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Differential responses to taxanes and PARP inhibitors in *ATM*- versus *BRCA2*-mutated metastatic castrate-resistant prostate cancer

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Abstract

Background: PARP (poly(ADP-ribose) polymerase) inhibitors (PARPi) are now standard of care in metastatic castrate-resistant prostate cancer (mCRPC) patients with select mutations in DNA damage repair (DDR) pathways, but patients with *ATM*- and *BRCA2* mutations may respond differently to PARPi. We hypothesized that differences may also exist in response to taxanes, which may inform treatment sequencing decisions.

Methods: mCRPC patients ($N = 158$) with deleterious *ATM* or *BRCA2* mutations who received taxanes, PARPi, or both were retrospectively identified from 11 US academic

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centers. Demographic, treatment, and survival data were collected. Kaplan–Meier analyses were performed and Cox hazard ratios (HR) were calculated for progression-free survival (PFS) as well as overall survival (OS), from time of first taxane or PARPi therapy.

Results: Fifty-eight patients with *ATM* mutations and 100 with *BRCA2* mutations were identified. Fourty-four (76%) patients with *ATM* mutations received taxane only or taxane before PARPi, while 14 (24%) received PARPi only or PARPi before taxane. Patients with *ATM* mutations had longer PFS when taxane was given first versus PARPi given first (HR: 0.74 [95% confidence interval [CI]: 0.37–1.50]; $p = 0.40$). Similarly, OS was longer in patients with *ATM* mutations who received taxane first (HR: 0.56 [CI: 0.20–1.54]; $p = 0.26$). Among patients with *BRCA2* mutations, 51 (51%) received taxane first and 49 (49%) received PARPi first. In contrast, patients with *BRCA2* mutations had longer PFS when PARPi was given first versus taxane given first (HR: 0.85 [CI: 0.54–1.35]; $p = 0.49$). Similarly, OS was longer in patients with *BRCA2* mutations who received PARPi first (HR: 0.75 [CI: 0.41–1.37]; $p = 0.35$).

Conclusions: Our retrospective data suggest differential response between *ATM* and *BRCA2* mutated prostate cancers in terms of response to PARPi and to taxane chemotherapy. When considering the sequence of PARPi versus taxane chemotherapy for mCRPC with DDR mutations, *ATM*, and *BRCA2* mutation status may be helpful in guiding choice of initial therapy.

KEYWORDS
ATM, *BRCA2*, DNA repair, mCRPC, overall survival, progression-free survival

1 | INTRODUCTION

Germline and somatic mutations in DNA damage repair (DDR) pathway genes are emerging therapeutic targets in advanced prostate cancer.[1–5] In particular, optimizing treatment for patients with mutations in the DDR genes (especially *BRCA1*, *BRCA2*, and *ATM*) is a key area of research, as these mutations portend aggressive clinical courses.[6–11] Poly(ADP-ribose) polymerase (PARP) inhibitors have revolutionized cancer therapy for patients with *BRCA2* mutations[5,12–15]; however, the utility of PARP inhibitors in patients with *ATM* mutations is less clear. Further, optimal sequencing of PARP inhibitors relative to taxane chemotherapy is undefined.

ATM is mutated in approximately 5% of all cancers, in malignancies as diverse as mantle cell lymphoma to lung cancer.[16] Early gene panel assays that identified *ATM* as a successful treatment target for PARP inhibitors required a complete loss of function in the gene.[17] In the real world, the mutational landscape of *ATM* is vast and the clinical phenotype of many of these mutations are yet unknown.[16]

Treatment outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients with *ATM* mutations is an area of active investigation. In the TOPARP-B trial, complete loss of the *ATM* protein by immunohistochemistry was associated with notable improved clinical response to olaparib, but the overall response of patients with *ATM* mutations to olaparib remained significantly lower than those observed in patients with *BRCA* mutations.[18] A large multicenter retrospective analysis of mCRPC patients with *BRCA2* and ATM mutations revealed that patients with *ATM* mutations had longer time to next treatment with first-line enzalutamide, similar times with taxanes, and shorter times with PARP inhibitors compared to patients with *BRCA* mutations, respectively.[19] Cell culture studies have demonstrated limited PARP inhibitor response, even when the prostate cancer cells are fully *ATM*-deficient.[20] This limited response parallels outcomes in patients with only *ATM* mutations in PROFOUND[21] (olaparib) and TRITON2[22] (rucaparib).

As there remains ambiguity regarding optimal treatment, we investigated the optimal sequencing of PARP inhibitors relative to conventional chemotherapy (taxanes) in *ATM*-mutated mCRPC via a large multicenter retrospective review. In light of the limited response to PARP inhibitors reported in previous studies, we hypothesized that using taxanes first (before PARP inhibition) may yield better survival than using PARP inhibitors first in mCRPC patients with *ATM* mutations, and vice versa in patients with *BRCA2* mutations. We assembled a retrospective cohort of 158 mCRPC

patients with *ATM* or *BRCA2* mutations to answer this question. For perspective, we analyzed 58 patients with *ATM* mutations, relative to the number of patients with *ATM* mutations in the prospective trials PROFOUND (86), TRITON2 (49), and TOPARP-B (21).

