Original Article

# Differential Treatment Outcomes in *BRCA1/2*-, *CDK12*-, and *ATM*-Mutated Metastatic Castration-Resistant Prostate Cancer

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**BACKGROUND:** DNA damage repair mutations (DDRm) are common in patients with metastatic castration-resistant prostate cancer (mCRPC). The optimal standard therapy for this population is not well described. **METHODS:** A multi-institutional, retrospective study of patients with mCRPC and DDRm was conducted. Patient data, including systemic therapies and responses, were collected. The decline in prostate-specific antigen ≥ 50% from baseline (PSA50) and overall survival (OS) from the treatment start were compared by mutation and treatment type. A multivariable Cox proportional hazards model for OS was created that controlled for DDRm, first-line treatment received for mCRPC, and clinical factors. **RESULTS:** The most common DDRm observed among 149 men with mCRPC were BRCA1/2 (44%), *CDK12* (32%), and *ATM* (15%). The majority received first-line abiraterone (40%) or enzalutamide (30%). The PSA50 rate with first-line abiraterone was lower for CDK12 (52%) than BRCA1/2 (89%; $P = .02$). After first-line abiraterone or enzalutamide, the median OS was longest with second-line carboplatin-chemotherapy (38 months) in comparison with abiraterone or enzalutamide (33 months), docetaxel (17 months), or cabazitaxel (11 months; $P = .02$). PSA50 responses to carboplatin-based chemotherapy were higher for BRCA1/2 (79%) than ATM (14%; $P = .02$) or CDK12 (38%; $P = .08$). In a multivariable analysis, neither the specific DDRm type nor the first-line treatment was associated with improved OS. **CONCLUSIONS:** Responses to standard therapies were generally superior in patients with BRCA1/2 mutations and inferior in patients with *ATM* or *CDK12* mutations. The DDRm type did not independently predict OS. After progression on first-line abiraterone or enzalutamide, carboplatin-based chemotherapy was associated with the longest OS. These findings may inform treatment discussions and clinical trial design and require prospective validation. ***Cancer* 2021;127:1965-1973**.


**KEYWORDS:** ATM, biomarkers, BRCA2, CDK12, DNA repair, prostate cancer.

## INTRODUCTION

Germline and somatic DNA damage repair mutations (DDRm) are common in metastatic castration-resistant prostate cancer (mCRPC) with a prevalence of 8% to 25%.[1-8] DDRm may lead to DNA repair deficiencies through various pathways, including mismatch repair (MMR) and homologous recombination,[9] and may confer synthetic lethality with poly(adenosine diphosphate ribose) polymerase (PARP) inhibitors. Clinical trials have shown a radiographic progression-free survival and overall survival (OS) benefit with the use of PARP inhibitors in patients with DDRm in the mCRPC setting,[10-14] primarily *BRCA1* and *BRCA2* (BRCA1/2)-mutated carriers.[15] As a result, the National Comprehensive Cancer Network recommends that men with mCRPC undergo germline testing and metastatic biopsy to assess for DDRm.[16]

There is conflicting evidence about the association of DDRm type with clinical outcomes of standard systemic therapies for mCRPC, including androgen signaling inhibitors (ASIs) abiraterone and enzalutamide and taxane chemotherapies docetaxel and cabazitaxel, likely because of cohort size and heterogeneity.[4-8,17-19] Platinum-based chemotherapy may potentially benefit patients with DDRm,[20] but it is unknown how efficacy varies by DDRm type. Furthermore, little is known about outcomes based on treatment sequencing.

As more patients with mCRPC are found to have DDRm through increased testing, it is important to address these evidence gaps to inform oncologists and patients of anticipated outcomes of standard therapies, assess

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for potential biomarkers, and inform the design of future clinical trials. Herein, we report and compare clinical outcomes in a multicenter cohort of patients with mCRPC and DDRm on the basis of therapy and DDRm type. These data expand on a previously reported data set of patients with *CDK12* mutations[19] and differ by comparing treatment outcomes by specific DDRm type and treatment line.

## MATERIALS AND METHODS

A pooled retrospective analysis of patients at the University of British Columbia (UBC), the University of California San Francisco (UCSF), and the University of Michigan (UM) with mCRPC and DDRm identified via somatic, germline, or circulating DNA next-generation sequencing (NGS) was conducted.

