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# Treatment strategies for DNA repair-deficient prostate cancer

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## Abstract

**Introduction:** Common recurrent genetic alterations have been identified in prostate cancer through comprehensive sequencing efforts, and the prevalence of mutations in DNA repair pathway genes in patients with advanced and metastatic disease approaches 20–25%. Identification of these underlying DNA repair defects may present unique treatment opportunities for patients, both in terms of standard-of-care treatments and selected investigational agents.

**Areas Covered:** We review our current understanding of the genomic landscape of prostate cancer, with special attention to alterations in DNA repair pathway genes in metastatic castration-resistant disease. For patients with tumors deficient in homologous recombination repair, potential opportunities for treatment include platinum chemotherapy, poly(ADP) ribose polymerase (PARP) inhibitors, bipolar androgen therapy, and maybe immune checkpoint blockade therapy. In addition, tumors with mismatch repair defects (*i.e.* microsatellite instability) may be particularly susceptible to checkpoint blockade immunotherapy.

**Expert Commentary:** We anticipate that genomic profiling of tumors will become necessary to guide treatment of advanced prostate cancer treatment in the coming years. Work is needed to define the optimal tissue to test, and to define the national history of tumors with specific genetic defects. The prognostic and therapeutic importance of germline *vs* somatic DNA repair alterations, and mono-allelic *vs* bi-allelic inactivation, also remains unclear. Finally, optimal strategies to sequence or combine targeted agents for these patients with ‘actionable’ mutations are now needed.

### Keywords

Prostate cancer; Homologous Recombination Deficiency; Microsatellite Instability; PARP inhibition; Immunotherapy

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Declaration of Interest

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## 1. Introduction

The field of prostate cancer has benefited from the emergence of multiple new therapies over the past several years. Recent FDA approvals of novel hormonal agents, chemotherapies, immunotherapies, and bone-targeting agents have expanded treatment options for patients with advanced disease. These strategies were fueled by identifying novel ways to attack androgen-receptor signaling (abiraterone [1] and enzalutamide [2]), stimulating the anti-tumor immune response (sipuleucel-T [3]), and leveraging cytotoxic mechanisms of action (cabazitaxel [4], radium-223 [5]). What was perhaps missing was a mechanistic approach at designing therapy based upon the underlying genetic makeup of prostate cancer. However, with the publication of multiple data sets with comprehensive genomic sequencing efforts of prostate cancer, commonly altered families of genes have now been identified. This review aims to summarize recent advances in our understanding of the underlying genetics of prostate cancer with special attention to mutations of genes involved in pathways regulating single-strand and double-strand DNA repair (Table 1). In particular, we will discuss lesions resulting in homologous recombination deficiency as well as mismatch repair deficiency. Furthermore, we will review prognostic implications and treatment opportunities for advanced prostate cancer based upon targeting these DNA repair pathways.

## 2. Genetic Landscape of Localized and Advanced Prostate Cancer

Several large DNA sequencing efforts have shed light on the underlying genetic alterations that are commonly observed in prostate cancer. Many key genetic drivers have been postulated based upon prior publications [6, 7, 8, 9], and the sequencing efforts have offered additional evidence via larger systemic approaches. The Cancer Genome Atlas (TCGA) sequenced 333 primary localized prostate cancers, which comprised a range of risk groups (age, PSA, Gleason score), without regard to subsequent recurrence or metastasis [10]. While smaller studies had characterized some commonly mutated genes in prostate cancer, this study represented the first larger effort to systematically describe the molecular underpinnings of primary prostate cancer.

The TCGA defined seven molecular subsets of prostate cancer. The largest subset was defined by the presence of *ERG* (an ETS transcription factor) fusions (46% of cases). Other subsets included those with fusions/overexpression of *ETV1* (8%), *ETV4* (4%), or *FLI1* (1%). The remaining subsets contained mutations of *SPOP* (11%), *FOXA1* (3%), or *IDH1* (1%). In primary prostate cancer, the *TMPRSS2-ERG* fusion was the most commonly observed large genomic alteration. This chromosomal rearrangement forms a novel gene product that fuses an androgen-regulated gene (*TMPRSS2*) with a transcription factor gene (*ETS*) [11]. In sum, the groups defined by presences of fusions of the ETS family of transcription factors makes up approximately half of all primary prostate cancers. The high incidence of these types of fusion genes in prostate cancer is explained by inaccurate reassembly of double-strand DNA breaks that occur during normal androgen-directed gene transcription in prostate epithelial cells [12]. Hypermethylation was also common in primary prostate cancer, particularly among the *IDH1*- mutated subset.