2 | METHODS

2.1 | Study population

A retrospective chart review of mCRPC patients across 11 academic centers in the United States was conducted from June to August 2021. Patients were included if any deleterious somatic or germline *ATM* or *BRCA2* mutation was detected on available clinical-grade genetic sequencing performed by individual study sites. Deleterious mutations were defined as genetic changes that led to predicted protein truncation or loss (frameshift, nonsense or splicing mutations, or homozygous deletions) or missense mutations that were classified as deleterious by the sequencing platform used. Patients were excluded from final analysis if they harbored a mutation in both *BRCA2* and *ATM*. In addition to the presence of a deleterious *ATM or BRCA2* mutation, patient must have also received a taxane (docetaxel or cabazitaxel) and/or a PARP inhibitor (any type) for the diagnosis of castration-resistant prostate cancer. Prior therapy with abiraterone and/or enzalutamide was permitted. Patients were additionally excluded from final analysis if they received ≤21 days of therapy.

2.2 | Study outcomes

Demographic, staging, treatment, and genomic characteristics were collected from all patients. This included age, Gleason sum, histology, presence of M1 disease at initial diagnosis, site of metastases, prior enzalutamide and abiraterone exposure, duration of taxane and PARP inhibitor therapy, progression (prostate-specific antigen [PSA] or radiologic/clinical), and vital status. Genomic data included mutation mechanism, mutation origin (germline or somatic), and zygosity status (monoallelic vs. biallelic). The presence of concurrent genomic alterations in *BRCA1*, *CDK12*, *CHD1*, *FOXA1*, *FOXO1*, *MED12*, *MYC*, *PIK3CA*, *PTEN*, *RB1*, *SPOP*, and *TP53* were also collected. Statistical analysis between cooccurrence of *BRCA2*, *ATM*, *PTEN*, *RB1*, and *TP53* alterations was performed.

The primary study outcome was progression-free survival (PFS) on first taxane or PARP inhibitor therapy. This PFS outcome was a composite outcome combining both PSA progression and investigator-assessed radiographic or clinical progression. Disease progression was defined as PSA progression (≥25% increase in PSA from baseline or nadir) or investigator-assessed radiographic or clinical progression. In patients with both PSA progression and investigator-assessed radiographic/clinical progression, the earlier date was denoted as the date of disease progression. The secondary study outcome was overall survival (OS), from the time of first taxane or PARP inhibitor therapy until death from any cause.

2.3 | Statistical analysis

Univariate analyses were performed for demographic, staging, treatment, and genomic characteristics using Pearson's χ^2 or Fisher's exact tests and Wilcoxon rank-sum test for categorical and continuous variables, respectively. Kaplan–Meier survival analysis was performed for the primary and secondary time-to-event outcomes. Multivariable Cox proportional-hazards modeling with backward stepwise selection was employed to assess the contribution of possible confounders on the primary and secondary outcomes. All analyses were performed using SAS version 9.4.

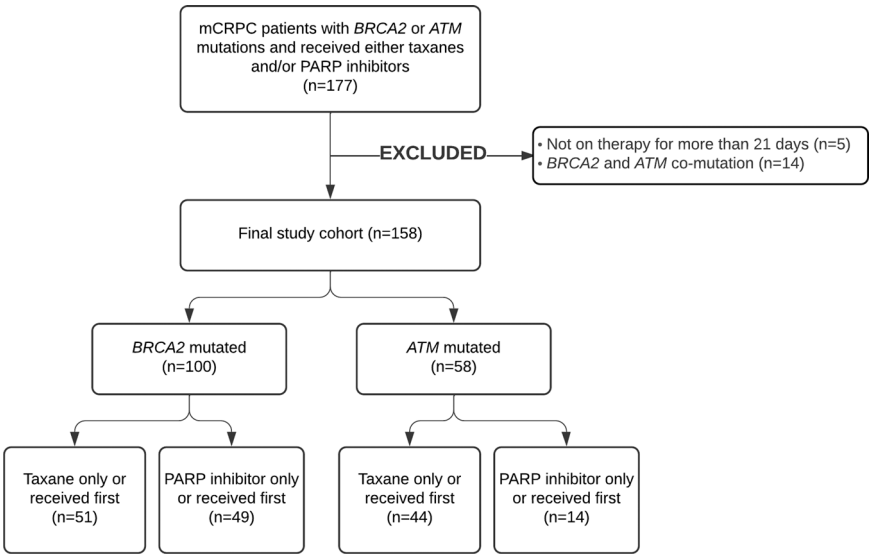

FIGURE 1 Patient selection schematic. mCRPC, metastatic castrate-resistant prostate cancer; PARP, poly(ADP-ribose) polymerase.

