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Germline DNA-repair Gene Mutations and Outcomes in Men with Metastatic Castration-resistant Prostate Cancer Receiving First-line Abiraterone and Enzalutamide

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Abstract

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Background—Inherited DNA-repair gene mutations are more prevalent in men with advanced prostate cancer than previously thought, but their clinical implications are not fully understood.

Objective—To investigate the clinical significance of germline DNA-repair gene alterations in men with metastatic castration-resistant prostate cancer (mCRPC) receiving next-generation hormonal therapy (NHT), with a particular emphasis on *BRCA/ATM* mutations.

Design, setting, and participants—We interrogated 50 genes for pathogenic or likely pathogenic germline mutations using leukocyte DNA from 172 mCRPC patients beginning treatment with first-line NHT with abiraterone or enzalutamide.

Outcome measurements and statistical analysis—We assessed the impact of germline DNA-repair gene mutation status on 50% and 90% PSA responses, PSA progression-free survival (PSA-PFS), clinical/radiologic progression-free survival (PFS), and overall survival (OS). Survival outcomes were adjusted using propensity score-weighted multivariable Cox regression analyses.

Results and limitations—Among 172 mCRPC patients included, germline mutations (in any DNA-repair gene) were found in 12% (22/172) of men, and germline *BRCA/ATM* mutations specifically in 5% (9/172) of men. In unadjusted analyses, outcomes to first-line NHT were better in men with germline *BRCA/ATM* mutations (vs no mutations) with respect to PSA-PFS (hazard ratio [HR] 0.47; $p = 0.061$), PFS (HR 0.50; $p = 0.090$), and OS (HR 0.28; $p = 0.059$). In propensity score-weighted multivariable analyses, outcomes were superior in men with germline *BRCA/ATM* mutations with respect to PSA-PFS (HR 0.48, 95% confidence interval [CI] 0.25–0.92; $p = 0.027$), PFS (HR 0.52, 95% CI 0.28–0.98; $p = 0.044$), and OS (HR 0.34, 95% CI 0.12–0.99; $p = 0.048$), but not in men with non-*BRCA/ATM* germline mutations (all $p > 0.10$). These results require prospective validation, and our conclusions are limited by the small number of patients ($n = 9$) with *BRCA/ATM* mutations.

Conclusions—Outcomes to first-line NHT appear better in mCRPC patients harboring germline *BRCA/ATM* mutations (vs no mutations), but not for patients with other non-*BRCA/ATM* germline mutations.

Patient summary—Patients metastatic castration-resistant prostate cancer and harboring germline mutations in *BRCA1/2* and *ATM* benefit from treatment with abiraterone and enzalutamide.

Keywords

DNA repair; Germline; Mutation; Abiraterone; Enzalutamide

1. Introduction

While prostate cancer is known to be one of the most heritable human malignancies [1], the prevalence of high-penetrance cancer-susceptibility alleles in prostate cancer patients has only recently begun to be elucidated. To this end, current estimates suggest that inherited germline mutations in DNA-repair genes may be found in 7–12% of men with metastatic prostate cancer; approximately 60–75% of these involve the *BRCA1*, *BRCA2*, and *ATM* genes (absolute prevalence in metastatic prostate cancer of 5–8%) [2,3]. It is now known that

germline mutations in certain DNA-repair genes (particularly *BRCA2*) are associated with early-onset prostate cancers with higher Gleason grades and higher recurrence rates following definitive local therapy [4]. In addition, our group has recently shown that germline *BRCA2* and *ATM* mutations distinguish lethal from indolent prostate cancers, and are associated with shorter survival times and earlier age at death [5].

What is less clear is the prognostic significance of germline DNA-repair gene alterations in the context of systemic therapies for metastatic castration-resistant prostate cancer (mCRPC) [6]. Early reports suggest that mCRPC patients with germline *BRCA2* mutations may respond more favorably to poly ADP-ribose polymerase (PARP) inhibitors as well as platinum-based chemotherapies [7,8], although these observations require confirmation. In addition, a recent publication suggested that patients with germline DNA-repair defects demonstrate poorer responses to first-line androgen deprivation therapy as well as next-generation hormonal therapies (abiraterone, enzalutamide) compared to those without germline mutations [3]. By contrast, a separate study evaluating germline and/or somatic DNA-repair mutations found that patients carrying mutations had superior responses to first-line abiraterone treatment than patients with the wild-type counterparts [9]. Therefore, the clinical impact of germline DNA-repair alterations in mCRPC patients receiving next-generation hormonal therapy remains uncertain [10].

