treatment, providing strong evidence that the original mutation sensitized the tumor to PARP inhibitor treatment (31). Although it is challenging to draw conclusions because of the small sample size, these data strongly support continued examination of patients with alterations in this subset of DDR genes to determine if the alterations are robustly associated with PARP inhibitor sensitivity.

In this manuscript, we describe a large population of patients with mCRPC who were prospectively enrolled based on a deleterious gene alteration in a non-*BRCA* DDR gene, enabling analysis of the impact of PARP inhibitor treatment on these relatively infrequent gene alterations. Additionally, many patients had genomic test results from 2 or 3 assays, helping to overcome some of the limitations inherent to both tissue and plasma profiling and allowing for a more comprehensive, real-world evaluation of genomic alterations. Furthermore, we present results grouped by presence of at least 1 alteration in a given DDR gene to enable better assessment of the predictive utility of a specific DDR gene alteration.

One limitation of this study is the small sample size for the *CDK12*, *CHEK2*, and other non-*BRCA* DDR gene cohorts. Additionally, tissue and plasma test results were not available for all patients. Thus, a complete evaluation of co-occurring alterations cannot be performed, and tumor zygosity could be determined only for a subset of patients with central tissue test results. Loss of heterozygosity may occur more frequently with certain gene alterations than others, calling into question if a lack of response is related to alteration zygosity or if loss of the gene is not truly synthetically lethal with PARP inhibition. Although biallelic DDR gene alterations were identified among these cohorts without apparent association with response, overall the number of biallelic alterations observed for each gene was small. Further research to add upon these findings with greater numbers is warranted.

Although PARP inhibitor treatment has demonstrated radiographic and PSA responses in patients with *BRCA* alterations (4–8), the data presented here offer compelling evidence that response to PARP inhibitors is limited in men with mCRPC harboring an *ATM*, *CDK12*, or *CHEK2* alteration. These data provide an optimistic outlook for treatment of prostate cancer with other DDR gene alterations, such as *PALB2*. Further work is needed to determine if PARP inhibitors provide disease stabilization in patients with an *ATM* or *CDK12* alteration or whether there are other genomic characteristics for patients who achieve a response, and to better define the subset of other DDR gene alterations that confer sensitivity to PARP inhibitors in the setting of mCRPC.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Disclosure of Potential Conflicts of Interest

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All other authors have nothing to disclose.

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**Statement of Translational Relevance**

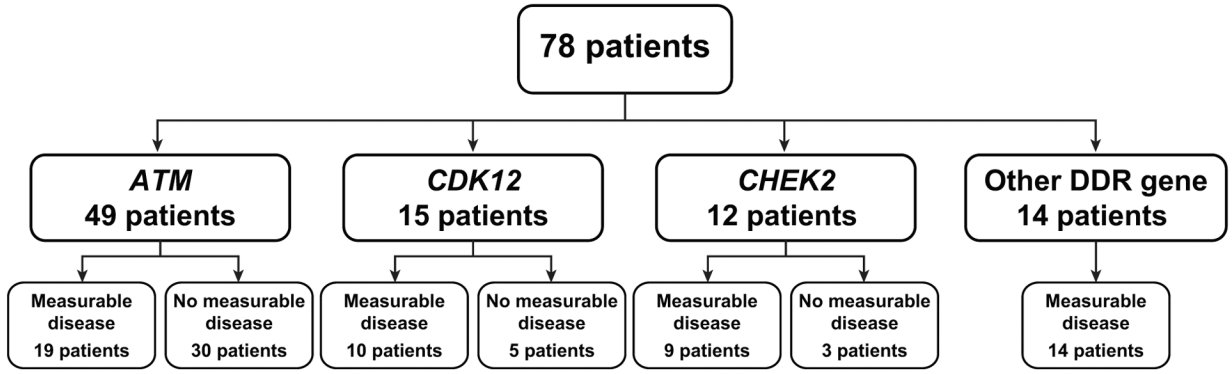
Deleterious alterations in *BRCA1*, *BRCA2*, and other DNA damage repair genes are thought to sensitize tumor cells to poly(ADP-ribose) polymerase (PARP) inhibition. In this analysis of patients with metastatic castration-resistant prostate cancer from TRITON2, loss of function alterations in *ATM*, *CDK12*, or *CHEK2* alone did not significantly confer synthetic lethality with the PARP inhibitor rucaparib, as measured by objective radiographic and prostate-specific antigen responses. Responses were observed, however, in a number of patients with alterations in *FANCA*, *PALB2*, *BRIP1*, or *RAD51B*, genes associated with homologous recombination repair; these promising results warrant further studies. This analysis expands current understanding of predictive genomic biomarkers for treatment with a PARP inhibitor in patients with prostate cancer, but as well in patients with other malignancies, including breast, pancreatic, and ovarian cancer, where these biomarkers are also being explored.