TABLE 1 Demographic, staging, and treatment characteristics of study population

Characteristic	Overall	*BRCA2*-mutated patients	*ATM*-mutated patients	*p* Value
N	158	100	58	
Median age at first taxane or PARP inhibitor therapy, years (interquartile range)	72 (62–72)	66 (60–71)	69 (63–74)	<0.01
Gleason sum at diagnosis (%)				0.34
8–10	107 (75%)	69 (78%)	38 (70%)	
6–7	36 (25%)	20 (22%)	16 (30%)	
Unknown	15	11	4	
M1 disease at initial diagnosis (%)				0.37
Yes	70 (44%)	47 (47%)	23 (40%)	
No	88 (56%)	53 (53%)	35 (60%)	
Presence of bone metastases				0.04
Yes	132 (84%)	79 (79%)	53 (91%)	
No	26 (16%)	21 (21%)	5 (9%)	
Presence of nodal metastases				0.25
Yes	99 (63%)	66 (66%)	33 (57%)	
No	59 (37%)	34 (34%)	25 (43%)	
Presence of liver metastases				0.32
Yes	35 (22%)	25 (25%)	10 (17%)	
No	123 (78%)	75 (75%)	48 (83%)	
Presence of lung metastases				0.43
Yes	35 (22%)	20 (20%)	15 (26%)	
No	123 (78%)	80 (80%)	43 (74%)	
Prior enzalutamide therapy				0.68
Yes	96 (61%)	62 (62%)	34 (59%)	
No	62 (39%)	39 (38%)	24 (41%)	
Prior abiraterone therapy				0.61
Yes	126 (80%)	81 (81%)	45 (78%)	
No	32 (20%)	19 (19%)	13 (22%)	
Taxane and PARP inhibitor treatment pattern				<0.001
Taxane only	51 (32%)	21 (21%)	30 (52%)	
PARP inhibitor only	38 (24%)	29 (29%)	9 (16%)	
Taxane first, then PARP inhibitor	44 (28%)	30 (30%)	14 (24%)	
PARP inhibitor first, then taxane	25 (16%)	20 (20%)	5 (9%)	

Abbreviation: PARP, poly(ADP-ribose) polymerase.

Institutional review board approval was obtained at the local level at each participating site.

3 | RESULTS

3.1 | Study population

The patient selection schema is shown in Figure 1. The final patient population comprised 158 patients, with 100 (63%) and 58 (37%) patients having deleterious *BRCA2* and *ATM* mutations, respectively. Among patients with *BRCA2* mutations, 51 (51%) received a taxane only or taxane before PARP inhibitor treatment, while 49 (49%) received a PARP inhibitor only or PARP inhibitor before taxane treatment. Among patients with *ATM* mutations, 44 (76%) received a taxane only or taxane before a PARP inhibitor, while 14 (24%) received a PARP inhibitor only or PARP inhibitor before a taxane.

3.2 | Patient characteristics

Patient demographic, staging, and treatment data are shown in Table 1. The median age of all patients at the time of first taxane or PARP inhibitor treatment was 67 years (interquartile range 62–72 years). There was a significant difference in age at receipt of first taxane or PARP inhibitor therapy between the patients with *BRCA2* and *ATM* mutations (median age 66 years for the *BRCA2*-mutated group and 69 years for the *ATM*-mutated group, $p < 0.01$). There was also a significant difference between bone metastases, present in 79% and 91% of patients with *BRCA2* and *ATM* mutations, respectively ($p = 0.04$). There were no significant differences between the *BRCA2*-mutated and *ATM*-mutated groups with respect to Gleason sum at diagnosis, M1 disease at diagnosis, presence of metastases (nodal, liver, or lung), prior enzalutamide therapy, or prior abiraterone therapy. Among patients with *BRCA2* mutations, 21 (21%) received a taxane only, 29 (29%) received a PARP inhibitor only, 30 (30%) received a taxane first then a PARP inhibitor, and 20 (20%) received a PARP inhibitor first then a taxane. Among patients with *ATM* mutations, 30 (52%) received a taxane only, 9 (16%) received a PARP inhibitor only, 14 (24%) received a taxane first then a PARP inhibitor, and 5 (9%) received a PARP inhibitor first then a taxane. This overall treatment pattern is significantly different between patients with *BRCA2* and *ATM* mutations ($p < 0.001$).

Mutation characteristics are shown in Table 2. Tissue samples were obtained from primary tumor (41%), metastatic tissue (36%), circulating tumor DNA (10%), or in some cases by germline-only testing (13%). The mechanisms of *BRCA2* mutation included homozygous deletions (55%), frameshift mutations (31%), missense mutations (6%), and nonsense mutations (8%); while the mechanisms for *ATM* mutations included deletions (28%), frameshift mutations (28%), missense mutations (22%), nonsense mutations (17%), and splice site mutations (5%). In the overall patient population, 50 (32%) had germline mutations, and 105 (68%) had somatic mutations. A total of 31 (20%) of patients had confirmed biallelic mutations. There was a significant difference in concurrent *RB1* alteration between *BRCA2*-mutated and *ATM*-mutated patients (35% vs. 17%, $p = 0.04$); there were no differences in cooccurrence in *TP53* and *PTEN* alterations between the two cohorts.