To shed additional light on this issue, we conducted an analysis investigating the clinical significance of germline DNA-repair gene mutations on the efficacy of next-generation hormonal therapy (NHT) among 172 mCRPC patients beginning treatment with first-line abiraterone or enzalutamide. Given the role of the androgen receptor (AR) in mediating and promoting DNA repair functions [11,12], we hypothesized that AR-targeted therapies would induce a “synthetic lethality” in patients with an inherited DNA repair–deficient state, resulting in superior responses to abiraterone and enzalutamide in men harboring germline DNA-repair gene mutations compared to those without germline mutations. We further hypothesized that this difference in outcomes would be driven primarily by mutations in *BRCA1/BRCA2/ATM* rather than other DNA-repair gene alterations, given the predominant role played by these genes in terms of both disease susceptibility and prognosis.

2. Patients and methods

2.1. Patients

This study included 172 consecutive men with mCRPC who were beginning NHT using enzalutamide or abiraterone: 115 men were prospectively enrolled at the time of first-line NHT, and 57 men were prospectively enrolled at the time of second-line NHT (requiring retrospective first-line NHT data). Patients were not selected based on prior knowledge of germline/somatic mutations, and thus this sample was not artificially enriched for DNA-repair alterations. Patients had to have histologically confirmed prostate adenocarcinoma, progressive disease despite “castration levels” of serum testosterone (<50 ng/dl), and radiographic metastases on computed tomography (CT) or technetium-99 bone scans. Patients had to have three or more rising serum prostate-specific antigen (PSA) values measured 2 wk apart, consistent with Prostate Cancer Working Group (PCWG2) guidelines [13]. Patients were excluded if they received additional concurrent anticancer therapies.

Prior taxane chemotherapy was permitted, as was previous treatment with first-generation hormonal agents (eg, flutamide, bicalutamide, ketoconazole). This study was approved by the Johns Hopkins University institutional review board, and all patients provided written informed consent before providing blood samples.

2.2. Study design

This was an observational study involving 172 men with mCRPC prospectively enrolled at the time of starting abiraterone or enzalutamide treatment as first-line ($n = 115$) or second-line ($n = 57$) NHT (for the latter, clinical outcomes data were collected retrospectively). We evaluated the presence or absence of germline DNA-repair gene mutations in general, as well as *BRCA1/BRCA2/ATM* mutations specifically, to predict the clinical benefit from first-line NHT (abiraterone or enzalutamide). Patients were asked to provide peripheral blood samples for germline DNA analysis. Enzalutamide was given at 160 mg daily, and abiraterone was given at 1000 mg daily (with prednisone 5 mg twice daily). Clinical outcomes to first-line NHT were collected prospectively for those starting first-line NHT ($n = 115$) and retrospectively for those starting second-line NHT ($n = 57$). In both groups, patients generally had PSA measurements every 1–2 mo, as well as CT (chest/abdomen/pelvis) and technetium-99 bone scans every 2–4 mo. Therapy with enzalutamide or abiraterone was generally continued until PSA progression or clinical/radiographic progression, or unmanageable drug-related toxicity.

