HHS Public Access

Author manuscript

Prostate. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

Prostate. 2021 December ; 81(16): 1382–1389. doi:10.1002/pros.24236.

Efficacy of systemic therapies in men with metastatic castration resistant prostate cancer harboring germline *ATM* versus *BRCA2* mutations

Alexandra O. Sokolova, MD[1], **Catherine H. Marshall, MD, MPH**[4], **Rebeca Lozano, MD**[5,6], **Roman Gulati, MS**[3], **Elisa M. Ledet, PhD**[7], **Navonil De Sarkar, PhD**[3], **Petros Grivas, MD, PhD**[2,3], **Celestia S. Higano, MD**[2,3], **Bruce Montgomery, MD**[2], **Peter S. Nelson, MD**[2,3], **David Olmos, MD, PhD**[5,6], **Vadim Sokolov, PhD**[7], **Michael T. Schweizer, MD**[2,3], **Todd A. Yezefski, MD**[2], **Evan Y. Yu, MD**[2,3], **Channing J. Paller, MD**[4], **Oliver Sartor, MD**[8], **Elena Castro, MD PhD**[5,6,9], **Emmanuel S. Antonarakis, MD**[4], **Heather H. Cheng, MD, PhD**[2,3]

[1]Oregon Health Science University, Division of Medical Oncology, Portland, OR, USA

[2] University of Washington, Department of Medicine, Division of Medical Oncology, Seattle, WA, USA

[3] Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[4] Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA

[5] Prostate Cancer Clinical Research Unit, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

[6] Genitourinary Cancer Traslational Research Group, Instituto de Investigación Biomédica de Málaga, Malaga, Spain

[7] George Mason University, Fairfax, VA, USA

[8] Tulane University School of Medicine, New Orleans, LA, USA

[9] Hospital Universitario Virgen de la Victoria y Regional de Málaga, Spain

Abstract

Background: Among men with metastatic prostate cancer, about 10% have germline alterations in DNA damage response genes. Most studies have examined *BRCA2* alone or an aggregate of *BRCA1/2* and *ATM.* Emerging data suggest that *ATM* mutations may have distinct biology and warrant individual evaluation. The objective of this study is to determine whether response to prostate cancer systemic therapies differs between men with germline mutations in *ATM (gATM)* and *BRCA2 (gBRCA2).*

Corresponding Author: Heather H. Cheng, MD, PhD, 1144 Eastlake Ave E, Seattle, WA 98109-1023 U.S.A. Phone: (206) 606-1406, hhcheng@uw.edu.

Ethics approval statement: This study was approved by IRB board at each participating site.

Methods: This is an international multicenter retrospective matched cohort study of men with prostate cancer harboring g*ATM* or g*BRCA2*. PSA_{50} response (≥50% decline in prostate-specific antigen) was compared using Fisher's exact test.

Results and Limitations: The study included 45 g*ATM* and 45 g*BRCA2* patients, matched on stage and year of germline testing. Patients with g*ATM* and g*BRCA2* had similar age, Gleason grade, and PSA at diagnosis. We did not observe differences in PSA_{50} responses to abiraterone, enzalutamide, or docetaxel in metastatic castration resistant prostate cancer between the two groups; however, 0/7 with g*ATM* and 12/14 with g*BRCA2* achieved PSA_{50} response to PARPi ($p<0.001$). Median (95% CI) overall survival from diagnosis to death was 10.9 years (9.5-not reached) vs. 9.9 years (7.1-not reached, $p=0.07$) for the g*ATM* and g*BRCA2* cohorts, respectively. Limitations include the retrospective design and lack of mutation zygosity data.

Conclusions: Conventional therapies can be effective in g*ATM* carriers and should be considered before PARPi, which shows limited efficacy in this group. Men with g*ATM* mutations warrant prioritization for novel treatment strategies.

Keywords

ATM; *BRCA2*; germline; homologous recombination deficiency; PARPi; platinum; abiraterone; enzalutamide; docetaxel

Introduction

Approximately 10% of men with metastatic prostate cancer have germline (inherited) DNA damage response (gDDR) gene alterations. *BRCA2* is a homologous recombination (HR) gene and is the most frequent pathogenic germline alteration in advanced prostate cancer (3–5%), followed by *ATM* (1.6–2%) and *BRCA1* (0.8–1.3%).[1–3] Several studies have shown that germline *BRCA2* mutations (g*BRCA2*) are associated with poor prognosis and worse prostate cancer outcomes and/or increased genomic instability.[3–8]

Castro, *et al.*, reported that at diagnosis, patients with prostate cancer and g*BRCA1/2* mutations are more likely to have Gleason Grade Group ≥4 disease, T3/4 stage, nodal involvement, metastases, and shorter cancer-specific survival compared to non-carriers.[6] The IMPACT study showed that g*BRCA2* mutation carriers have a higher incidence of prostate cancer and are more likely to be diagnosed at a younger age and have clinically significant disease compared to non-carriers, whereas no difference in age or tumor characteristics was detected between g*BRCA1*- and non-carriers.[5] Na, *et al.*, reported that the combined g*BRCA1/2* and germline *ATM* (g*ATM*) mutation rate was higher in lethal prostate cancer compared to localized disease.[9] However, features of tumors and treatment responses linked to g*ATM* mutations as a separate cohort are not characterized.