TABLE 2 Baseline mutation characteristics of study population

Characteristic	Overall	*BRCA2*-mutated patients	*ATM*-mutated patients	*p* Value
N	158	100	58	
Sample source				0.21
Primary tissue	60 (41%)	42 (46%)	18 (33%)	
Metastatic tissue	52 (36%)	30 (33%)	22 (41%)	
Circulating tumor DNA	14 (10%)	6 (7%)	8 (15%)	
Germline-only testing	19 (13%)	13 (14%)	6 (11%)	
Unknown	13	9	4	
Mechanism of mutation				<0.001
Homozygous deletion	69 (45%)	53 (55%)	16 (28%)	
Frameshift	46 (30%)	30 (31%)	16 (28%)	
Missense	19 (12%)	6 (6%)	13 (22%)	
Nonsense	18 (12%)	8 (8%)	10 (17%)	
Splicing	3 (2%)	0 (0%)	3 (5%)	
Unknown	3	3	0	
Origin of mutation				0.09
Germline	50 (32%)	36 (37%)	14 (24%)	
Somatic	105 (68%)	61 (63%)	44 (76%)	
Unknown	3	3	0	
Allelic status of mutation				0.49
Bialleic	31 (20%)	21 (22%)	10 (17%)	
Monoalleic or unconfirmed	123 (80%)	75 (78%)	48 (83%)	
Unknown	4	4	0	
TP53 comutation (missing data = 35)				0.70
No	80 (65%)	49 (64%)	31 (67%)	
Yes	43 (35%)	28 (36%)	15 (33%)	
PTEN comutation (missing data = 35)				0.85
No	76 (62%)	47 (61%)	29 (63%)	
Yes	47 (38%)	30 (39%)	17 (37%)	
RB1 comutation (missing data = 35)				0.04
No	88 (72%)	50 (65%)	38 (83%)	
Yes	35 (28%)	27 (35%)	8 (17%)	

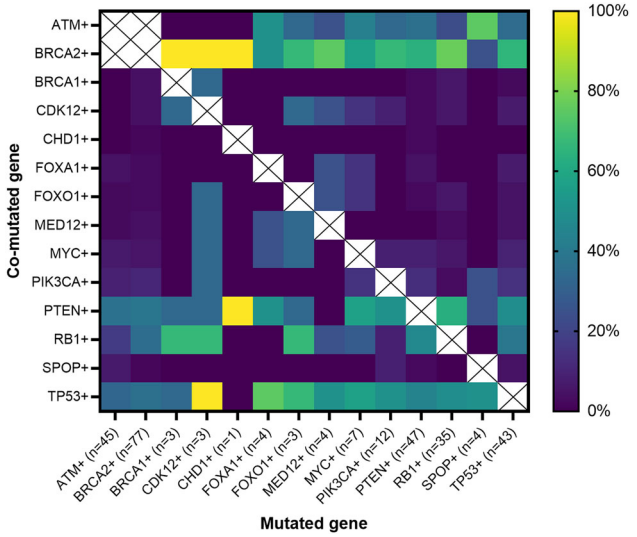

FIGURE 2 Heatmap of cooccurring alterations. The *X*-axis indicates the primary mutated gene (*n* indicates the number of patients), and the *Y*-axis indicates the second comutated gene. The colored squares demonstrate the percentage of patients with a genetic mutation shown in the *X*-axis, who also have a concurrent mutation denoted by the *Y*-axis. Patients with both *BRCA2* and *ATM* mutations were specifically excluded. [Color figure can be viewed at wileyonlinelibrary.com]

The pattern of cooccurring mutations in 14 preselected prostate cancer-relevant genes is shown in Figure 2. Statistical analyses between the most commonly expressed genes other than *ATM* and *BRCA2* (*PTEN*, *RB1*, *and TP53*) demonstrate significant coalteration of *RB1* in *PTEN* mutated patients (47% vs. 17% in *PTEN* nonmutated patients, $p < 0.001$).

3.3 | Study outcomes

The primary outcome of PFS on first taxane or PARP inhibitor therapy by *ATM* or *BRCA2* mutation status is shown in Figure 3. Patients with *ATM* mutations who received a taxane first had numerically longer median PFS compared to those who received a PARP inhibitor first (6.2 vs. 3.3 months, hazard ratio [HR] with 95% confidence interval [CI] 0.74 [0.37–1.50]; $p = 0.40$). In contrast, patients with *BRCA2* mutations who received a PARP inhibitor first had numerically longer median PFS compared to those who received a taxane first (11.2 vs. 7.2 months, HR: 0.85 (0.54–1.35); $p = 0.49$). These differences were not statistically significant.