2.3. Detection of germline DNA-repair gene mutations

Inherited gene mutations were examined using whole-exome sequencing (WES) of germline DNA extracted from leukocytes (Supplementary material). For the purposes of this study, we focused on the exonic regions of 50 genes, most of which are established DNA-repair genes (except for *EPCAM* and *CENPQ*): *ATM*, *ATR*, *BAP1*, *BARD1*, *BLM*, *BRAP*, *BRCA1*, *BRCA2*, *BRIPI*, *CDH1*, *CDK12*, *CENPQ*, *CHEK1*, *CHEK2*, *EPCAM1*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC6*, *FAM175A*, *FAM175B*, *FANCA*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *GEN1*, *HDAC2*, *MLH1*, *MLH3*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIF1*, *PMS2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*, *RDM1*, *TP53*, and *XRCC2*. Only protein-truncating alterations (nonsense/stop-gains, frameshift insertions and deletions, and donor and acceptor splice-site mutations) were coded as pathogenic or likely pathogenic for the current analysis, while missense and other variants of undetermined significance or alterations with lower levels of evidence were excluded, unless specifically designated as pathogenic in ClinVar [14]. We made mutation calls for these genes for a total of 190 germline DNA samples processed for WES. Eighteen duplicated samples (blinded in the data generation process) were included for quality control, leaving 172 unique patient samples for analysis after unblinding.

2.4. Outcome measures

The primary endpoint was clinical/radiographic progression-free survival (PFS); progression was defined as symptomatic progression (worsening disease-related symptoms or new cancer-related complications), or radiologic progression (on CT scans, 20% enlargement in sum diameter of target lesions according to RECIST criteria [15]; on bone scans, 2 new bone lesions not due to flare), or death, whichever occurred first [13]. Secondary endpoints

included PSA response rate (< 50% and < 90% PSA declines), PSA-PFS, and overall survival (OS). The duration of first-line androgen deprivation therapy (ADT) was also captured. PSA response was defined as the proportion of patients with a < 50% or < 90% PSA decline from baseline at any time point after therapy (and maintained for < 3 wk); the best PSA response (maximal percentage decrease from baseline) was determined, as was the PSA response at 12 wk after first-line NHT (19 patients were excluded because of progression in <12 wk following treatment initiation). PSA progression was defined as a > 25% increase in PSA from nadir (and by > 2 ng/ml), requiring confirmation > 3 wk later (PCWG2 criteria) [13]. OS was defined as the interval from enrolment to death from any cause. For all time-to-event endpoints, the start time was defined as the date of the first dose of abiraterone/enzalutamide. Censoring took place on the date of the last documented PSA value that did not show PSA progression for the PSA-PFS endpoint, on the date of the last known negative CT and bone scans for the PFS endpoint, and on the last date that the patient was confirmed to be alive for the OS endpoint. The last date of follow-up (database lock) was May 26, 2017. All outcome measures were predefined, with the exception of PSA response at 12 wk, which was a post hoc analysis.

2.5. Statistical analyses

This was an observational study and the sample size was not prospectively defined. Statistical analyses were performed on the cohort as a whole ($n = 172$), combining prospectively and retrospectively collected outcomes for first-line NHT. The primary analysis involved comparing clinical outcomes in patients with and without (any) germline DNA-repair gene mutations. A secondary prespecified analysis involved comparing outcomes in patients with and without *BRCA1/BRCA2/ATM* mutations specifically (denoted as *BRCA/ATM*). PSA response rates were compared using Fisher's exact test. Time-to-event outcomes (ADT duration, PFS, PSA-PFS, and OS) were evaluated using Kaplan-Meier analysis, and survival time differences were compared using the log-rank test. Univariate and propensity score-weighted multivariable Cox regression models were used to evaluate the primary and secondary time-to-event endpoints.

Because the number of patients with mutations was small with few events, a conventional multivariable model including many baseline covariates might have led to unreliable results, with bias and increased variability in the effect estimate. In our propensity score-weighted multivariable Cox regression analysis, the propensity score represented the probability of having a DNA-repair mutation, and was estimated for each patient according to boosted logistic regression in which the indicator of whether a patient had a DNA-repair mutation was the dependent variable and the baseline characteristics were entered as independent variables. Boosted regression allows for a flexible and nonlinear relationship between the propensity score and a large number of covariates. The baseline variables included in propensity score estimates were treatment (abiraterone or enzalutamide), age, tumor stage, presence/absence of bone pain, presence/absence of bone metastases, Eastern Cooperative Oncology Group (ECOG) performance status, baseline alkaline phosphatase level, and presence/absence of visceral metastases. To assess the prognostic effect of germline DNA-repair mutations, we performed weighted multivariable Cox regression analysis, adjusting for age, baseline PSA, number of prior hormonal therapies, Gleason score at diagnosis, and

prior chemotherapy, and stratified for treatment, in three prespecified categories: (1) presence of *BRCA/ATM* mutations; (2) presence of other (non-*BRCA/ATM*) mutations; and (3) no germline mutations. All statistical tests were two-sided, and *p* values were not corrected for multiple comparisons. Statistical analyses were performed using R v.3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients and germline DNA-repair status