g*ATM* mutation carriers have not been well-characterized despite *ATM* being the second most frequently observed DNA damage response gene alteration in metastatic prostate cancer. Several retrospective and prospective studies have reported that *ATM*-deficient prostate tumors may have attenuated response to poly-ADP-ribose polymerase inhibitors (PARPi) and platinum chemotherapy.[7,10–15] Preliminary results of the phase II TRITON2 study demonstrated radiographic response to PARPi rucaparib in 51% (50/98) of men with

BRCA1/2 and only 4% (2/49) of men with *ATM* mutations.[11,16] The U.S. Food and Drug Administration (FDA) granted rucaparib an accelerated approval for men with metastatic castration resistant prostate cancer (mCRPC) and *BRCA1/2* mutations who were previously treated with docetaxel. In the phase III randomized PROfound study of the PARPi olaparib vs AR targeting agent, the primary endpoint of radiographic progression-free survival (rPFS) in men with mCRPC harboring mutations in *BRCA1/2* and/or *ATM* (cohort A) was met, and olaparib also received FDA approval. While the primary endpoint was met for cohort A, in a post-hoc subgroup analysis of men whose prostate cancer harbored *ATM* alterations, olaparib did not significantly improve rPFS (median 5.4 months vs. 4.7 months for controls).[12] One potential explanation for the observed differences in clinical activity of PARPi in men with *BRCA2* vs. *ATM* mutations may relate to the distinctive roles these proteins play in HR repair, with *ATM* acting as a sensor of DNA double strand break and *BRCA2* being a core effector of HR DNA repair.

Conventional systemic prostate cancer therapies, such as androgen receptor (AR) targeted or taxane agents, are not currently selected by biomarkers. These therapies have been reported to be effective in g*BRCA1/2* carriers with prostate cancer.[3,17] PROREPAIR-B, a prospective cohort study, compared response outcomes for mCRPC treatments among g*BRCA2* carriers and non-carriers and showed similar response rates.[3] Efficacy in patients with g*ATM*, as a distinct cohort, has not been evaluated. Given the uncertain response to HR-deficiency targeted treatments in these men, we sought to investigate whether these patients respond to conventional biomarker-agnostic therapies. We hypothesized that, compared to men carrying g*BRCA2,* those carrying g*ATM* would have a similar response to AR-targeted agents and docetaxel yet attenuated responses to platinum and PARPi therapies.

Methods

This is an international, retrospective, matched cohort study of Consecutive patients with prostate cancer who underwent clinical germline genetic testing between 2014 and 2019 at the University of Washington (UW), Johns Hopkins (JH) Hospital, CNIO-IBIMA Genitourinary Cancer Unit, or Tulane University Cancer Center. We selected patients who had g*ATM* or g*BRCA2* mutations identified with germline genetic testing panels (Ambry Color, Invitae, Myriad, or in-house germline genetic testing at CNIO, JH and UW). Only alterations designated as pathogenic or likely pathogenic by the American College of Medical Genetics were included.[18] The g*BRCA*2 cohort was chosen as a comparison group because it has the most characterized HR-deficient prostate cancer phenotype and established management guidelines. To facilitate comparisons, the g*BRCA2* cohort was individually matched (1:1) to the g*ATM* group by stage at diagnosis (metastatic vs. non-metastatic), year of germline testing and by center at which patients were treated.

A total of 45 patients with g*ATM* and 45 matched g*BRCA2* cases were included. Two patients included in the current study were also reported in the analysis by Marshall *et al.:* one g*ATM* and one g*BRCA2* mutation carrier.[10] Medical records review was performed after local institutional review board approvals at participating centers.

Statistical Analysis

Baseline characteristics for g*ATM* and g*BRCA2* cohorts were compared using the Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables. The primary efficacy endpoint was the percentage of men achieving at least one prostate-specific antigen value that was ≥50% below baseline (PSA_{50} response). Treatment-specific PSA_{50} responses were compared using Fisher's exact tests. Follow-up was calculated using reverse Kaplan-Meier estimation. Metastasis-free survival (MFS) was defined as time from diagnosis to death, last clinical evaluation, or evidence of metastasis on conventional imaging, determined at the local radiologists' discretion and broadly consistent with the Prostate Cancer Clinical Trials Working Group 3 guidelines.[19] Overall survival (OS) was defined as time from prostate cancer diagnosis to death or last clinical evaluation. Time on therapy was defined as time from initiation to termination of therapy or last clinical evaluation, and time to next treatment was defined as time from the start of treatment to the initiation of the next regimen or last clinical evaluation. OS, MFS, median time on therapy, and median time to next treatment were estimated using Kaplan-Meier methods. Differences between g*ATM* and g*BRCA2* cohorts were estimated using the log-rank test. All tests were two-sided and $p < 0.05$ was considered statistically significant. R, version 3.6.3, was used for statistical analysis.