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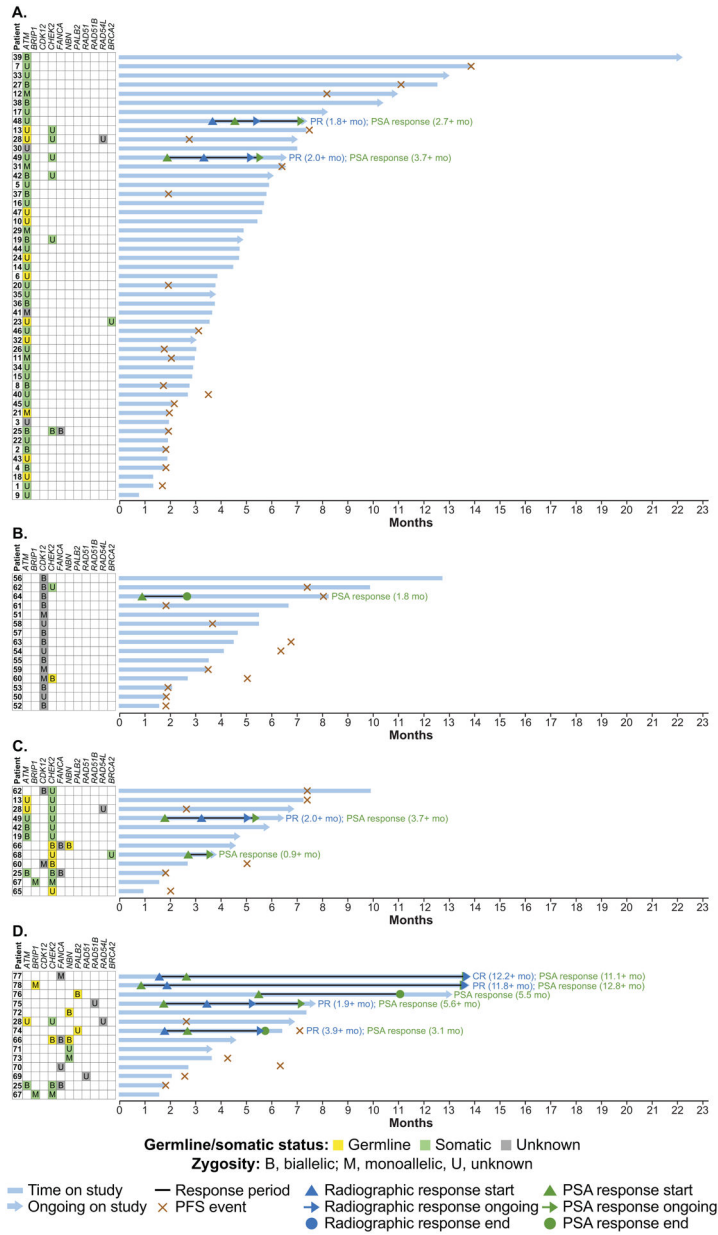
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**Figure 1.** Overview of analysis groups for patients from TRITON2 with non-*BRCA* DDR gene alterations. Groups are not mutually exclusive and contain patients with co-occurring DDR gene alterations (see Supplementary Table). The “other DDR gene” group includes patients with an alteration in *FANCA* (n = 4), *NBN* (n = 4), *BRIP1* (n = 2), *PALB2* (n = 2), *RAD51* (n = 1), *RAD51B* (n = 1), and/or *RAD54L* (n = 1). Abbreviation: DDR, DNA damage repair.