### *Patients and Data Collection*

Genomic, clinical, and demographic data were obtained from electronic medical records from January 1, 1988, to March 16, 2018, for UBC and UM; the data cutoff for UCSF was July 22, 2019. At UBC, deep targeted sequencing of plasma cell-free DNA was performed with a 72-gene panel.[19] At UCSF, NGS was performed with the UCSF500 Cancer Gene Panel for metastatic biopsies, with FoundationOne for metastatic biopsies and circulating tumor DNA, with Strata for prostatectomy specimens, and with Color Genomics for germline mutations. At UM, the Clinical Laboratory Improvement Amendments/College of American Pathologists–approved Michigan Oncology Sequencing Center NGS program was used for the analysis of metastatic biopsies. University of Washington patients sequenced at UM via Stand Up to Cancer were included in the UM cohort. All sites obtained institutional review board approval, and deidentified patient data were shared among the institutions in a Health Insurance Portability and Accountability Act–compliant manner.

Only patients with the following pathogenic or likely pathogenic DDRm were included in the analysis: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK2*, Fanconi anemia genes, MMR genes (*MSH1*, *MLH3*, *MSH2*, *MSH3*, *MSH6*, *PMS1*, and *PMS2*), *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. Patients were categorized into 5 DDRm mutation groups: BRCA1/2, ATM, CDK12, MMR, and other.

In addition to disease-related clinicopathologic data, data for systemic therapy initiated after the onset of mCRPC (defined as ≥2 consecutively rising serum prostate-specific antigen values and/or new radiographic metastases in the setting of suppressed testosterone levels) were obtained for patients with DDRm. For each systemic therapy, the treatment line, the decline in prostate-specific antigen ≥ 50% from baseline (PSA50), the time from treatment start to next treatment start (TNT), and the OS from the start of treatment were obtained. Concurrent taxane chemotherapy with carboplatin was categorized as carboplatin-based chemotherapy. Patients were followed until the date of death or last follow-up.

### *Statistical Methods*

Clinical and demographic characteristics were summarized by mutation group in contingency tables. The PSA50 response rates, TNT, and OS of systemic therapies received in the first- and second-line mCRPC settings were compared by therapy type and by mutation group with the Fisher exact test, the Wilcoxon rank sum test, and the log-rank test, respectively. A multivariable Cox proportional hazards model of OS was used to account for age, stage, and prostate-specific antigen at diagnosis; ethnicity; presence of visceral metastases at the time of mCRPC or metastasis; type of first-line treatment received; and mutation group. $P < .05$ was considered significant for statistical testing. No multiple testing adjustments were performed. Analyses were performed with R statistical computing software (https://www.r-project.org).

## RESULTS

### *Patient Characteristics*

We identified 149 patients with mCRPC and DDRm. These DDRm were *BRCA2* (60 [40%]); *CDK12* (47 [32%]); *ATM* (23 [15%]); *BRCA1* (5 [3%]); MMR (5 [3%]); *PALB2* (4 [3%]); and *BRIP1*, *FANCA*, *FANCC*, *FANCG*, and *RAD51C* (1 each). Demographic and clinical characteristics are described in Table 1. Characteristics, including the presence of visceral metastases (n = 17; 11% of overall cohort) and the source of genomic testing (n = 128; 86% treatment-emergent), did not vary by mutation group apart from a lower age of diagnosis in the ATM group compared with the other groups ($P = .02$). The median follow-up from the start of the first mCRPC treatment was 22.2 months.

### *PSA50 Response Rates*

Among the 137 patients who received systemic therapy after mCRPC onset, the most common first-line treatments