Results

Cohort Characteristics

The study included 90 men with prostate cancer: 45 with g*ATM* mutations and 45 with g*BRCA2* mutations. Specific mutations in g*ATM* and g*BRCA2* genes are documented in Figure 1. Baseline characteristics, including age, PSA, Gleason Grade Group, were similar in the g*ATM* and g*BRCA2* cohorts (Table 1). A similar number of patients had a family history of cancer, meeting Prostate Cancer NCCN Guidelines[20] for germline testing. Distribution of pathology patterns (*e.g.*, cribriform, neuroendocrine), definitive treatment, and anatomical sites of metastases were also similar between the two cohorts. The median follow-up time since diagnosis was 11.8 years in the g*ATM* cohort and 8.0 years in the g*BRCA2* cohort. Metastases developed in 23/28 g*ATM* and 20/28 g*BRCA2* patients after a median follow-up of 15.7 and 15.0 years, respectively, for the subgroup of men diagnosed with localized prostate cancer. Of the 12 men in the g*ATM* cohort and 14 men in the g*BRCA2* cohort for whom tumor sequencing results were available, none were reported to have somatic alterations in other HR genes.

PSA_{50} Response Rates

Responses to systemic therapies in the mCRPC setting, as measured by $PSA_{50,}$ are summarized in Table 2. Comparing patients with g*ATM* versus g*BRCA2* mutations, there was no evident difference in PSA_{50} response to abiraterone: 9/16 (56%) vs. 11/19 (58%); to enzalutamide: 9/16 (56%) vs. 8/12 (67%); or to docetaxel: 9/13 (69%) vs. 9/16 (60%). Only 1 of 3 patients with g*ATM* vs. 5 of 7 patients with g*BRCA2* responded to platinum, numbers are too small to draw conclusions. In contrast, there appeared to be a difference in responses to PARPi—0/7 (0%) patients with g*ATM* mutations responded vs. 12/14 (86%) patients with g*BRCA2* mutations ($p<0.001$).

Time on Treatment

Median time on mCRPC treatment for the g*ATM* and g*BRCA2* cohorts is shown in Table 3. Overall, for abiraterone, enzalutamide, and docetaxel, there was no evidence of different duration from the start to the end of treatment between the cohorts. In the mCRPC setting, median (95% CI) time on AR-targeted therapies in g*ATM* compared to g*BRCA2* cohort was 9.7 (6.5–23) vs. 6.4 (5.4–15.5) months for abiraterone (p=0.5); 6.5 (4.6-not reached) vs 9 (4.9-not reached) months for enzalutamide (p>0.9); and 5.1 (3.7-not reached) vs. 4 (3–6) months for docetaxel-based chemotherapy (p=0.06). Median time on platinum-based chemotherapy in the mCRPC setting was 3 (1-not reached) months in the g*ATM* cohort compared to 6 (4-not reached) months in the g*BRCA2* cohort (p=0.11). We observed a difference in treatment duration on PARPi: 3 (2-not reached) months in the g*ATM* cohort compared to 12 (6.9-not reached) months in the g*BRCA2* cohort (p=0.004). Time on treatment for each therapy is shown in Supplemental Figures 5 A–E.

Overall Survival

During the study follow-up period, 15/45 (33.3%) g*ATM* and 18/45 (40%) g*BRCA2* patients died. Median (95% CI) OS from diagnosis to death was 10.9 years (9.5-not reached) vs. 9.9 years (7.1-not reached, p=0.07) for the g*ATM* and g*BRCA2* cohorts, respectively (Figure 2). There was no evidence of OS difference between g*ATM* and g*BRCA2* cohorts when analyzing subgroups of patients initially diagnosed with localized (not reached vs 9.9 years, respectively, p=0.07) or metastatic disease (8.7 vs 3.6 years, respectively, p=0.4; Supplemental Figure 3).

Among the 28 patients in each cohort diagnosed with localized prostate cancer, median (95% CI) MFS was 5.7 years (5.1–11.1) vs 5.0 years (4.1–7.0, p=0.13) for the g*ATM* and g*BRCA2* cohorts, respectively (Supplemental Figure 4).

Discussion

Prostate tumors with alterations in DDR genes, particularly those in the HR repair pathway, represent a group of interest particularly in light of recent FDA approvals of the PARP inhibitors rucaparib and olaparib. While broadly grouped with g*BRCA1/2* carriers, patients with prostate cancer in the setting of g*ATM* mutations have not been characterized as an independent cohort. This study focuses on patients with prostate cancer and g*ATM* mutations and describes responses to conventional and emerging systemic therapies with the aim of improving our understanding of therapeutic approaches for these patients.

Among men diagnosed with prostate cancer, those carrying g*BRCA2* mutations are recognized to have a more aggressive phenotype (Supplemental Table 3).[6] Another retrospective study, albeit with limited numbers of g*ATM* carriers, found that g*BRCA1/2* and g*ATM* are associated with earlier age of death and shorter cancer-specific survival.[9] Dedicated attention is warranted for g*ATM* mutation carriers to further define specific prostate cancer risks and response to treatment.

