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*Case Report*

# Next-generation sequencing identifies the presence of protein phosphatase 1D, PPM1D, as a potential biomarker of resistance to PARP inhibition in metastatic castration-resistant prostate cancer

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**Abstract:** The landscape for the treatment of advanced and metastatic prostate cancer is rapidly changing. For patients with metastatic castration-resistant prostate cancer (mCRPC), next-generation sequencing (NGS) may identify those with Homologous Recombination Deficiency (HRD) who may benefit from Poly ADP [adenosine diphosphate]-ribose polymerase inhibitors (PARP) inhibition therapy. Ongoing questions remain, however, regarding how patients and clinicians can best select therapies to optimize patient outcomes. In this case report, we highlight a patient with rapidly progressive mCRPC with germline BRCA2 for whom olaparib was added with abiraterone and prednisone resulting in a significant but brief response. Using next-generation sequencing of a liquid biopsy, we identified Protein Phosphatase 1D (PPM1D) as a potential resistance mechanism to PARP inhibition. While this alteration has been previously reported in other tumor types, the role of PPM1D and its contribution to PARP inhibitor resistance in mCRPC has not been described; the aim of this report was to highlight the potential role it may play in prostate cancer. With the increasing availability of circulating tumor DNA (ctDNA) to assist clinicians with monitoring patients' responses on therapy, the results from this case study underscore the necessity of exploring optimal timing of liquid and/or repeat tumor biopsies to help longitudinally personalize targeted therapy to improve patient outcomes.

**Keywords:** Prostate cancer, PARP inhibition, personalized medicine, next generation sequencing

## Introduction

Prostate cancer leads to more than 34,000 deaths annually in the United States [1]. As an androgen-driven disease, prostate cancer is treated with therapies targeting the androgen receptor including androgen deprivation therapy and androgen receptor signaling inhibitors. While these therapies are initially successful, most cases progress to castration-resistant prostate cancer (CRPC), which is associated with a poor prognosis.

Recently, numerous Poly ADP [adenosine diphosphate]-ribose polymerase inhibitors (PARPi) have been approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) with specific HRD alterations [2-6]. However, questions remain regarding the role of PARPi in the prostate cancer patient treatment timeline, specifically optimizing the timing of initiation, increasing synergistic effects with combination strategies, and decreasing drug resistance [7]. In this case study, the combination treatment of PARPi olaparib with abiraterone and prednisone in a patient with rapidly progressive mCRPC and germline BRCA2 and ATM mutations resulted in a significant but brief response. Next-generation sequencing of a liquid biopsy from this patient identified Protein Phosphatase 1D (PPMD1) as a potential resistance mechanism. While this alteration has

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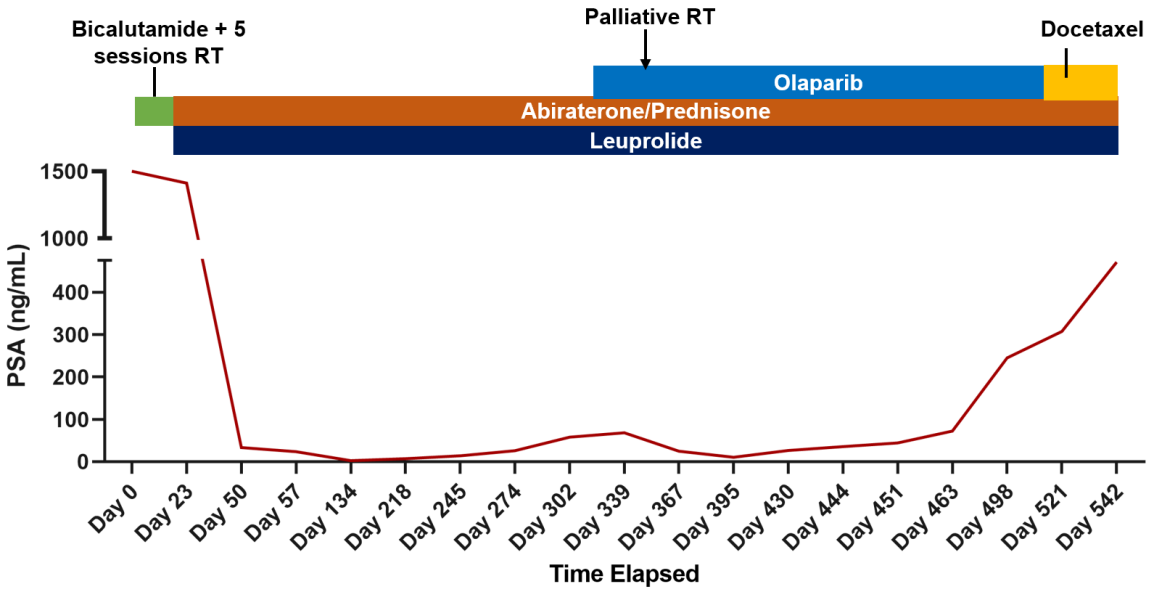