The secondary outcome of OS from the time of first taxane or PARP inhibitor therapy to death, by *ATM* or *BRCA2* mutation status, is shown in Figure 4. Patients with *ATM* mutations who received taxanes first had numerically longer median OS compared to those who received PARP inhibitors first (38.1 vs. 33.0 months, HR: 0.56 (0.20–1.54); $p = 0.26$). In contrast, patients with *BRCA2* mutations who received PARP inhibitors first had numerically longer median OS compared to those who received taxanes first (36.6 vs. 32.8 months, HR: 0.75 (0.41–1.37); $p = 0.35$). Again, these differences did not reach statistical significance.

Multivariable Cox proportional-hazards modeling using backward stepwise selection to evaluate the impact of possible factors, including choice of first therapy (taxane vs. PARP inhibitor), age, Gleason score, presence of M1 disease at initiation diagnosis, presence of metastases (nodal, liver, or lung), and prior enzalutamide or abiraterone exposure on patients with *ATM* or *BRCA2* mutations did not demonstrate a significant association of any factor with PFS or OS in our model.

4 | DISCUSSION

In our multicenter retrospective chart review investigating the optimal sequencing of PARP inhibitors and taxanes in mCRPC patients with *ATM* or *BRCA2* mutations, we found that patients with *ATM* mutations demonstrated a trend toward longer PFS and OS when taxane was given first rather than PARP inhibitors. The reverse was true for patients with *BRCA2* mutations: that PARP inhibitors demonstrated numerically longer PFS and OS when given first over taxanes. However, none of these survival analyses were statistically significant.

The following factors may have contributed to the observed PFS and OS results. First, previous studies[17,18] have demonstrated that complete loss of *ATM* is associated with improved response to PARP inhibitors. As 28% of patients with *ATM* mutations in our cohort had homozygous deletions in *ATM*, these patients may have demonstrated a better response to PARP inhibitors compared to other *ATM*-mutated patients. It is important to note, however, that other types of *ATM*-mutations observed in our cohort may have also led to a loss-of-function phenotype, increasing the number of patients in this group. Second, there may have been other unmeasured differences in baseline demographics, clinical characteristics, or previous prostate cancer therapy between the cohorts that affected survival. However, our baseline demographics and clinical characteristics are similar to *ATM* and *BRCA2* patient cohorts in other mCRPC studies.[19,23] Third, our cohorts may not have contained sufficient patient numbers to detect a significant difference in outcomes given the unknown relative hazard of PARP inhibitor and taxane therapy in patients with *ATM* or *BRCA2* mutations, and thus our analysis was likely underpowered to interrogate differential treatment sequences.

Although the PFS and OS differences did not reach statistical significance, our study provides insight into the current treatment landscape of mCRPC patients with *ATM* or *BRCA2* mutations. First, the observed numeric advantage in PFS and OS of upfront taxanes compared to upfront PARP inhibitors in *ATM*-mutated mCRPC should be confirmed in larger datasets and prospective studies, such as TRITON3. Since mCRPC patients with *ATM* mutations also appear to be less sensitive to platinum chemotherapy,[19,24] ascertaining an efficacious treatment agent in this population is especially important. Second, 49% of patients with *BRCA2* mutations in our cohort received PARP inhibitors as the first line of mCRPC therapy, compared to only 25% of patients with *ATM* mutations, showing the increasing uptake of upfront PARP inhibitor therapy in mCRPC patients with *BRCA2* mutations.