**Figure 3.** Treatment duration in patients with an *ATM* alteration (A), *CDK12* alteration (B), *CHEK2* alteration (C), or other DDR gene alteration (D). Patients 55, 56, 57, 61, 62, 63, and 64 had 2 distinct *CDK12* alterations identified through tissue and/or plasma testing and were considered to have biallelic loss. Abbreviations: CR, complete response; DDR, DNA damage repair; PFS, progression-free survival; PR, partial response; PSA, prostate-specific antigen

**Table 1:**

Baseline patient demographics and disease characteristics

	DDR gene group			
	<i>ATM</i> (n = 49)	<i>CDK12</i> (n = 15)	<i>CHEK2</i> (n = 12)	Other <sup>a</sup> (n = 14)
Age, median (IQR), years	73.0 (68.0–77.0)	64.0 (56.0–72.0)	71.5 (64.5–75.0)	66.5 (61.0–72.0)
Race, n (%)				
White	35 (71.4)	6 (40.0)	6 (50.0)	11 (78.6)
Black or African American	3 (6.1)	2 (13.3)	1 (8.3)	0
Unknown	11 (22.4)	7 (46.7)	5 (41.7)	3 (21.4)
ECOG PS, n (%)				
0	21 (42.9)	7 (46.7)	5 (41.7)	2 (14.3)
1	27 (55.1)	8 (53.3)	7 (58.3)	11 (78.6)
2	1 (2.0)	0	0	1 (7.1)
Baseline PSA, median (IQR), ng/mL	108.7 (19.7–286.8)	72.7 (37.2–615.0)	119.9 (33.2–256.5)	98.8 (33.2–255.8)
Baseline alkaline phosphatase, median (IQR), U/L	102.0 (72.0–198.0)	107.0 (78.0–172.0)	88.5 (66.5–164.5)	84.5 (72.0–126.0)
Baseline albumin, median (IQR), g/L	38.6 (36.0–41.0)	39.0 (35.0–44.0)	37.0 (34.5–40.0)	38.5 (35.0–42.0)
Baseline lactate dehydrogenase, median (IQR), ukat/L	3.9 (3.2–6.3)	4.4 (2.8–6.7)	4.2 (3.6–7.3)	4.4 (3.3–7.2)
Gleason score 8 at diagnosis, n (%)	20 (40.8)	14 (93.3)	6 (50.0)	8 (57.1)
No. prior CRPC therapies, median (IQR) <sup>b</sup>	2 (2–3)	3 (2–4)	3 (2–4)	2 (2–3)
Prior therapies, n (%) <sup>c</sup>				
Abiraterone	34 (69.4)	11 (73.3)	11 (91.7)	12 (85.7)
Enzalutamide	36 (73.5)	14 (93.3)	9 (75.0)	7 (50.0)
Abiraterone and enzalutamide	23 (46.9)	10 (66.7)	8 (66.7)	5 (35.7)
Docetaxel	46 (93.9)	13 (86.7)	12 (100)	13 (92.9)
Cabazitaxel	4 (8.2)	2 (13.3)	0	2 (14.3)
Sipuleucel-T	6 (12.2)	1 (6.7)	1 (8.3)	0
Radium-223	11 (22.4)	2 (13.3)	3 (25.0)	1 (7.1)
Measurable disease status and type (per investigator), n (%)				
Measurable disease	19 (38.8)	10 (66.7)	9 (75.0)	14 (100)
Only measurable nodal disease	9 (47.4)	6 (60.0)	8 (88.9)	9 (64.3)
Measurable visceral ± nodal disease	10 (52.6)	4 (40.0)	1 (11.1)	5 (35.7)
Nonmeasurable disease	30 (61.2)	5 (33.3)	3 (25.0)	0
Bone-only disease	25 (83.3)	2 (40.0)	1 (33.3)	0
Other non-measurable disease	5 (16.7)	3 (60.0)	2 (66.7)	0

Visit cutoff date: April 29, 2019.

<sup>a</sup>Includes patients with an alteration in *FANCA* (n = 4), *NBN* (n = 4), *BRIP1* (n = 2), *PALB2* (n = 2), *RAD51* (n = 1), *RAD51B* (n = 1), and/or *RAD54L* (n = 1).

<sup>b</sup> Does not include luteinizing hormone–releasing hormone analogues, first-generation antiandrogens, hormones, corticosteroids, bone-targeted agents, hematopoietic growth factors, or docetaxel given for hormone-sensitive disease.

<sup>c</sup> Categories are not mutually exclusive.

Abbreviations: CRPC, castration-resistant prostate cancer; DDR, DNA damage repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; PSA, prostate-specific antigen.