A total of 172 patients with germline DNA available and who began first-line NHT treatment between October 2011 and December 2015 were included in this analysis. Of these, 22/172 (12.8%) had a germline DNA-repair gene mutation (any), and 9/172 (5.2%) had a germline *BRCA/ATM* mutation. The median follow-up for OS among the alive patients was 34.5 mo (42.6 and 34.4 mo for those with and without *BRCA/ATM* mutations, respectively). Table 1 shows the distribution and types of DNA-repair mutations identified in this patient population. Baseline patient characteristics for the whole cohort, and separately for men with and without (any) germline DNA-repair gene mutations, are summarized in Table 2. As shown, patients with DNA-repair gene mutations were younger at the time of NHT initiation (median age 64 vs 70 yr; $p < 0.001$), had a higher prevalence of T3/T4 disease at diagnosis (79% vs 44%; $p = 0.006$), and had better performance status (ECOG 0, 95% vs 68%; $p = 0.014$). Similarly, when comparing baseline characteristics for men with and without germline *BRCA/ATM* mutations specifically (Supplementary Table 1), men with *BRCA/ATM* mutations were younger (median age 59 vs 70 yr; $p = 0.006$) and had a higher prevalence of T3/T4 disease (100% vs 46%; $p = 0.006$).

3.2. PSA responses

PSA response rates to first-line NHT treatment were higher in men with germline DNA-repair mutations compared to patients with the wild-type counterparts. PSA reductions 50% were observed in 77% and 59% of men with and without (any) DNA-repair gene mutation ($p = 0.158$), and PSA reductions 90% were observed in 59% and 26% of such men ($p = 0.003$), respectively (Fig. 1A). Similarly, PSA reductions 50% were observed in 78% and 61% of men with and without *BRCA/ATM* mutations specifically ($p = 0.485$), and PSA reductions 90% were observed in 78% and 28% of such men ($p = 0.004$), respectively (Fig. 2A). Among the 153 patients with evaluable PSA data at 12 wk following first-line NHT, PSA reductions 50% were observed in 100% and 66% of men with and without *BRCA/ATM* mutations specifically ($p = 0.097$), and PSA reductions 90% were observed in 100% and 30% of such men ($p < 0.001$), respectively (Supplementary Fig. 1). The specific mutation status for each of the mutation-positive patients is annotated in Supplementary Figure 2.

3.3. PSA-PFS

PSA-PFS to first-line NHT treatment (abiraterone or enzalutamide) was greater in patients with versus without (any) germline DNA-repair mutations (median 10.2 vs 7.6 mo; hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.39–1.04; $p = 0.070$; Fig. 1B). PSA-PFS was also greater in patients with versus without *BRCA/ATM* mutations specifically (median 12.7

vs 8.4 mo; HR 0.47, 95% CI 0.21–1.06; $p = 0.061$; Fig. 2B). Supplementary Figure 3A shows PSA-PFS estimates according to the three mutational groups (*BRCA/ATM* mutation vs other mutation vs no mutation); the results suggest that *BRCA/ATM* carriers have the best prognosis. In the propensity score–weighted multivariable model, the presence of *BRCA/ATM* mutations (HR 0.48, 95% CI 0.25–0.92; $p = 0.027$), but not other non-*BRCA/ATM* mutations (HR 0.94, 95% CI 0.61–1.43; $p = 0.764$), was independently associated with longer PSA-PFS (Table 3). Additional factors associated with PSA-PFS in this model were Gleason score ($p = 0.018$) and presence/absence of prior chemotherapy ($p < 0.001$).