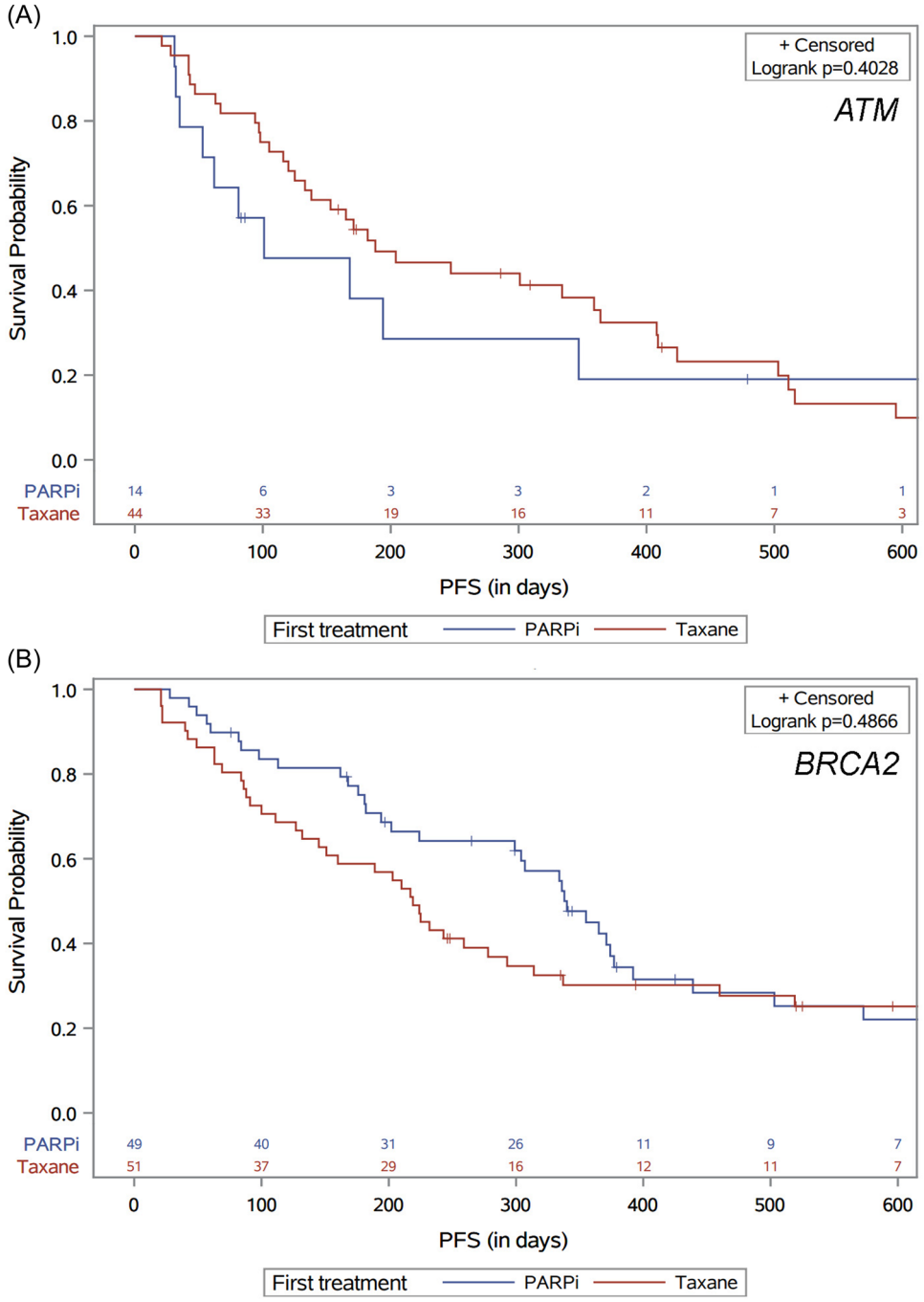

FIGURE 3 Progression-free survival (PFS) by first taxane or PARP inhibitor therapy, in (A) patients with *ATM* mutations and (B) patients with *BRCA2* mutations.PARP, poly(ADP-ribose) polymerase. [Color figure can be viewed at wileyonlinelibrary.com]

There were several limitations to our study, including the retrospective nature and the possible heterogenous phenotypes in our *ATM*-mutated cohort. Second, composite PFS was defined as the earliest of three possible indicators of disease progression (biochemical progression, radiological progression, investigator-determined clinical progression) in this study which may have affected the PFS analysis. Although using a defined biochemical progression would be preferable, limitations in retrospective clinical data across multiple institutions made standardizing this data challenging. Third, retrospective sequencing studies in the metastatic population require controlling for previous treatment courses that may have affected tumor biology at the time of receipt of the treatments of interest. To address this, we did account for prior abiraterone and enzalutamide use in our analysis. Despite these limitations, we were able to collate the largest retrospective *ATM*- and *BRCA2*-mutated mCRPC cohort in the literature to our knowledge that contains detailed diagnostic and treatment data with respect to sequencing of taxane and PARP inhibitor agents in these patients.[19,23]