**Figure 1.** Prostate-specific antigen (PSA) trend in conjunction with initiation and cessation of PCa therapies. Administration of bicalutamide at initial diagnosis led to a decrease in PSA, and PSA continued to decrease with the transition to abiraterone/prednisone and leuprolide. PSA reached a nadir before gradually increasing throughout the following six months. olaparib was added to the treatment regimen, with a resulting PSA decrease until a rebound several months later, at which point taxane chemotherapy was initiated.

been previously reported as a mechanism of resistance to PARPi in other tumor types, the role of PPM1D in PARPi resistance in mCRPC is not well established.

## Case presentation

A 64-year-old male patient presented to the emergency department with rib pain. The prostate-specific antigen (PSA) level was found to be >1500 ng/dL. Magnetic resonance imaging (MRI) showed diffuse osseous disease, including the cervical, lumbar, and thoracic spine, with pathological compression fractures of the T3 and T4 vertebral bodies. Patient tissue core histology/pathology analysis confirmed a metastatic prostate cancer diagnosis (Gleason Score 9). He received five sessions of palliative radiation therapy to the thoracic spine and initiated bicalutamide with a rapid drop in PSA (**Figure 1**). He was then started on leuprolide and abiraterone/prednisone but declined treatment with chemotherapy at that time. PSA levels reached a nadir of 2.7 ng/dL. Unfortunately, after six months of therapy, the patient developed worsening pain and increasing PSA levels, suggesting progression to castration resistance (**Figure 1**). Next-generation sequencing (NGS) through the Tempus platform was utilized for both germline DNA sequencing (xG) and transcriptome sequencing (xT) as part of routine clinical care [8] (**Table 1**). Considering the HRD loss-of-function BRCA2 mutation (**Table 1**), the patient began treatment with olaparib (300 mg twice daily) and continued leuprolide, abiraterone, and prednisone. He also received 800 cGy palliative radiation to his shoulder for treatment of significant pain. While his PSA initially responded, it increased again in a short period of four months. Worsening pain, suggestive of PARPi resistance, prompted his transition to taxane chemotherapy (**Figure 1**).

## Next-generation sequencing insights

The Tempus xG 52-gene panel was utilized to determine germline DNA mutations from blood samples. This assay identified a pathogenic germline mutation in BRCA2 and a variant of uncertain significance (VUS) in ATM (**Table 1**). The Tempus xT 648-gene panel was utilized for transcriptome sequencing for somatic mutations in the archived initial biopsy of the treatment-naïve tumor. We identified a copy number loss for somatic BRCA2 (**Table 1**). The xT screen also identified somatic mutations in FOXA1, NCOR2, PIK3CD, and ZFHX3 (**Table 1**). After his rapid progression on PARPi, a liquid biopsy