3.4. PFS

Clinical/radiologic PFS to first-line NHT treatment was the primary endpoint in our predefined analysis plan because of its clinical significance. PFS was longer in patients with versus without (any) germline DNA-repair mutations (median 13.3 vs 10.3 mo; HR 0.67, 95% CI 0.41–1.09; $p = 0.107$; Fig. 1C). PFS was also longer in patients with versus without *BRCA/ATM* mutations specifically (median 15.2 vs 10.8 mo; HR 0.50, 95% CI 0.22–1.13; $p = 0.090$; Fig. 2C). Supplementary Figure 3B shows PFS estimates according to the three mutational groups; the results suggest that *BRCA/ATM* carriers have the best prognosis. In the propensity score–weighted multivariable model, the presence of *BRCA/ATM* mutations (HR 0.52, 95% CI 0.28–0.98; $p = 0.044$), but not other non-*BRCA/ATM* mutations (HR 0.93, 95% CI 0.61–1.41; $p = 0.718$), was independently associated with greater PFS (Table 3). Additional factors associated with PFS in this model were Gleason score ($p = 0.020$) and presence/absence of prior chemotherapy ($p < 0.001$).

3.5. OS

All deaths in this study were due to prostate cancer. Overall survival to first-line NHT was greater in patients with versus without (any) germline DNA-repair gene mutations (median 41.1 vs 28.3 mo; HR 0.58, 95% CI 0.30–1.11; $p = 0.097$; Fig. 1D). OS was also greater in patients with versus without *BRCA/ATM* mutations specifically (median not reached vs 28.6 mo; HR 0.28, 95% CI 0.07–1.15; $p = 0.059$; Fig. 2D). Supplementary Figure 3C shows OS estimates according to the three mutational groups; the results suggest that *BRCA/ATM* carriers have the best prognosis. In the propensity score–weighted multivariable model, the presence of *BRCA/ATM* mutations (HR 0.34, 95% CI 0.12–0.99; $p = 0.048$), but not other non-*BRCA/ATM* mutations (HR 1.08, 95% CI 0.64–1.83; $p = 0.785$), was independently associated with longer OS (Table 3). Additional factors associated with OS in this model were baseline PSA level ($p = 0.009$), Gleason score ($p = 0.020$), and presence/absence of prior chemotherapy ($p = 0.002$).

4. Discussion

While inherited DNA-repair gene mutations are relatively prevalent in patients with mCRPC [2], their clinical significance in the setting of NHT (abiraterone and enzalutamide) is uncertain [10]. Here, we report that the presence of particular germline mutations (in *BRCA1*, *BRCA2*, *ATM*), but not mutations in other DNA-repair genes, is associated with better PSA response rates (90% declines) as well as longer PSA-PFS, radiographic PFS,

and OS. Importantly, we report statistically significant HRs (Table 3) for PSA-PFS (HR 0.48), PFS (HR 0.52), and OS (HR 0.34), all of which have potential clinical significance, specifically in this predefined group of patients carrying germline mutations in *BRCA1*, *BRCA2*, or *ATM*. We decided to focus our attention on these genes for several reasons: (1) these were the three genes initially identified in men with mCRPC to have germline loss-of-function mutations in the seminal study by Robinson et al [16]; (2) extensive studies in breast and ovarian cancers established *BRCA1* and *BRCA2* as the most critical functional components of the homologous recombination repair pathway, which, upon inactivation by mutation, leads to sensitivity to PARP inhibitors; and (3) *BRCA2* and *ATM* are the most commonly mutated DNA-repair genes in mCRPC.

Our data appear to be in conflict with another recent publication suggesting that mCRPC patients with germline DNA-repair gene defects may have inferior responses to first-line ADT and first-line NHT compared to patients with the wild-type counterparts [3]. However, our findings appear more concordant with another recent study suggesting that men with germline and/or somatic DNA-repair gene alterations may have a better response to first-line abiraterone treatment (with or without concurrent use of a PARP inhibitor) than those without mutations [9]. This latter study, together with our current data, supports the hypothesis that the androgen receptor (AR) may promote DNA repair, particularly DNA-PK-dependent repair [12], and that treatment with more effective AR-targeted therapies in this setting may induce a “synthetic lethality” in patients by augmenting an inherited DNA repair-deficient state, resulting in superior responses to abiraterone and enzalutamide in men harboring germline DNA-repair mutations. However, these results are only hypothesis-generating, and further prospective confirmation is needed before firm conclusions are drawn.