**TABLE 1.** Baseline Characteristics of Patients With mCRPC and DDRm (n = 149)

| Characteristic | Overall (n = 149) | BRCA1/2 (n = 65) | ATM (n = 23) | CDK12 (n = 47) | MMR (n = 5) | Other (n = 9)[a] |
|---|---|---|---|---|---|---|
| Age at diagnosis, median (range), y | 63 (34-87) | 61 (34-86) | 54 (46-75) | 66 (48-87) | 63 (51-77) | 61 (57-87) |
| Ethnicity, No. (%) | | | | | | |
| White | 101 (68) | 42 (65) | 12 (52) | 35 (74) | 5 (100) | 7 (78) |
| Asian | 12 (8) | 7 (11) | 2 (9) | 2 (4) | 0 | 1 (11) |
| African American | 7 (5) | 1 (2) | 2 (9) | 3 (6) | 0 | 1 (11) |
| Hispanic | 2 (1) | 0 | 2 (9) | 0 | 0 | 0 |
| Other | 10 (7) | 2 (3) | 2 (9) | 6 (13) | 0 | 0 |
| Missing | 17 (11) | 13 (20) | 3 (13) | 1 (2) | 0 | 0 |
| Stage at diagnosis, No. (%) | | | | | | |
| Localized | 66 (44) | 31 (48) | 14 (61) | 15 (32) | 1 (20) | 5 (56) |
| Regional lymph nodes | 18 (12) | 7 (11) | 1 (4) | 8 (17) | 1 (20) | 1 (11) |
| Metastatic | 63 (42) | 27 (42) | 8 (35) | 22 (47) | 3 (60) | 3 (33) |
| Missing | 2 (1) | 0 | 0 | 2 (4) | 0 | 0 |
| Visceral disease at time of metastasis or CRPC, No. (%) | | | | | | |
| Yes | 17 (11) | 8 (12) | 3 (13) | 6 (13) | 0 | 0 |
| No | 123 (83) | 51 (78) | 20 (87) | 38 (81) | 5 (100) | 9 (100) |
| Missing | 9 (6) | 6 (9) | 0 | 3 (6) | 0 | 0 |
| PSA at diagnosis, median (range), ng/mL | 18 (2-5000) | 18 (4-5000) | 16 (4-143) | 20 (2-1647) | 14 (4-2000) | 17 (8-687) |
| Gleason score at diagnosis, No. (%) | | | | | | |
| <8 | 28 (19) | 17 (26) | 3 (13) | 5 (11) | 1 (20) | 2 (22) |
| ≥8 | 108 (72) | 43 (66) | 16 (70) | 39 (83) | 3 (60) | 7 (78) |
| Missing | 13 (9) | 5 (8) | 4 (17) | 3 (6) | 1 (20) | 0 |
| Definitive local therapy, No. (%) | | | | | | |
| Surgery | 45 (30) | 20 (31) | 7 (30) | 13 (28) | 0 | 5 (56) |
| Radiation therapy | 36 (24) | 18 (28) | 6 (26) | 8 (17) | 3 (60) | 1 (11) |
| None | 65 (44) | 27 (42) | 10 (43) | 23 (49) | 2 (40) | 3 (33) |
| Missing | 3 (2) | 0 | 0 | 3 (6) | 0 | 0 |
| Source of tissue, No. (%) | | | | | | |
| Prostate | 20 (13) | 7 (11) | 6 (26) | 6 (13) | 1 (20) | 0 |
| Lymph node | 5 (3) | 2 (3) | 0 | 2 (4) | 0 | 1 (11) |
| Blood (ctDNA or cfDNA) | 64 (43) | 38 (58) | 11 (48) | 15 (32) | 0 | 0 |
| Germline | 8 (5) | 2 (3) | 3 (13) | 0 | 0 | 1 (11) |
| Liver | 7 (5) | 2 (3) | 1 (4) | 2 (4) | 1 (20) | 1 (11) |
| Bone | 2 (1) | 0 | 1 (4) | 1 (2) | 0 | 0 |
| Other soft tissue[b] | 8 (5) | 5 (8) | 0 | 2 (4) | 1 (20) | 0 |
| Unknown metastasis | 34 (23) | 9 (14) | 1 (4) | 18 (38) | 2 (40) | 4 (44) |
| Missing | 1 (1) | 0 | 0 | 1 (2) | 0 | 2 (22) |
| Lines of therapy received in mCRPC setting, No. (%) | | | | | | |
| 0 | 5 (3) | 3 (5) | 0 | 1 (2) | 1 (20) | 0 |
| 1 or 2 | 67 (45) | 36 (55) | 8 (35) | 18 (38) | 1 (20) | 4 (44) |
| ≥3 | 72 (48) | 24 (37) | 14 (61) | 27 (57) | 2 (40) | 5 (56) |
| Missing | 5 (3) | 2 (3) | 1 (4) | 1 (2) | 1 (20) | 0 |

Abbreviations: cfDNA, cell-free DNA; CRPC, castration-resistant prostate cancer; ctDNA, circulating tumor DNA; DDRm, DNA damage repair mutation; mCRPC, metastatic castration-resistant prostate cancer; MMR, mismatch repair; PSA, prostate-specific antigen.
[a]*Other* included the following: *PALB2* (n = 4), *BRIP1* (n = 1), *FANCA* (n = 1), *FANCC* (n = 1), *FANCG* (n = 1), and *RAD51C* (n = 1).
[b]*Other soft tissue* included the following: bladder (n = 2), epidural (n = 2), lung (n = 1), pelvic mass (n = 1), skin (n = 1), and testis (n = 1).

were abiraterone (n = 59), enzalutamide (n = 44), docetaxel (n = 19), and carboplatin-based chemotherapy (n = 5; Table 2). In the overall cohort, there was no difference in PSA50 rate by first-line treatment type (Table 2). Among the 59 patients who received first-line abiraterone, those with BRCA1/2 mutations had a higher PSA50 rate (89% [16 of 18]) than those with *CDK12* mutations (52% [11 of 21]; $P = .02$; Table 2). There was no difference in the PSA50 rate for first-line enzalutamide in patients with BRCA1/2 mutations (55% [6 of 11]) versus *CDK12* mutations (64% [9 of 14]; $P = .70$; Table 2)