Our data support the concept that while *ATM*-deficient prostate cancer may share features with *BRCA2*-deficient tumors, such as enrichment in the metastatic setting and response

to non-targeted agents, they have distinct clinical characteristics. For example, we observed an attenuated response to PARPi in the g*ATM* cohort compared to the g*BRCA2* cohort, consistent with a retrospective study by Marshall *et al.*, in which 0/8 patients with germline or somatic *ATM* mutations responded to PARPi.[10] This difference in sensitivity to PARPi may partially be explained by different roles for *ATM* and *BRCA2* in the HR repair pathway. ATM's primary role is to recognize double-strand break and to activate downstream HR repair proteins, such as Chk2.[21–23] Once activated, Chk2 has an overlapping function with ATM and phosphorylates the core HR repair pathway effectors, *e.g.,* BRCA1, BRCA2.[21] Chk2 can be activated by proteins other than ATM, such as DNA-dependent protein kinase, suggesting that HR repair pathway can be activated even in cells with loss of ATM function.[22] These mechanistic differences in *ATM* and *BRCA2* may account for observed differences in sensitivity to HR-targeted therapies between the two cohorts of our study. In addition, Neeb, *et al.,* have recently reported that ATM protein expression as measured by ATM IHC is not perfectly overlapping with *ATM* mutations identified by NGS and suggest that protein expression may be another factor for treatment selection, potentially more predictive than DNA sequencing.[7]

Abiraterone, enzalutamide, and docetaxel have mechanisms of action largely independent of *BRCA2* and *ATM.* A previous study reported that these therapies are similarly effective in g*BRCA2* mutation carriers compared to non-carriers and g*BRCA2* mutation carriers might benefit from upfront androgen-directed therapy rather than taxanes.[3] We observed comparable PSA_{50} response rates in the two cohorts in our study. Thus, our data suggest that abiraterone, enzalutamide, and docetaxel should be offered to patients with mCRPC who carry g*ATM* mutations.

Recent data suggest that platinum chemotherapy is effective in patients with *BRCA2* mutations.[24–26] In our study, patients with g*ATM* mutations appeared to have a reduced response to platinum chemotherapy compared to the g*BRCA2* cohort, but this comparison was not statistically significant owing to the small numbers. However, our observations are consistent with other studies reporting disappointing responses to platinum chemotherapy among *ATM* mutation carriers with prostate cancer.[15,26] To date, reported numbers of patients with mCRPC and *ATM* alterations treated with platinum chemotherapy remain small and further studies are needed.

Our data highlight the need to explore new targeted therapies in patients with mCRPC and *ATM* alterations. Preclinical data suggest that *ATM*-deficient prostate tumors may be sensitive to *ATR* inhibitors, which, when combined with PARPi, result in apoptosis in PARPi-resistant prostate cancer cell lines.[7,28] Several ongoing clinical trials are evaluating *ATR* inhibitors in prostate cancer (*e.g.,* NCT04267939, NCT03787680).

We did not observe a significant difference in OS between the two cohorts, although this could be attributable to the limited numbers of patients and deaths and to different proportions of men receiving PARPi in the two groups. More men in g*BRCA2* cohort received PARPi, which has a proven OS benefit for these patients.[12,29]

There are a number of important limitations to our study. First, this is a non-randomized retrospective study with a relatively small sample size. Second, the indications for germline testing in prostate cancer have been and remain evolving, so there are likely differences in practice from 2014 to 2019, as well as ascertainment biases. We attempted to minimize confounding effect by matching cases by year of testing; we acknowledge that men undergoing germline testing 2014–2019 will have been largely those with a strong family history of cancer and/or aggressive phenotype, although both g*ATM* and g*BRCA2* cohorts are likely to have been similarly affected. Third, the two cohorts are matched only for the year of testing, stage at diagnosis and treatment center; other patient characteristics were not matched. Fourth, the study does not include a control group of men without g*ATM* and g*BRCA2* mutations, which limits broader implications for treatment response. Fifth, the study does not include radiographic response assessment or confirmed PSA_{50} responses, limiting treatment response assessments. Clinical practices at different institutions may vary. For example, imaging was performed at clinician discretion without predefined standard intervals, which may have affected the time on treatment and MFS assessments. Finally, somatic alterations in other genes, mutation zygosity and protein expression were not fully addressed, but interference from clonal hematopoiesis of indeterminant potential would be less of an issue.[30] Nevertheless, given the greater prevalence of g*ATM* mutations[31,32] in general population, compared to g*BRCA2* mutations,[33,34] we believe that specific examination of g*ATM* remains important to this patient population.

Conclusions

Our data provide evidence that standard therapies may be similarly effective in g*ATM*- and g*BRCA2*-associated prostate cancer, whereas PARPi appear less effective in g*ATM*-associated prostate cancer. We did not find that abiraterone, enzalutamide, and docetaxel were less effective in patients with prostate cancer with g*ATM* mutations and thus these agents should remain standard of care options for patients. This important subgroup of patients should continue to be studied and incorporated into clinical trials—especially those incorporating novel agents and combination strategies, e.g., ATR inhibitors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We thank Agnes Gawne for data collection assistance. We gratefully acknowledge funding support from the Institute for Prostate Cancer Research, Prostate Cancer Foundation, Washington State Medical Oncology Society, Advancing Cancer Treatment, Patrick Walsh Prostate Cancer Research Fund, and NCI award numbers CA097186 (Pacific Northwest Prostate Cancer SPORE), P30 CA015704, P30 CA006973–52, R01 CA238384, R50 CA221836, and T32CA009515; PCF YI VALor award, CDMRP Awards W81XWH-17–2-0043, W81XWH-15–1-0430, PC170503, PC171001, DOD EIRA award W81XWH-17–1-0380 and the DOD Clinical Consortium award W81XWH-16-PCRP-CCRSA.