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**Table 2:**

Response by DDR gene alteration

	By DDR gene group			
	<i>ATM</i> (n = 49)	<i>CDK12</i> (n = 15)	<i>CHEK2</i> (n = 12)	Other <sup>a</sup> (n = 14)
Confirmed investigator-assessed objective response <sup>b</sup>	2/19 (10.5) [1.3–33.1]	0/10 (0) [0.0–30.8]	1/9 (11.1) [0.3–48.2]	4/14 (28.6) [8.4–58.1]
Complete response	0/19 (0.0)	0/10 (0)	0/9 (0)	1/14 (7.1)
Partial response	2/19 (10.5)	0/10 (0)	1/9 (11.1)	3/14 (21.4)
Stable disease	9/19 (47.4)	6/10 (60.0)	6/9 (66.7)	8/14 (57.1)
Progressive disease	7/19 (36.8)	3/10 (30.0)	2/9 (22.2)	1/14 (7.1)
Not evaluable	1/19 (5.3)	1/10 (10.0)	0/9 (0)	1/14 (7.1)
6-month clinical benefit rate <sup>c</sup>	12/42 (28.6) [15.7–44.6]	3/15 (20.0) [4.3–48.1]	3/8 (37.5) [8.5–75.5]	6/11 (54.5) [23.4–83.3]
12-month clinical benefit rate <sup>d</sup>	3/18 (16.7) [3.6–41.4]	1/14 (7.1) [0.2–33.9]	0/5 (0) [0.0–52.2]	3/8 (37.5) [8.5–75.5]
Confirmed PSA response <sup>e</sup>	2/49 (4.1) [0.5–14.0]	1/15 (6.7) [0.2–31.9]	2/12 (16.7) [2.1–48.4]	5/14 (35.7) [12.8–64.9]
Median time to PSA progression, mo (95% CI)	3.1 (2.8–4.6)	3.2 (2.8–4.6)	7.4 (2.8–7.4)	11.1 (3.0–NR)

Visit cutoff date: April 29, 2019. Data are n/N (%) [95% CI] unless stated otherwise.

<sup>a</sup>Includes patients with an alteration in *FANCA* (n = 4), *NBN* (n = 4), *BRIP1* (n = 2), *PALB2* (n = 2), *RAD51* (n = 1), *RAD51B* (n = 1), and/ or *RAD54L* (n = 1).

<sup>b</sup>Per modified RECIST/PCWG3 criteria; includes patients who had measurable disease at baseline per the investigator and 16 weeks of follow-up.

<sup>c</sup>Proportion of patients without radiographic progression per RECIST/PCWG3 criteria who were ongoing with treatment at 6 months.

<sup>d</sup>Proportion of patients without radiographic progression per RECIST/PCWG3 criteria who were ongoing with treatment at 12 months.

<sup>e</sup>Defined as 50% reduction in PSA from baseline; includes patients who had 16 weeks of follow-up.

Abbreviations: CI, confidence interval; NR, not reached; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

**Table 3:**

Most common (10% or more of patients) TEAEs of any grade in the safety population

	Overall (n = 78)	
	Any grade	Grade 3
Asthenia or fatigue	41 (52.6)	7 (9.0)
Nausea	35 (44.9)	1 (1.3)
Decreased appetite	27 (34.6)	1 (1.3)
Anemia <sup>a</sup>	24 (30.8)	12 (15.4)
Constipation	18 (23.1)	0
Vomiting	18 (23.1)	1 (1.3)
Diarrhea	17 (21.8)	1 (1.3)
ALT or AST increased	14 (17.9)	2 (2.6)
Back pain	14 (17.9)	2 (2.6)
Edema, peripheral	14 (17.9)	0
Dizziness	13 (16.7)	0
Weight decreased	13 (16.7)	0
Blood creatinine increased	12 (15.4)	0
Dysgeusia	10 (12.8)	0
Thrombocytopenia <sup>b</sup>	10 (12.8)	4 (5.1)
Arthralgia	9 (11.5)	1 (1.3)
Cough	8 (10.3)	0
Hematuria	8 (10.3)	1 (1.3)
Pain in extremity	8 (10.3)	0

Visit cutoff date: April 29, 2019. Data are n (%).

<sup>a</sup>Includes preferred terms of anemia and decreased hemoglobin.

<sup>b</sup>Includes preferred terms of thrombocytopenia and decreased platelets.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.