Among the 108 patients who received a second-line therapy after mCRPC onset, most received enzalutamide, abiraterone, or docetaxel (Table 2). Overall, second-line

**TABLE 2.** PSA50 Response Rates of Treatments Received for mCRPC in Patients With DDRm by Order Received and Mutation Group

| | | First Line in mCRPC Setting (n = 137) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mutation Group | | | | | *P* (Pairwise) | | |
| Treatment[a] | Any DDRm | BRCA1/2 (n = 39) | ATM (n = 20) | CDK12 (n = 39) | MMR (n = 3) | Other (n = 8) | BRCA vs ATM | BRCA vs CDK12 | ATM vs CDK12 |
| Abiraterone (n = 59) | 70%<br>37/53 | 89%<br>16/18 | 86%<br>6/7 | 52%<br>11/21 | 100%<br>3/3 | 25%<br>1/4 | 1.00 | **.02** | .19 |
| Enzalutamide (n = 44) | 65%<br>24/37 | 55%<br>6/11 | 75%<br>9/12 | 64%<br>9/14 | — | — | .40 | .70 | .68 |
| Docetaxel (n = 19) | 57%<br>8/14 | 86%<br>6/7 | 0<br>0/1 | 0<br>0/3 | — | 67%<br>2/3 | NA[c] | NA[c] | NA[c] |
| Carboplatin-based (n = 5) | 40%<br>2/5 | 33%<br>1/3 | — | 0<br>0/1 | — | 100%<br>1/1 | NA[c] | NA[c] | NA[c] |
| *P*[b] | .50 | .06 | .33 | .18 | NA[c] | NA[c] | | | |
| | | Second Line in mCRPC Setting (n = 108) | | | | | | | |
| | | Mutation Group | | | | | *P* (Pairwise) | | |
| Treatment[d] | Any DDRm | BRCA1/2 (n = 38) | ATM (n = 15) | CDK12 (n = 13) | MMR (n = 2) | Other (n = 6) | BRCA vs ATM | BRCA vs CDK12 | ATM vs CDK12 |
| Abiraterone (n = 27) | 29%<br>5/17 | 30%<br>3/10 | 0<br>0/4 | — | — | 67%<br>2/3 | .51 | NA[c] | NA[c] |
| Enzalutamide (n = 31) | 30%<br>9/30 | 42%<br>5/12 | 0<br>0/3 | 8%<br>1/12 | 100%<br>1/1 | 100%<br>2/2 | NA[c] | .16 | NA[c] |
| Docetaxel (n = 21) | 33%<br>4/12 | 17%<br>1/6 | 40%<br>2/5 | — | — | 100%<br>1/1 | .55 | NA[c] | NA[c] |
| Carboplatin-based (n = 7) | 57%<br>4/7 | 100%<br>3/3 | 0<br>0/2 | 100%<br>1/1 | 0<br>0/1 | — | NA[c] | NA[c] | NA[c] |
| Cabazitaxel (n = 8) | 33%<br>1/3 | 50%<br>1/2 | 0<br>0/1 | — | — | — | NA[c] | NA[c] | NA[c] |
| Olaparib (n = 5) | 20%<br>1/5 | 20%<br>1/5 | — | — | — | — | NA[c] | NA[c] | NA[c] |
| *P*[b] | .44 | .22 | NA[c] | NA[c] | NA[c] | NA[c] | | | |

Abbreviations: DDRm, DNA damage repair mutation; mCRPC, metastatic castration-resistant prostate cancer; MMR, mismatch repair; NA, not applicable; PSA50, decline in prostate-specific antigen ≥ 50% from baseline.

[a]Not shown: sipuleucel-T (n = 8), olaparib (n = 1), and itraconazole (n = 1).

[b]Comparison of PSA50 rates by treatment.

[c]The sample size was too small for statistical testing.

[d]Not shown: sipuleucel-T (n = 6), pembrolizumab (n = 4), clinical trial (n = 2), radium-223 (n = 1), and other checkpoint inhibitor (n = 1).

*P* values < 0.05 are considered statistically significant and are bolded.