Funding statement: gratefully acknowledge funding support from the Institute for Prostate Cancer Research, the Prostate Cancer Foundation, the Washington State Medical Oncology Society, Patrick Walsh Prostate Cancer Research Fund, and NCI award numbers CA097186 (Pacific Northwest Prostate Cancer SPORE), P30 CA015704, R50 CA221836, and T32CA009515, CDMRP Awards PC170503, PC171001, 5P30 CA006973–52, R01 CA238384, and the DOD Clinical Consortium award W81XWH-16-PCRP-CCRSA.

Conflict of Interest Statement:

Alexandra O. Sokolova: nothing to disclose

Catherine H. Marshall: Consulting from Dendreon, Bayer, McGraw-Hill Publishing Company. Travel from Dava Oncology.

Rebeca Lozano: speaker fees from Roche, Janssen, Sanofi and Bayer. Travel support from Roche, Janssen, Sanofi and Astellas Pharma.

Roman Gulati: nothing to disclose

Elisa M. Ledet: nothing to disclose

Navonil De Sarkar: nothing to disclose

Petros Grivas: received grants from Bavarian Nordic, Bristol Myers Squibb, Clovis Oncology, Debiopharm, EMD Serono, GlaxoSmithKline, Immunomedics, Kure It Cancer Research, Merck & Co., Mirati Therapeutics, Pfizer, QED Therapeutics. Dr. Grivas has received consulting fees from AstraZeneca, Astellas Pharma, Bayer, Bristol Myers Squibb, Clovis Oncology, Dyania Health, Driver, EMD Serono, Exelixis, Foundation Medicine, Genentech/Roche, Genzyme, GlaxoSmithKline, Guardant Health, Heron Therapeutics, Immunomedics/Gilead, Infinity Pharmaceuticals, Janssen, Merck & Co., Mirati Therapeutics, Pfizer, QED Therapeutics, Regeneron Pharmaceuticals, Seattle Genetics, 4D Pharma PLC.Celestia S. Higano: Institutional research funding: Aptevo, Aragon, Astellas, AstraZeneca, Clovis, Dendreon, eFFECTOR Therapeutics, Emergent, Ferring, Genentech, Hoffman-Laroche, Medivation, Pfizer; Consulting, scientific advisory boards: Astellas, Bayer, Blue Earth Diagnositics, Clovis, Dendreon, Ferring, Hinova, Janssen, Merck, Orion, Pfizer, Tolmar, Carrick Therapeutics, Novartis, Genentech; Other: spouse holds stock and former officer of CTI Biopharma

Bruce Montgomery: Institutional research funding: Astellas, AstraZeneca, Beigene, Clovis, Janssen.

Peter S. Nelson: Consultant for Bristol Myers Squibb, Astellas, and Janssen Pharmaceuticals and received fees from UpToDate.

David Olmos: grant research support (to the institution) from AstraZeneca, Astellas, Bayer, Jansen. Advisory board and speaker fees from AstraZeneca, Astellas, Bayer, BioOncotech (Uncompensated), Clovis, Daiichi-Sankyo, Jansen, MSD, Pfizer. Travel support from AstraZeneca, Astellas, Bayer, F. Hoffman La Roche, Genetech, Ipsen, Jansen

Vadim Sokolov: nothing to disclose

Michael T. Schweizer: Paid consultant for Janssen and Resverlogix. Research funding from Bristol Myers Squibb, Merck, Immunomedics, Janssen, AstraZeneca, Pfizer, Madison Vaccines, Tmunity and Hoffman-La Roche

Todd A. Yezefski: consultant for Dendreon

Evan Y. Yu: Consulting – Advanced Accelerator Applications, Bayer, Clovis, Janssen, Merck. Research to institution – Bayer, Blue Earth, Dendreon, Merck, Taiho

Channing J. Paller: nothing to disclose

Oliver Sartor: Grant support to institution for AAA Pharma, AstraZeneca, Bayer, Endocyte, Progenics, Novartis, and Janssen, consulting fees from Astellas, Blue Earth Diagnostics, EMD Serono, Pfizer, Constellation, Dendreon, Bristol-Myers Squibb, Invitae, Merck, Innocrin, and Sotio, Consulting fees from AAA Pharma, AstraZeneca, Bayer, Endocyte, Progenics, Novartis, Janssen, Astellas, Blue Earth Diagnostics, EMD Serono, Pfizer, Constellation, Noria Therapeutics, Clovis, Myriad, Noxopharm, Point Biopharm, Tenebio, Theragnostics, Telix, Clarity Pharmaceuticals, and Fusion

Elena Castro: honoraria and consulting CLOVIS, Astra Zeneca, Astellas, Jansen, MSD, Roche, Pfizer; research funding Astra Zeneca, Bayer, Janssen, travel accommodations Astra Zeneca, Bayer, Janssen

Emmanuel S. Antonarakis: has served as a paid consultant/advisor for Invitae, Janssen, Pfizer, Sanofi, Dendreon, Merck, Bristol-Myers Squibb, AstraZeneca, Clovis, Bayer, Constellation, Eli Lilly and Amgen; and has received research funding to his institution from Janssen, Johnson & Johnson, Sanofi, Dendreon, Genentech, Novartis, Bayer, Merck, Bristol-Myers Squibb, AstraZeneca, ESSA and Constellation.