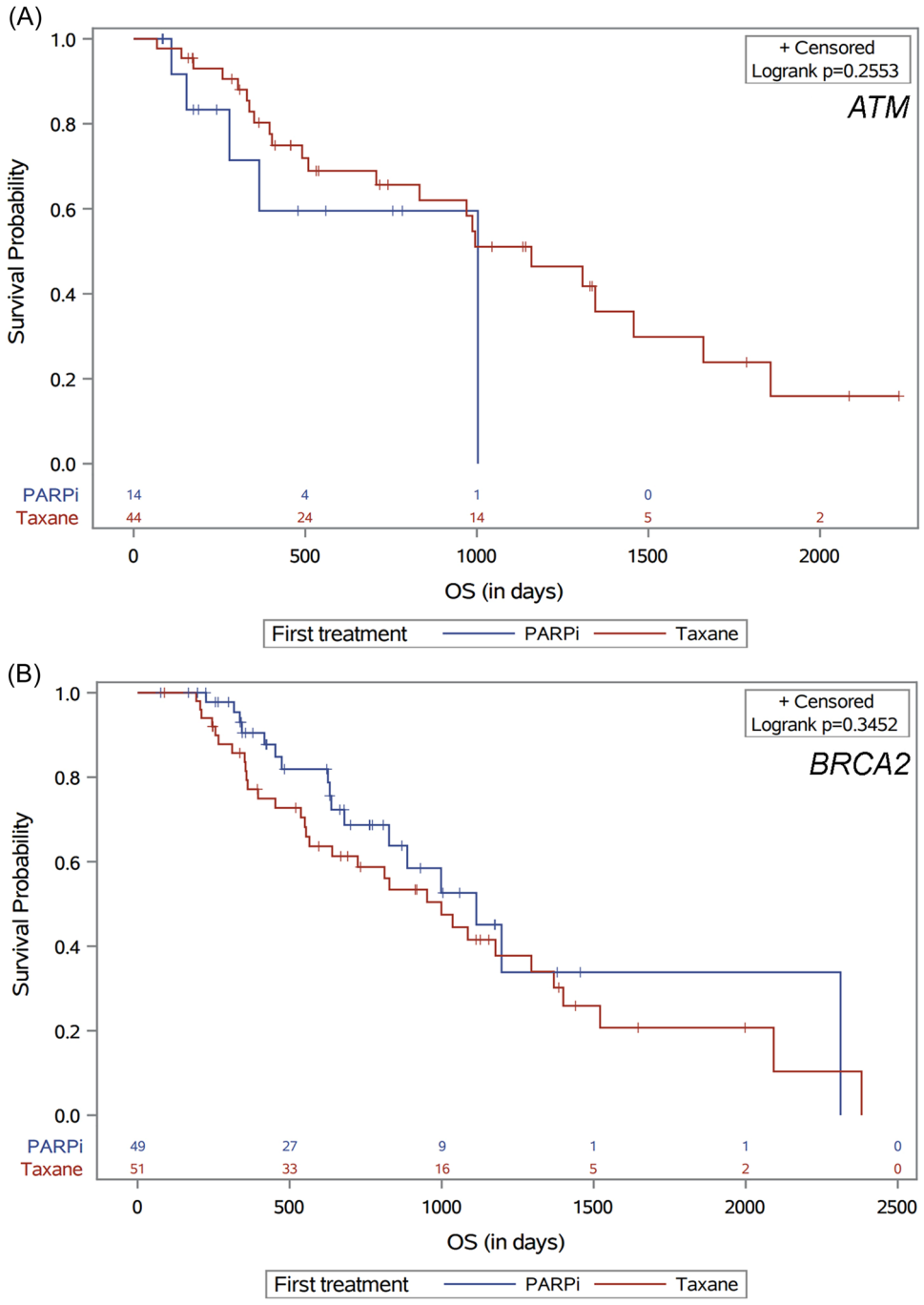

FIGURE 4 Overall survival (OS) by first taxane or PARP inhibitor therapy, in (A) patients with *ATM* mutations and (B) patients with *BRCA2* mutations.PARP, poly(ADP-ribose) polymerase. [Color figure can be viewed at wileyonlinelibrary.com]

5 | CONCLUSION

Our retrospective multicenter analysis of mCRPC patients with *ATM* or *BRCA2* mutations demonstrates a numerically increased PFS and OS when taxanes are given upfront in patients with *ATM* mutations, and vice versa with PARP inhibitors in patients with *BRCA2* mutations. These differences in clinical outcomes, while not statistically significant, support increasing genomic profiling uptake and the use of tailored optimal sequencing of therapies for mCRPC patients with specific classes of DDR mutations. We hope that these hypothesis-generating results inspire additional clinical consortia to confirm or refute these findings in larger genetically-defined mCRPC populations.