**TABLE 3.** PSA50 Response Rates of Treatments Received for mCRPC in Patients With DDRm, Regardless of Treatment Line

| | | Mutation Group | | | | | *P* (Pairwise) | | |
|---|---|---|---|---|---|---|---|---|---|
| Treatment[a] | Any DDRm | BRCA1/2 | ATM | CDK12 | MMR | Other | BRCA vs ATM | BRCA vs CDK12 | ATM vs CDK12 |
| Abiraterone (n = 93) | 56% | 65% | 55% | 47% | 100% | 43% | .72 | .21 | .74 |
| | 47/84 | 20/31 | 6/11 | 15/32 | 3/3 | 3/7 | | | |
| Enzalutamide (n = 93) | 39% | 45% | 64% | 39% | 0 | 0 | .34 | .62 | .20 |
| | 36/92 | 15/33 | 9/14 | 12/31 | 0/1 | 0/13 | | | |
| Docetaxel (n = 58) | 46% | 61% | 33% | 33% | — | 60% | .24 | .18 | 1.00 |
| | 23/50 | 11/18 | 3/9 | 6/18 | | 3/5 | | | |
| Carboplatin-based (n = 34) | 55% | 79% | 14% | 38% | 0 | 100% | **.02** | .08 | .57 |
| | 18/33 | 11/14 | 1/7 | 3/8 | 0/1 | 3/3 | | | |
| Cabazitaxel (n = 30) | 22% | 33% | 50% | 14% | — | 0 | NA[c] | .55 | NA[c] |
| | 6/27 | 2/6 | 2/4 | 2/14 | | 0/3 | | | |
| Olaparib (n = 25) | 33% | 50% | 20% | 0 | — | 0 | .34 | NA[c] | NA[c] |
| | 8/24 | 7/14 | 1/5 | 0/3 | | 0/2 | | | |
| Pembrolizumab (n = 19) | 33% | 100% | 33% | 22% | 100% | 0 | NA[c] | NA[c] | NA[c] |
| | 6/18 | 1/1 | 1/3 | 2/9 | 2/2 | 0/3 | | | |
| Other checkpoint inhibitor[b] (n = 8) | 14% | 0 | 0 | 33% | — | — | NA[c] | NA[c] | NA[c] |
| | 1/7 | 0/2 | 0/2 | 1/3 | | | | | |

Abbreviations: DDRm, DNA damage repair mutation; mCRPC, metastatic castration-resistant prostate cancer; MMR, mismatch repair; NA, not applicable; PSA50, decline in prostate-specific antigen ≥ 50% from baseline.
[a]Not shown: sipuleucel-T (n = 16) and radium-223 (n = 11).
[b]Ipilimumab/nivolumab (n = 1) and unknown (n = 7).
[c]The sample size was too small for statistical testing.
*P* values < 0.05 are considered statistically significant and are bolded.

PSA50 rates were lower than first-line PSA50 rates for abiraterone (29% [5 of 17] vs 70% [37 of 53]; $P < .01$) and enzalutamide (30% [9 of 30] vs 65% [24 of 37]; $P < .01$). Responses in this second-line setting did not vary by treatment type or by DDRm. When we restricted the cohort to patients who received an ASI in the first-line setting, the second-line treatment PSA50 rate was highest in patients treated with carboplatin-based chemotherapy at 67% (4 of 6) versus 13% (3 of 24) for enzalutamide following abiraterone and 0% (0 of 8) for abiraterone following enzalutamide ($P = .01$ across therapies; Supporting Table 1).

PSA50 rates in the overall cohort, regardless of treatment line, are summarized in Table 3. The PSA50 rates for carboplatin-based chemotherapy differed by mutation type: they were higher in patients with BRCA1/2 mutations (79% [11 of 14]) than patients with *ATM* mutations (14% [1 of 7]; $P = .02$) or *CDK12* mutations (38% [3 of 8]; $P = .08$). The PSA50 rates for patients treated with docetaxel (46% [23 of 50]), olaparib (33% [8 of 24]), and pembrolizumab (33% [6 of 18]) did not vary by DDRm (Table 3).

### *Time to Next Treatment*

No differences in TNT were observed on the basis of the treatment type or sequence in the overall cohort or within mutation groups (Supporting Table 2 and Supporting Fig. 1). However, among patients who received first-line enzalutamide, those with *ATM* mutations had a longer TNT than those with BRCA1/2 or *CDK12* mutations (16 vs 4 and 8 months, respectively; $P < .01$). The times to next treatment for systemic therapies, regardless of the order in which they were received, are described in Supporting Table 3.