**Table 1.** Next-generation sequencing results

| xT 648-Gene Panel[a] | | | | xG 52-Gene Germline Panel[b] | | | | xF+ 523-Gene Liquid Biopsy[c] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gene | Alteration | Pathogenicity | Potential Targeted Therapies | Gene | Alteration | Pathogenicity | Potential Targeted Therapies | Gene | Alteration | Pathogenicity | Potential Targeted Therapies |
| - | - | - | - | - | | - | - | ALK | c.2336G>A p.G779E | VUS | NA |
| - | - | - | - | ATM | c.6998C>T p.(T2333I) | VUS | NA | ATM | c.6998C>T p.T2333I | VUS | NA |
| BRCA2 | Copy number loss | Biologically Relevant | Olaparib, Rucaparib | BRCA2 | c.5073dup p.(W1692Mfs*3) | Pathogenic | Olaparib, Rucaparib | BRCA2 | c.5073dup p.(W1692Mfs*3) | Potentially Actionable | Olaparib, Rucaparib |
| FOXA1 | c.790_857del p.K264fs | Biologically Relevant | NA | - | - | - | - | - | - | - | - |
| - | - | - | - | - | - | - | - | KMT2C (MLL3) | c.919C>A p.H307N | VUS | NA |
| - | - | - | - | - | - | - | - | | c.878C>T p.A293V | VUS | NA |
| - | - | - | - | - | - | - | - | MTHFR | c.780+3G>A | VUS | NA |
| NCOR2 | c.5995C>A p.L1999I | VUS | NA | - | - | - | - | - | - | - | - |
| - | - | - | - | - | - | - | - | NF1 | c.8458C>G p.Q2820E | VUS | NA |
| PIK3CD | c.2983A>T p.I995F | VUS | NA | - | - | - | - | - | - | - | - |
| - | - | - | - | - | - | - | - | PPM1D | c.1593_1600del p.T532fs | Biologically Relevant | NA |
| - | - | - | - | - | - | - | - | | c.1349T>G p.L450* | Biologically Relevant | NA |
| - | - | - | - | - | - | - | - | | c.1654C>T p.R552* | Biologically Relevant | NA |
| - | - | - | - | - | - | - | - | SMARCB1 | c.880G>A p.A294T | VUS | NA |
| - | - | - | - | - | - | - | - | TP53 | c.734G>A p.G245D | Biologically Relevant | NA |
| ZFHX3 | c.1126G>T p.E376* | Biologically Relevant | NA | - | - | - | - | - | - | - | - |

[a]Tempus xT 648-gene somatic panel, source: tumor specimen, blood; [b]Tempus xG 52-gene germline panel, source: blood in EDTA; [c]Tempus xF+ 523-gene cell-free DNA liquid biopsy panel, source: peripheral blood.

sample for xF+ sequencing was taken from peripheral blood. This targeted sequencing identified persistent BRCA2 loss as previously identified, as well as variants of unknown significance in ALK, KMT2C/MLL3, MTHFR, NF1, and SMARCB1 (**Table 1**). However, additional actionable alterations were identified in TP53 and PPM1D that were not found in the original pre-treatment specimen (**Table 1**).

## Discussion

Multiple PARP inhibitors were recently approved for the treatment of metastatic castration-resistant prostate cancer patients with specific HRD alterations [9-11]. Here, we present a case where PARP inhibition with olaparib in a patient with biallelic BRCA2 loss/mutation produced an initial significant response; however, this response was not durable, and PSA rose once more after only a few months of therapy. A liquid biopsy sample obtained during progression detected TP53 loss-of-function and three gain-of-function alterations in PPM1D. Interestingly, PPM1D alterations have been linked with PARPi resistance in ovarian, breast, and brain cancers, but it's role in prostate cancer progression has not been described [12-14]. PPM1D may provide insight into an important mechanism of PARP inhibitor resistance in prostate cancer as well.

Protein phosphatase 1D (PPM1D or WIP1), established as a negative regulator of DNA damage response (DDR), dephosphorylates ATM, ATR, Chk1/2, TP53, and γH2AX resulting in DDR pathway reversal [15-18]. Recently, PPM1D was shown to promote homologous recombination (HR) by forming a stable complex with BRCA1 and BARD1 [14]. In diffuse intrinsic pontine glioma, PPM1D was required for the formation of RAD51 nuclear foci after olaparib treatment [12]; notably, RAD51 nuclear foci formation is an indication of functional HR and has been correlated with PARPi resistance in breast cancer [19]. While both loss-of-function and gain-of-function PPM1D alterations are found in cancer models and genomics datasets, gain-of-function mutations are more common in cancer, including truncating mutations in the C-terminal domain that results in prolonged protein stability [12, 16]. Mechanistically, these truncating mutations in PPM1D result in constitutively active PPM1D and subsequent HR restoration, potentially serving as a resistance mechanism for PARPi treatment.

In this case study, we report a patient with three distinct alterations in the C-terminal domain of PPM1D: a frameshift gain-of-function mutation at T532 and two gain-of-function truncating mutations at L450 and R552 (**Table 1**). According to the treatment and sequencing timeline, these alterations occurred during olaparib treatment, suggesting they contributed to treatment resistance (**Figure 1**). However, gain-of-function mutations are not the only mechanism through which PPM1D can be upregulated, with some studies suggesting PPM1D can be upregulated by ionizing radiation [17]. This patient also received palliative radiation therapy during the course of olaparib treatment, and it is possible that PPM1D expression and subsequent PPM1D-mediated HR activity were induced by radiation therapy and not as a result of gain-of-function mutations induced during PARP inhibitor treatment. Regardless of how PPM1D activity is altered, it is likely that increased PPM1D activity conferred olaparib resistance and contributed to rapid progression despite the molecularly targeted precision oncology treatment strategy. Given the significant emphasis in the field on PARP inhibition in prostate cancer, as illustrated by the numerous recent approvals of PARP inhibitors, future studies should address the regulation of PPM1D in advanced prostate cancer to better predict, address, and prevent mechanisms of treatment resistance.