In order to better understand the relative contributions to prognosis of different DNA-repair gene alterations, and consistent with published data that *BRCA1/BRCA2/ATM* mutations may have different clinical implications from other mutations [17], we separately examined the effect of these three genes to determine whether these might be driving the clinical associations observed. To this end, the favorable impact of DNA-repair gene mutations on first-line NHT outcomes was further enhanced when considering these genes separately (rather than together with other DNA-repair genes). In fact, only the presence of *BRCA1/BRCA2/ATM* mutations (and not other non-*BRCA/ATM* mutations) was independently prognostic for all time-to-event outcomes in multivariable Cox regression models. These data suggest that pathogenic germline mutations in these three genes drive the more favorable prognosis to first-line NHT treatment. This raises the notion that perhaps not all DNA-repair mutations are created equal [17], though confirmatory studies will be required to discern the potential differences among different DNA-repair mutations in prognosis or response to systemic therapy.

What might have caused the apparent divergent results observed in this study and that by Annala et al [3]? A key difference is that our study included consecutive NHT-treated patients with germline data available from a single cohort, while Annala et al included four different cohorts, two of which were enriched for patients with poor prognosis. Therefore, it is likely that the patients included by Annala et al had a generally higher disease burden and

therefore inferior outcomes overall. Indeed, a large fraction of the poor responses in mutation carriers reported by Annala et al had indicators of high disease burden, including the presence of very high circulating-tumor DNA (ctDNA) content and prior treatment with chemotherapy. Moreover, limited patient numbers in both studies (particularly mutation-positive patients), along with the extensive heterogeneity of disease presentation and prior treatments, could have played a role in the seemingly disparate results observed. Clearly, additional prospective data are needed to shed further light on this issue and to resolve this debate.

Our study has several shortcomings. The greatest limitation is that this was not entirely a prospective study, and included a subset of patients with retrospectively collected first-line NHT data. As a result, this cohort represents a “convenience sample” and the sample size was not prospectively determined using hypothesis testing. In addition, the trends observed between mutational status and outcomes were dependent on only nine patients with germline *BRCA/ATM* alterations, and may be unreliable. A second limitation is that we lacked concurrent tumor biopsies or ctDNA samples from most patients, so we were unable to determine what proportion of patients with a germline mutation had loss of heterozygosity (LOH) of the second allele. To this end, we were unable to determine whether monoallelic DNA-repair gene alterations may have had a different prognosis compared to biallelic alterations, or to determine whether some genes (eg, *BRCA2*) were more often associated with somatic LOH compared to other genes. We were also unable to assess whether germline versus somatic mutations have differential effects on prognosis. Third, our mutational analysis probably did not detect all inactivating mutations since large deletions, insertions, and other complex structural rearrangements were not assessed. While such mutations have been investigated for mismatch-repair genes [18], the contribution of such alterations to the overall DNA-repair mutation burden in mCRPC is unknown.

5. Conclusions

In conclusion, our study suggests that mCRPC patients with germline DNA-repair gene alterations have superior clinical outcomes to first-line NHT treatment (abiraterone, enzalutamide), and that this improvement in prognosis is likely driven by mutations in *BRCA1/BRCA2/ATM* rather than other DNA-repair genes. However, owing to conflicting results in the literature, these findings will require prospective validation in larger patient cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

(A) Waterfall plot showing best PSA response in patients with and without (any) germline mutations. (B–D) Kaplan-Meier curves showing (B) PSA-PFS, (C) PFS, and (D) OS in patients with and without (any) germline mutations. Kaplan-Meier curves were truncated at 24 mo for PSA-PFS and PFS and at 48 mo for OS. PSA = prostate-specific antigen; PFS = progression-free survival; OS = overall survival.