### *Overall Survival*

In the overall cohort, there was no association between first-line treatment type and OS (Fig. 1A). Among patients with BRCA1/2 mutations, the median OS was longest for those who received abiraterone (33 months) versus docetaxel (23 months) or enzalutamide (16 months; $P = .02$; Fig. 1B). Among patients with *ATM* mutations, the median OS was longest for those who received enzalutamide (not reached) or abiraterone (12 months) versus docetaxel (10 months; $P = .02$; Fig. 1C). In the multivariable model, there was no difference in OS based on the first-line treatment type or the DDRm type (Table 4). Only the presence of visceral metastases (hazard ratio for death, 2.1; 95% confidence interval, 1.1-4.2; $P = .03$) was independently associated with OS. Patients with MMR or other mutations were excluded from the model because of the small sample size. Among 67 patients who received a second-line therapy after a first-line ASI, those who received another ASI or carboplatin-based chemotherapy had a longer median OS (39 or 38 months, respectively) than those who received docetaxel

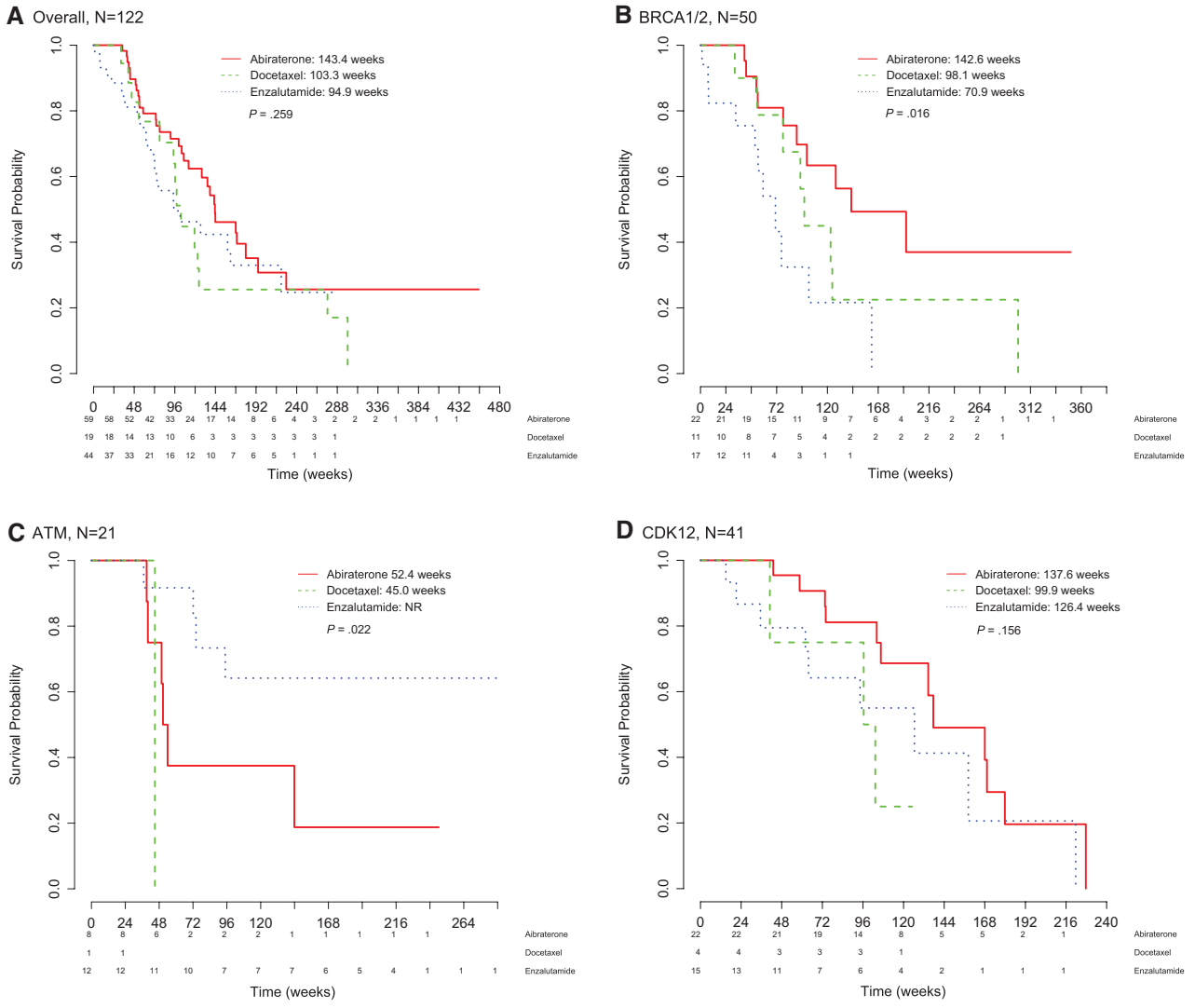


**Figure 1.** Overall survival from the start of first-line mCRPC therapy in patients with DDRm by treatment type and DDRm. Analyses of overall survival from the start of first-line therapy (abiraterone, enzalutamide, or docetaxel) in mCRPC, illustrated with Kaplan-Meier curves, demonstrated the following: (A) overall, no differences in survival by therapy type ($P = .26$); (B) BRCA1/2, longest survival in patients who received abiraterone ($P = .02$); (C) ATM, longest survival in patients who received enzalutamide ($P = .02$); and (D) CDK12, no differences in survival. Mismatch repair and other mutation groups are not shown because of the small sample size. DDRm indicates DNA damage repair mutation; mCRPC, metastatic castration-resistant prostate cancer.