An ongoing clinical trial in ovarian cancer aims to assess PPM1D as a biomarker for PARPi resistance in tumor tissue pre- and post-olaparib (NCT02489006) [20]. While there are many ongoing clinical trials of PARPi as the primary therapeutic strategy in various stages of prostate cancer, none, to our knowledge, include assessment of PPM1D status. We mined Genomic data from the SU2C-PCF Dream Team dataset on cBioPortal and found PPM1D alterations in 29/429 (7%) of metastatic castration-resistant prostate cancer patient samples [21-23]. The majority, 26/29 (90%) of these alterations were copy number gain (CNG) amplifications, one was a gain-of-function truncating mutation, one was a missense mutation, and one had both CNG and a missense mutation (**Figure 2**). Given this current case study and

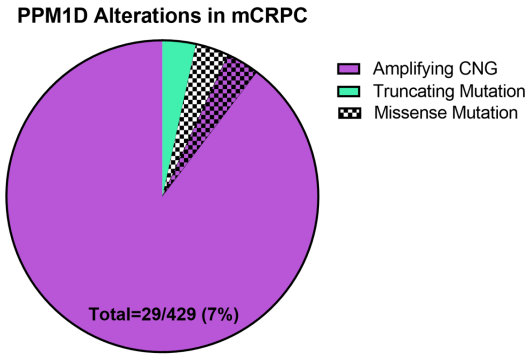


**Figure 2.** Genomic data from the SU2C-PCF Dream Team dataset on cBioPortal found PPM1D alterations in 29/429 (7%) of metastatic castration-resistant prostate cancer patient samples. The majority, 26/29 (90%) of these alterations, were copy number gain (CNG) amplifications, one was a gain-of-function truncating mutation, one was a missense mutation, and one had both CNG and a missense mutation.

evidence of PPM1D alterations in mCRPC in combination with the increasing use of olaparib and other PARPi in mCRPC, PPM1D may be a valuable biomarker to assess prospectively in clinical trials as an indicator of therapy resistance. Further elucidation on the role and frequency of liquid biopsies and/or repeat tumor biopsies in monitoring advanced disease is needed to identify resistance mechanisms.

In the context of prostate cancer, several trials have investigated the potential synergy of PARP inhibitor treatment with second-generation AR-targeted therapies [6, 24]. However, remaining questions in the field pertain to the optimal timing (sequential, additive, vs. concurrent) for combination treatment strategies against PARP and AR. This patient's treatment course predated both the approval of the PROPEL regimen [6], as well as the presentation of preliminary results of the BRCAAway trial, which suggests concurrent initiation is superior to sequential exposure in mCRPC [24]. As PARPi therapy becomes more mainstream in the treatment landscape for prostate cancer, future studies must also focus on determining, preventing, and combating the development of PARPi treatment resistance.

## Conclusion

The landscape for the treatment of advanced and metastatic prostate cancer is rapidly changing, and for patients with metastatic castration-resistant prostate cancer, NGS may identify those with actionable HRD alterations who may benefit from PARP inhibition therapy. Ongoing questions remain, however, regarding how patients and clinicians can best select therapies to optimize patient outcomes. In this case report, we highlight a patient with rapidly progressive mCRPC with germline BRCA2 alterations for whom olaparib was added in combination with abiraterone and prednisone. Though this treatment regimen significantly reduced PSA, it was not durable, and biochemical progression was observed after only 4 months. Using NGS of a liquid biopsy, we identified PPM1D as a potential resistance mechanism to olaparib. While this alteration has been previously reported in other tumor types, the role of PPM1D and its contribution to PARP inhibitor resistance in mCRPC has not been described. With both the increasing availability of PARP inhibitor regimens approved for this disease, as well NGS and ctDNA assays to assist clinicians with monitoring patients' responses on therapy, these results highlight the importance of longitudinal sequencing of liquid and/or repeat tumor biopsies to optimize personalized targeted therapies, and provide insight into resistance mechanisms using patient data.

## Disclosure of conflict of interest

NR has served on advisory boards for Sanofi, Exelexis, Janssen and received compensation from AstraZeneca, EMD Serono, Janssen, Merck, and Tempus outside the submitted work.

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