Fig. 2.

(A) Waterfall plot showing best PSA response in patients with and without germline *BRCA/ATM* mutations. (B–D) Kaplan-Meier curves showing (B) PSA-PFS, (C) PFS, and (D) OS in patients with and without germline *BRCA/ATM* mutations. Kaplan-Meier curves were truncated at 24 mo for PSA-PFS and PFS and at 48 mo for OS. PSA = prostate-specific antigen; PFS = progression-free survival; OS = overall survival.

Table 1List of pathogenic and likely pathogenic germline mutations ($n = 22$)

Sample ID	Mutated gene	Chr	Start	End	Ref.	Alt.	Function	NC change	AA change
211A	<i>ATM</i>	11	108158439	108158439	C	A	Stop-gain	c.C4106A	p.S1369X
64A	<i>ATM</i>	11	108178655	108178655	–	A	Frameshift insertion	c.5707dupA	p.D1902*fs
68A	<i>ATM</i>	11	108188128	108188128	T	–	Frameshift deletion	c.6227delT	p.I2076*fs
29A	<i>ATR</i>	3	142272241	142272241	C	T	Splicing	c.2634-1G>A	N/A
109A	<i>BLM</i>	15	91337589	91337589	T	–	Splicing	c.3210+2delT	N/A
27B	<i>BLM</i>	15	91290721	91290721	G	A	Splicing	c.98+1G>A	N/A
249B	<i>BRCA1</i>	17	41243655	41243655	G	T	Stop-gain	c.C3893A	p.S1298X
106A	<i>BRCA2</i>	13	32914438	32914438	T	–	Frameshift deletion	c.5946delT	p.S1982*fs
200A	<i>BRCA2</i>	13	32954009	32954009	C	T	Stop-gain	c.C9076T	p.Q3026X
288A	<i>BRCA2</i>	13	32914438	32914438	T	–	Frameshift deletion	c.5946delT	p.S1982*fs
329A	<i>BRCA2</i>	13	32954009	32954009	C	T	Missense ^a	c.C9285T	p.D3095E
374A	<i>BRCA2</i>	13	32914438	32914438	T	–	Frameshift deletion	c.5946delT	p.S1982*fs
194A	<i>CHEK2</i>	22	29121326	29121326	T	C	Missense ^a	c.A349G	p.R117G
48A	<i>FAM175B</i>	10	126523291	126523291	–	C	Frameshift insertion	c.1000dupC	p.R333*fs
13A	<i>FANCC</i>	9	97933360	97933360	C	T	Splicing	c.521+1G>A	N/A
86A	<i>FANCG</i>	9	35077335	35077335	A	C	Stop-gain	c.T572G	p.L191X
98A	<i>FANCG</i>	9	35079166	35079166	–	C	Frameshift insertion	c.156dupG	p.L53*fs
128A	<i>FANCI</i>	15	89837194	89837194	A	T	Stop-gain	c.A2422T	p.K808X
11A	<i>FANCL</i>	2	58386928	58386928	–	TAAT	Frameshift insertion	c.1114_1115insATTA	p.T372*fs
76A	<i>FANCL</i>	2	58386928	58386928	–	TAAT	Frameshift insertion	c.1114_1115insATTA	p.T372*fs
265A	<i>RAD51</i>	15	41023301	41023301	C	T	Stop-gain	c.C823T	p.R275X
112A	<i>RDM1</i>	17	34245430	34245430	C	T	Stop-gain	c.G771A	p.W257X

chr = chromosome; Ref. = reference; Alt. = alternative; N/A = not applicable.

^aDesignated as pathogenic in ClinVar.