(17 months) or cabazitaxel (11 months; $P < .01$ across therapies; Supporting Fig. 2).

## DISCUSSION

This multi-institutional, retrospective cohort of patients with mCRPC and DDRm highlights important differences in patient outcomes based on the mutation type and the treatment received. In the era of precision medicine, in which genomic findings are leveraged to develop tailored treatment plans, this analysis provides essential insights to inform clinical decision-making for patients with a lethal form of prostate cancer. Among patients treated with first-line abiraterone, those with *CDK12* mutations had lower PSA50 response rates than those with BRCA1/2 mutations. Tumors with BRCA1/2 mutations were also more sensitive to carboplatin-based chemotherapy than tumors with *ATM* mutations. A multivariable model of OS did not reveal significant differences based on the DDRm type or the type of first-line treatment received for mCRPC. Overall outcomes were worse for all therapies in the second-line mCRPC setting versus the first-line mCRPC setting, with the highest response rates and longest survival observed for second-line

**TABLE 4.** Multivariable Model of Overall Survival From the Start of First-Line mCRPC Therapy in Patients With DDRm

| | Hazard Ratio for Death | 95% Confidence Interval | *P* |
|---|---|---|---|
| Age at diagnosis | 1.01 | 0.98-1.05 | .55 |
| Presence of visceral metastases | 2.13 | 1.10-4.15 | **.03** |
| Metastases at diagnosis | 1.51 | 0.80-2.86 | .20 |
| PSA at diagnosis (log 10) | 0.86 | 0.55-1.36 | .53 |
| White ethnicity | 1.11 | 0.55-2.23 | .76 |
| First-line therapy | | | |
| Abiraterone | Reference | | .09 |
| Enzalutamide | 1.30 | 0.62-2.73 | |
| Docetaxel | 1.92 | 0.94-3.97 | |
| Carboplatin-based chemotherapy | 3.40 | 0.70-16.6 | |
| Other[a] | 0.34 | 0.08-1.46 | |
| Mutation[b] | | | |
| BRCA1/2 | Reference | | .97 |
| ATM | 0.88 | 0.33-2.35 | |
| CDK12 | 0.98 | 0.52-1.87 | |

Abbreviations: DDRm, DNA damage repair mutation; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.
[a]Sipuleucel-T (n = 8), olaparib (n = 1), and cabazitaxel (n = 1).
[b]Mismatch repair and other mutations are not included because of the small sample size.
*P* values < 0.05 are considered statistically significant and are bolded.

carboplatin-based chemotherapy in comparison with other standard therapies in the post-ASI setting.

CDK12 is a kinase that regulates transcription and genomic stability, and *CDK12* alterations are more prevalent in mCRPC (7%) than localized prostate cancer.[21] Our findings build on mounting evidence showing that *CDK12* mutations define an aggressive prostate cancer subtype with poor outcomes, such as a shorter time on the first-line ASI, as we and others have shown.[19,22-24] Although Nguyen et al[22] recently reported that patients with *CDK12* mutations had similar times on first-line ASIs as wild-type controls, our study and those of Antonarakis et al[23] and Schweizer et al[24] found similar rates of PSA50 response to first-line ASIs in these patients. No prospective data exist for therapies given in the first-line mCRPC setting compared by specific DDRm type. Exploratory analyses in the phase 3 PROfound study found that median progression-free survival on second-line ASIs was lowest in patients with *CDK12* mutations (2.2 months) in comparison with patients with BRCA1/2 (3.0 months) or *ATM* mutations (4.7 months).[25] The different PSA50 rates for abiraterone underscore the different genomic signatures identified in *CDK12*- and *BRCA2*-mutated tumors.[26-28] In particular, whole genome and transcriptome studies in patients with mCRPC after progression on an ASI have demonstrated that *CDK12* and *BRCA2* alterations are associated with distinct structural variations that modify key regulators of progression.[28,29] Unsupervised clustering analysis has demonstrated that *CDK12* mutations are highly associated with tandem duplications and that *BRCA2* inactivation is associated with deletions.[29] These differences, as well as *CDK12*'s role in other cellular processes such as transcription regulation, may lead to differential sensitivity and/or resistance to ASIs.[30] For example, *CDK12* is known to activate transduction pathways involved in ASI resistance, such as the PI3K-AKT and WNT–β-catenin pathways.[30,31] It is unclear why a similar difference was not identified for first-line enzalutamide in our cohort.