Heather H. Cheng; Research funding to institution from Clovis, Janssen, Sanofi, Medivation/Astellas, Color Foundation; Consultancy to AstraZeneca; Royalties from UpToDate

Data availability statement:

Data available on request due to privacy/ethical restrictions

References

1. Pritchard CC et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N. Engl. J. Med. 375, 443–453 (2016). [PubMed: 27433846]
2. Nicolosi P et al. Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines. JAMA Oncol. 5, 523–528 (2019). [PubMed: 30730552]
3. Castro E et al. PROREPAIR-B: A Prospective Cohort Study of the Impact of Germline DNA Repair Mutations on the Outcomes of Patients With Metastatic Castration-Resistant Prostate Cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 37, 490–503 (2019).
4. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ & Higano CS Germline and Somatic Mutations in Prostate Cancer for the Clinician. J. Natl. Compr. Cancer Netw. JNCCN 17, 515–521 (2019).
5. Page EC et al. Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers. Eur. Urol. 76, 831–842 (2019). [PubMed: 31537406]
6. Castro E et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 31, 1748–1757 (2013).
7. Neeb A et al. Advanced Prostate Cancer with ATM Loss: PARP and ATR Inhibitors. Eur. Urol. 0, (2020).
8. Carter HB et al. Germline Mutations in ATM and BRCA1/2 Are Associated with Grade Reclassification in Men on Active Surveillance for Prostate Cancer. Eur. Urol. (2018) doi:10.1016/j.eururo.2018.09.021.
9. Na R et al. Germline Mutations in ATM and BRCA1/2 Distinguish Risk for Lethal and Indolent Prostate Cancer and are Associated with Early Age at Death. Eur. Urol. 71, 740–747 (2017). [PubMed: 27989354]
10. Marshall CH et al. Differential Response to Olaparib Treatment Among Men with Metastatic Castration-resistant Prostate Cancer Harboring BRCA1 or BRCA2 Versus ATM Mutations. Eur. Urol. 76, 452–458 (2019). [PubMed: 30797618]
11. Abida W et al. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. J. Clin. Oncol. JCO.20.01035 (2020) doi:10.1200/JCO.20.01035.
12. de Bono J et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N. Engl. J. Med. 382, 2091–2102 (2020). [PubMed: 32343890]
13. Sokolova AO, Yu EY & Cheng HH Honing in on PARPi Response in Prostate Cancer: from HR Pathway to Gene-by-Gene Granularity. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 26, 2439–2440 (2020).
14. Athie A et al. Targeting DNA Repair Defects for Precision Medicine in Prostate Cancer. Curr. Oncol. Rep. 21, 42 (2019). [PubMed: 30919167]
15. Mota JM et al. Platinum-Based Chemotherapy in Metastatic Prostate Cancer With DNA Repair Gene Alterations. JCO Precis. Oncol. 355–366 (2020) doi:10.1200/PO.19.00346. [PubMed: 32856010]
16. Abida W et al. Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: Analysis From the Phase II TRITON2 Study. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 26, 2487–2496 (2020).
17. Carlson AS et al. Impact of mutations in homologous recombination repair genes on treatment outcomes for metastatic castration resistant prostate cancer. PLoS ONE 15, (2020).
18. Karbassi I et al. A Standardized DNA Variant Scoring System for Pathogenicity Assessments in Mendelian Disorders. Hum. Mutat. 37, 127–134 (2016). [PubMed: 26467025]

19. Scher HI et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J. Clin. Oncol. 34, 1402–1418 (2016). [PubMed: 26903579]
20. National Comprehensive Cancer Network. Prostate Cancer (Version 2.2020). https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf. Accessed November 10, 2020.
21. Zannini L, Delia D & Buscemi G CHK2 kinase in the DNA damage response and beyond. J. Mol. Cell Biol. 6, 442–457 (2014). [PubMed: 25404613]
22. Li J & Stern DF Regulation of CHK2 by DNA-dependent protein kinase. J. Biol. Chem. 280, 12041–12050 (2005). [PubMed: 15668230]
23. Lavin MF, Delia D & Chessa L ATM and the DNA damage response. Workshop on ataxia-telangiectasia and related syndromes. EMBO Rep. 7, 154–160 (2006). [PubMed: 16439996]
24. Pomerantz MM et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer 123, 3532–3539 (2017). [PubMed: 28608931]
25. Cheng HH, Pritchard CC, Boyd T, Nelson PS & Montgomery B Biallelic inactivation of BRCA2 in platinum sensitive, metastatic castration resistant prostate cancer. Eur. Urol. 69, 992–995 (2016). [PubMed: 26724258]
26. Schmid S et al. Activity of Platinum-Based Chemotherapy in Patients With Advanced Prostate Cancer With and Without DNA Repair Gene Aberrations. JAMA Netw. Open 3, e2021692 (2020). [PubMed: 33112397]
27. Mota JM et al. Platinum-Based Chemotherapy in Metastatic Prostate Cancer With DNA Repair Gene Alterations. JCO Precis. Oncol. 355–366 (2020) doi:10.1200/PO.19.00346. [PubMed: 32856010]
28. Rafiei S et al. ATM Loss Confers Greater Sensitivity to ATR Inhibition Than PARP Inhibition in Prostate Cancer. Cancer Res. 80, 2094–2100 (2020). [PubMed: 32127357]
29. Hussain M et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N. Engl. J. Med. 383, 2345–2357 (2020). [PubMed: 32955174]
30. Sokolova AO et al. Complexities of Next-Generation Sequencing in Solid Tumors: Case Studies. J. Natl. Compr. Canc. Netw. 18, 1150–1155 (2020). [PubMed: 32886903]
31. Broeks A et al. ATM-Heterozygous Germline Mutations Contribute to Breast Cancer–Susceptibility. Am. J. Hum. Genet. 66, 494–500 (2000). [PubMed: 10677309]
32. Hall MJ et al. Germline Pathogenic Variants in the Ataxia Telangiectasia Mutated (ATM) Gene are Associated with High and Moderate Risks for Multiple Cancers. Cancer Prev. Res. (Phila. Pa.) 14, 433–440 (2021).
33. Maxwell KN, Domchek SM, Nathanson KL & Robson ME Population Frequency of Germline BRCA1/2 Mutations. J. Clin. Oncol. 34, 4183–4185 (2016).
34. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br. J. Cancer 83, 1301–1308 (2000). [PubMed: 11044354]