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CONFLICTS OF INTEREST

Emily Nizialek: Consulting or Advisory Role: AstraZeneca. Jacob E. Berchuck: Honoraria: Digital Science Press. Consulting or Advisory Role: Genome Medical, VetOncoDx. Equity: Genome Medical, VetOncoDx, Cityblock Health (spouse). Employment: Cityblock Health (spouse). Travel, Accommodations, Expenses: Digital Science Press. Patents: Institutional patent filed on methods to detect neuroendocrine prostate cancer through tissue-informed cell-free DNA methylation analysis. Pedro C. Barata: Consultant (Institutional): Astellas; Eisai; AVEO Oncology, Janssen, EMD Serono; Dendreon; Pfizer, Seattle Genetics, BMS, Bayer, Guardant Health. Contracted Research (Institutional): AstraZeneca, Merck, AVEO Oncology. Research Grant (Institutional): Blue Earth Diagnostics. Speaker's Bureau (Institutional): Bayer, Caris, Myovant. Rahul R. Aggarwal: Honoraria: Clovis Oncology. Consulting or Advisory Role: Advanced Accelerator Applications; Alessa Therapeutics; Alessa Therapeutics; Amgen; AstraZeneca; Axiom Biotechnologies; Clovis Oncology; Dendreon; Jubilant Pharmaceuticals; Merck; Pfizer. Research Funding: Abbvie (Inst); Amgen (Inst); AstraZeneca (Inst); BioXCel therapeutics (Inst); Cancer Targeted Technology (Inst); Janssen (Inst); Merck (Inst); Novartis (Inst); Xynomic Pharma (Inst); Zenith Epigenetics (Inst). Rana R. McKay: Consulting or Advisory Role: Aveo, Astellas, Medivation, AstraZeneca, Bayer, Bristol Myers Squibb, Calithera Biosciences, Caris, Dendreon, Exelixis, Janssen, Merck, Myovant, Novartis, Pfizer, Sanofi, Sorrento Therapeutics, Tempus, and Vividion Therapeutics. R. R. M. receives research funding from Tempus, Bayer. Neerja Agarwal: Consulting or Advisory Role: Astellas, Astra Zeneca, Aveo, Bayer, Bristol Myers Squibb, Calithera, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Gilead, Janssen, Merck, MEI Pharma, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics. Funding to Institution: Astellas, Astra Zeneca, Bavarian Nordic, Bayer, Bristol Myers Squibb, Calithera, Celldex, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Gilead, Glaxo Smith Kline, Immunomedics, Janssen, Medivation, Merck, Nektar, New Link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon. Alan H. Bryce: Funding to Institution: Janssen, AstraZeneca, Gilead. Consulting: Merck, Bayer. Honoraria: Elsevier, Fallon Medica, Horizon CME, PRIME Education, MJH Life Sciences. Patents: Therapeutic Targeting of Cancer Patients wiht NRG1 Rearrangements 15/735,289. Oliver Sartor: Consulting: Advanced Accelerator Applications (AAA), Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Inc., Bavarian Nordic, Bristol Myers Squibb, Clarity Pharmaceuticals, Clovis, Constellation, Dendreon, EMD Serono, Fusion, Isotopen Technologien Meunchen, Janssen, Myovant, Myriad, Noria Therapeutics, Inc., Novartis, Noxopharm, Progenics, POINT Biopharma, Pfizer, Sanofi, Tenebio, Telix, Theragnostics. Grant/Research Support: Advanced Accelerator Applications, Amgen, AstraZeneca, Bayer, Constellation, Endocyte, Invitae, Janssen, Lantheus, Merck, Progenics, Tenebio. Heather H. Cheng: Research Funds to Institution: Clovis Oncology, Color Genomics, Janssen, Medivation, Phosplatin, Sanofi; Consultant: AstraZeneca; Royalties: UpToDate. Nabil Adra: Consulting or Advisory Role: Astellas Pharma; Aveo; Bristol Myers Squibb Foundation; Bristol Myers Squibb Foundation; Exelixis; Merck; Sanofi. Research Funding: Exelixis (Inst); Genentech (Inst); Merck (Inst). Cora N. Sternberg: Funding, consultancy, advisory: Astellas Pharma/AstraZeneca/Bayer/Genzyme/Gilead/Medscape/Janssen; Merck/MSD/Pfizer/Roche/Impact Pharma/BMS/Sanofi-Genzyme/UroToday/CCO Clinical, GLC; NCI. Mary-Ellen Taplin: Consulting or Advisory Role: Janssen, Arcus Bioscience, Roviant, Arvinas, Blue Earth, Clovis, AstraZeneca, Epizyme, Research To Practice, Pfizer, UpToDate. Ajjai S. Alva: Consulting or Advisory Role: AstraZeneca; BMS; Merck; Pfizer. Research Funding: Arcus Biosciences (Inst); Astellas Pharma (Inst); AstraZeneca (Inst); Bayer (Inst); Bristol-Myers Squibb (Inst); Celgene (Inst); Genentech (Inst); Harpoon Therapeutics (Inst); Janssen (Inst); Merck Sharp & Dohme (Inst); Mirati Therapeutics (Inst); Progenics (Inst); Progenics (Inst); Prometheus (Inst); Roche (Inst). Travel, Accommodations, Expenses: BMS; Merck. Emmanuel S. Antonarakis: Consulting or Advisory Role: Janssen, Astellas, Sanofi, Dendreon, Bayer, BMS, Amgen, ESSA, Constellation, Blue Earth, Exact Sciences, Invitae, Curium, Pfizer, Merck, AstraZeneca, Clovis, Eli Lilly. Grant/Research Support: Janssen, J&J, Sanofi, BMS, Pfizer, AstraZeneca, Novartis, Curium, Constellation, ESSA, Celgene, Merck, Bayer, Clovis. Inventions/patents: Coinventor of AR-V7 technology licensed to Qiagen. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Deidentified data that support the findings of this study may be available upon reasonable request from the corresponding author. The data set is not publicly available due to privacy concerns related to protected health information.

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