Table 2

Baseline characteristics for patients with and without any germline mutations

Baseline characteristic	No GM (<i>n</i> = 150)	Any GM (<i>n</i> = 22)	<i>p</i> value *
Median age (yr)	70	64	<0.001
Race (%)			1.000
Non-White	12.7	13.6	
White	87.3	86.4	
Mean time since diagnosis (yr)	7.4	6.3	0.711
Gleason sum ≥ 8 at diagnosis (%)	65.2	68.2	1.000
Type of primary local therapy (%)			0.581
Surgery only	20.4	31.8	
Radiation only	28.6	27.3	
Both	21.8	22.7	
None	29.3	18.2	
T stage at diagnosis (%)			0.006
T1/T2	55.8	21.1	
T3/T4	44.2	78.9	
M1 disease at diagnosis (%)	26.1	19.0	0.852
Median no. of prior hormonal therapies (<i>n</i>)	2	2	0.795
Median duration of first-line ADT (yr)	1.5	2.1	0.458
Prior chemotherapy (%)	23.3	22.7	1.000
Bone metastases present (%)	89.7	80.0	0.254
Visceral metastases present (%)	20.8	38.9	0.130
ECOG performance status ≥ 1 (%)	32.1	5.3	0.014
Presence of pain (%)	37.1	47.4	0.578
Median baseline PSA (ng/ml)	22.6	22.9	0.782
Median baseline alkaline phosphatase (U/L)	89.5	84.0	0.542

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; GM = germline mutation.

* *p* values are for Fisher's exact test and the Wilcoxon Mann-Whitney *U* test for categorical and continuous variables, respectively.

Table 3

Propensity score-weighted multivariable Cox model (stratified by treatment) for PSA progression-free survival, clinical/radiologic progression-free survival, and overall survival

Model and variable	HR	(95% CI)	p value
PSA progression-free survival			
Germline mutation status			
No mutation	1.00	(reference)	
Other mutation (excluding <i>ATM/BRCA</i>)	0.94	(0.61–1.43)	0.764
<i>ATM</i> or <i>BRCA1/2</i> mutation	0.48	(0.25–0.92)	0.027
Age	1.01	(0.98–1.03)	0.681
Baseline PSA	1.00	(1.00–1.01)	0.294
Number of prior hormonal therapies	1.09	(0.88–1.34)	0.422
Gleason sum at diagnosis			
5–7	1.00	(reference)	
8	1.49	(1.07–2.06)	0.018
Prior chemotherapy			
No	1.00	(reference)	
Yes	2.10	(1.44–3.05)	<0.001
Progression-free survival			
Germline mutation status			
No mutation	1.00	(reference)	
Other mutation (excluding <i>ATM/BRCA</i>)	0.93	(0.61–1.41)	0.718
<i>ATM</i> or <i>BRCA1/2</i> mutation	0.52	(0.28–0.98)	0.044
Age	1.00	(0.98–1.03)	0.726
Baseline PSA	1.00	(1.00–1.01)	0.116
Number of prior hormonal therapies	1.10	(0.88–1.37)	0.402
Gleason sum at diagnosis			
5–7	1.00	(reference)	
8	1.48	(1.06–2.06)	0.02
Prior chemotherapy			
No	1.00	(reference)	
Yes	2.05	(1.41–2.96)	<0.001
Overall survival			
Germline mutation status			
No mutation	1.00	(reference)	
Other mutation (excluding <i>ATM/BRCA</i>)	1.08	(0.64–1.83)	0.785
<i>ATM</i> or <i>BRCA1/2</i> mutation	0.34	(0.12–0.99)	0.048
Age	1.03	(1.00–1.05)	0.068
Baseline PSA	1.00	(1.00–1.01)	0.009
Number of prior hormonal therapies	0.80	(0.61–1.05)	0.113
Gleason sum at diagnosis			
5–7	1.00	(reference)	

Model and variable	HR	(95% CI)	p value
8	1.66	(1.08–2.54)	0.02
Prior chemotherapy			
No	1.00	(reference)	
Yes	1.93	(1.28–2.93)	0.002

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.

To determine whether and how germline DNA-repair gene mutations influence clinical outcomes to abiraterone or enzalutamide in patients with castration-resistant prostate cancer (CRPC), we performed germline genotyping for 50 DNA-repair genes using blood samples from 172 patients with CRPC beginning first-line systemic therapy with abiraterone or enzalutamide. We discovered that the presence of germline DNA-repair gene defects (particularly mutations in the *BRCA1/2* and *ATM* genes) were associated with better outcomes to abiraterone and enzalutamide.