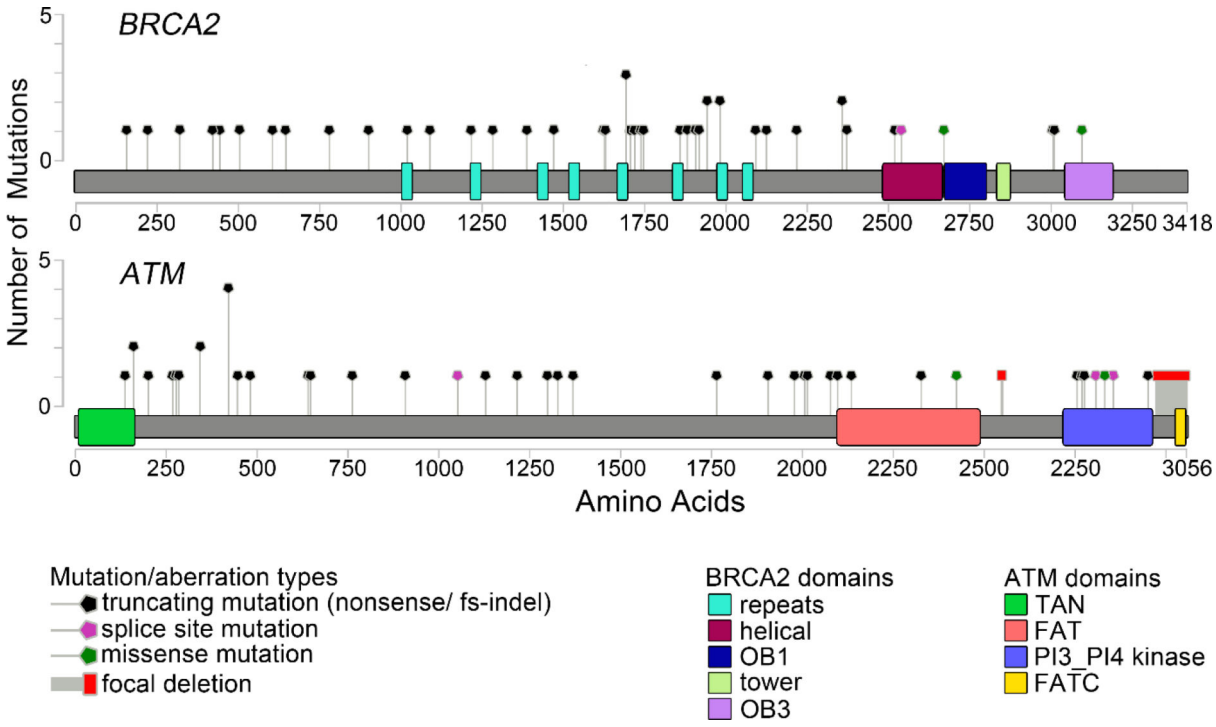

Figure 1.
Distribution of *ATM* and *BRCA2* Mutations

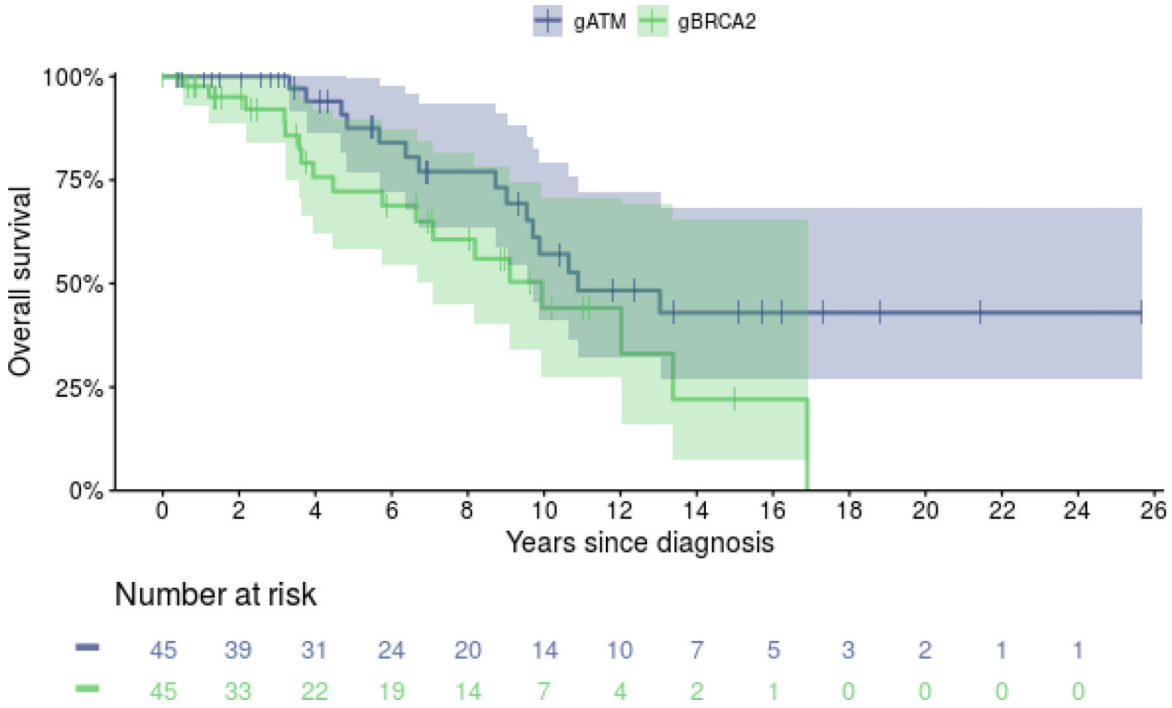

Figure 2.
Overall Survival

Table 1.

Patient Characteristics

Characteristics	**g*ATM***	**g*BRCA2***	***P***
Number of patients	45	45	
Stage M1 at diagnosis (%)	17 (38)	17 (38)	
Age (median [IQR])	58 [54, 66]	62 [55, 67]	0.2
PSA (median [IQR])	24 [9, 76]	11 [6, 46]	0.13
Grade (%)			
2	6 (17)	4 (11)	
3	7 (20)	5 (14)	
4	5 (14)	8 (22)	
5	17 (49)	20 (54)	
Family history of cancer meeting Prostate Cancer NCCN Guidelines for germline testing[20] (%)	25 (60)	29 (71)	0.4
Known other primary cancers (%)	5 (11)	4 (9)	>0.9
Pathology (%)			
acinar	24 (80)	22 (76)	
ductal	3 (10)	3 (10)	
intraductal	0 (0)	1 (3)	
cribriform	1 (3)	1 (3)	
neuroendocrine	2 (7)	2 (7)	
Prostatectomy (%)	20 (44)	22 (50)	0.7
Radiotherapy (%)	22 (51)	24 (56)	0.8
Bone metastasis at the time of diagnosis (%)	14 (31)	15 (33)	>0.9
Nodal metastasis at the time of diagnosis (%)	13 (29)	11 (24)	0.8
Visceral metastasis at the time of diagnosis (%)	1 (2)	3 (7)	0.6

Table 2.

PSA_{50} Response

Therapy	Prior	*gATM*	*gBRCA2*	*P*
Abiraterone	Overall	9/16 (56%)	11/19 (58%)	>0.9