Moreover, we found that outcomes of standard therapies differed between patients with BRCA1/2 and *ATM* mutations. Patients with *ATM* mutations had longer TNTs for first-line enzalutamide than patients with BRCA1/2 mutations and lower PSA50 response rates with carboplatin-based chemotherapy given at any time. Response rates and TNTs for taxanes were similar in BRCA1/2- and *ATM*-mutant subgroups, and this reflected the nonselectivity of microtubule-targeting agents. It is recognized that *ATM*-mutated tumors have a distinct genomic signature in comparison with BRCA1/2-mutated tumors, and this may explain lower rates of response to PARP inhibitors[21,32] and perhaps differential outcomes of androgen receptor-targeted therapies and chemotherapy as well. Although inactivation of *BRCA2* may predict sensitivity to platinum chemotherapy in mCRPC,[18,20] sensitivity in *ATM*-mutated patients may be limited.[18]

Not surprisingly, response rates and TNTs were worse in the second-line mCRPC setting versus the first-line mCRPC setting. In particular, responses to the second ASI received upon progression on the first-line ASI were limited, and they were similar to responses in unselected patients.[33] However, we found higher responses and longer OS with second-line carboplatin-based chemotherapy after first-line ASIs in comparison with second-line ASIs or taxanes. This may be explained by the fact that most patients receiving carboplatin-based chemotherapy had *BRCA2* mutations (a group particularly sensitive to platinum-based chemotherapy), and this suggests that this therapy may be a viable second-line treatment option for this patient subgroup. The sample size precluded stratification by mutation type.

The multivariable model of OS from the start of first-line treatment did not reveal any differences based on first-line treatment type or DDRm type. It is challenging to make definitive conclusions about OS from this model because of the likely selection bias for particular

treatments based on disease and patient factors and the heterogeneity of subsequent therapies, which were likely tailored to the DDRm type.

The overall PSA50 response rate of 46% with docetaxel in this DDRm population is comparable to that of historical controls in an unselected mCRPC population (eg, 45% in the first-line mCRPC setting and 40% in the postenzalutamide setting).[34,35] Notably, the PSA50 response rate of 33% with pembrolizumab was higher than that in the phase 2 KEYNOTE-199 trial (6%).[36] This may be due to our smaller sample size and the inclusion of 2 patients with MMR mutations who responded to pembrolizumab. Further investigation of DDRm as a biomarker for checkpoint inhibitor response is warranted.

The limitations of the study include its retrospective nature, the small sample size of several subgroups (limiting the interpretation of negative results), and the heterogeneous patient population and methods of tissue collection. Strengths include the large number of patients with DDRm, the multicenter cohort, and the inclusion of somatic DDRm because most studies of DDRm have focused on germline variants. These aspects highlight the real-world perspective offered by this study. Notably, PARP inhibitors olaparib and rucaparib have recently become standard options for mCRPC harboring DDRm after an ASI (and after a taxane for rucaparib). Our largely pre–PARP inhibitor findings may not apply to the post–PARP inhibitor setting. Because ASIs are now standard of care in the castration-sensitive setting, ASI treatment outcomes based on specific DDRm types must also be investigated in the castration-sensitive setting.

In conclusion, the DDRm type was associated with divergent responses to standard therapies for mCRPC. These differences could help to inform oncologists' discussions of anticipated outcomes of standard therapies with patients with DDRm. Further functional and prospective DDRm biomarker studies are still needed, and our study also underscores the importance of reporting gene-level outcomes in clinical trials of DDRm when possible.

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## CONFLICT OF INTEREST DISCLOSURES

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**Daniel H. Kwon:** Conceptualization, data curation, formal analysis, methodology, writing–original draft, and writing–review and editing. **Jonathan Chou:** Data curation and writing–review and editing. **Steven M. Yip:** Data curation and writing–review and editing. **Melissa A. Reimers:** Data curation and writing–review and editing. **Li Zhang:** Formal analysis, methodology, and writing–review and editing. **Francis Wright:** Data curation. **Mallika S. Dhawan:** Resources and writing–review and editing. **Hala T. Borno:** Resources and writing–review and editing. **Arpita Desai:** Resources and writing–review and editing. **Rahul R. Aggarwal:** Resources and writing–review and editing. **Alexander W. Wyatt:** Writing–review and editing. **Eric J. Small:** Resources and writing–review and editing. **Ajjai S. Alva:** Resources and writing–review and editing. **Kim N. Chi:** Resources and writing–review and editing. **Felix Y. Feng:** Writing–review and editing. **Vadim S. Koshkin:** Conceptualization, resources, supervision, and writing–review and editing.

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