	Pre-enza	9/14 (64%)	10/17 (59%)	
	Post-enza	0/2 (0%)	1/2 (50%)	
Enzalutamide	Overall	9/16 (56%)	8/12 (67%)	0.7
	Pre-abi	7/10 (70%)	5/7 (71%)	
	Post-abi	2/6 (33%)	3/5 (60%)	
Docetaxel	Overall	9/13 (69%)	9/16 (56%)	0.7
	Pre-abi/enza	7/9 (78%)	4/7 (57%)	
	Post-abi/enza	2/4 (50%)	5/9 (56%)	
PARPi	Overall	0/7 (0%)	12/14 (86%)	<0.001
	Pre-plat	0/3 (0%)	10/11 (91%)	
	Post-plat	0/4 (0%)	2/3 (67%)	

Table 3.

Time on Treatment

Therapy	Setting	*gATM*		*gBRCA2*		*P*
		Number of pts	Median time on therapy (95% CI)	Number of pts	Median time on therapy (95% CI)	
Abiraterone	Overall	19	9.71 (6.5–23)	24	6.44 (5–15.5)	0.6
	HSPC	2	3 (3–N/A)	5	6 (5–N/A)	>0.9
	CRPC	17	9.71 (6.5–23)	19	6.44 (5.38–15.5)	0.5
Enzalutamide	CRPC	16	6.5 (4.62–N/A)	12	9 (4.92–N/A)	>0.9
PARPi	CRPC	7	3 (2–N/A)	15	12 (6.9–N/A)	0.004
Platinum	CRPC	3	3 (1–N/A)	7	6 (4–N/A)	0.11
Docetaxel	Overall	18	4.13 (4–7)	21	4 (3–6)	0.12
	HSPC	5	4 (N/A–N/A)	4	4.5 (3–N/A)	0.4
	CRPC	13	5.12 (3.7–N/A)	17	4 (3–6)	0.06
			Median time to next therapy (CI 95%)		Median time to next therapy (CI 95%)	
	CRPC	13	10.47 (6.47–N/A)	15	7 (4.16–12.82)	0.15

Pts - patients; HSPC – hormone sensitive prostate cancer; CRPC – castration resistant prostate cancer.