While these molecular subsets are illustrative of clusters of underlying genomic alterations, perhaps more informative in the TCGA analysis was an effort to summarize potentially 'actionable' mutations. The *PI3K* pathway had alterations in 25% of cases, with *PTEN* inactivation accounting for most (19%). DNA-repair pathway genes were altered through either mutations or deletions in 17% of cases. The majority of these cases involved genes related to the homologous recombination repair pathway that is responsible for fixing double-strand DNA breaks: *FANCD2* (7% of cases), *ATM* (4%), *BRCA2* (3%), *RAD51C* (3%), *CDK12* (2%), and *BRCA1* (1%). Importantly, bi-allelic (as opposed to mono-allelic) inactivation of these homologous recombination genes was only present in 8% of cases, probably reflecting the true prevalence of pathogenic lesions in these genes (which usually function as tumor suppressors). Notably, mutations in mismatch repair genes involved in fixing single-strand DNA breaks (*MSH2, MLH6*) were very rare (<1%). A second study evaluating the genomic landscape of 477 localized intermediate-risk (Gleason 6–7) prostate cancers found that 47 patients (10%) harbored DNA repair mutations in homologous recombination genes: *FANCA* (n=9), *ATM* (n=8), *RAD51* (n=7), *CDK12* (n=6), and *BRCA2* (n=5) [13]. Therefore, the prevalence of homologous recombination mutations in primary prostate cancer is likely between 8–10%.

While these data sets helped to define the genomics of primary prostate cancers and may have implications for future screening, risk stratification, or adjuvant treatment decisions; in general, applicability of these data from localized prostate cancer to patients with advanced and metastatic cancer is unclear. A minority of prostate cancers result in mortality to patients, as evidenced by the large divide between incidence (161,360) and deaths (26,730) annually in the United States [14]. In the TCGA cohort, just 10% of patients were known to have experienced a biochemical recurrence at last follow up. To supplement our understanding of cancers that progress to metastases, another effort examined 150 metastatic tumors from patients with castration-resistant prostate cancer (mCRPC) [15]. In that study of metastatic biopsies in patients with mCRPC, the most common genetic alterations observed were amplifications or mutations in the androgen receptor (AR) gene (63%), ETS transcription factor fusions (57%), *TP53* alterations (53%) or *PTEN* alterations (41%). One of the most striking differences in comparing the data for localized and metastatic tumors was the significant enrichment of AR alterations in mCRPC tumors—presumably as a result of selective pressure from treatment with AR-directed therapeutics. Other genes that were enriched in metastatic vs. localized disease included *PTEN, TP53* and *BRCA2*.

Like the TCGA analysis of localized prostate cancer, the analysis of mCRPC similarly sed on genetic alterations that were potentially clinically actionable. Among the 150 iCRPC tumors that were sequenced, the authors identified potentially clinically actionable somatic alterations in the pathways of *PI3K* (49% of cases), DNA repair (19%), *CDK* inhibitors (7%), *WNT* signaling (5%), and *RAF* signaling (3%). Specifically focusing on homologous recombination pathway genes (total prevalence: 21%), mutations or alterations were identified in *BRCA2* (13%), *ATM* (7%), *CDK12* (5%), and *BRCA1* (1%). Alterations in mismatch repair genes (*MLH1, MSH2*) remained relatively rare (2%), yet were identified at a slightly higher frequency compared to the TCGA data. In an updated analyses from these same investigators encompassing genomic data from 335 mCRPC samples, the overall prevalence of somatic pathogenic DNA repair alterations was 20% (primarily involving

*FANCD2, BRCA2, ATM* and *CDK12*) [16]. Therefore, the prevalence of homologous recombination mutations in advanced prostate cancer (mCRPC) is likely between 20–25% (approximately 2 to 3-fold higher than what is observed in localized disease). In particular, this updated analysis showed very significant enrichment of *BRCA2* lesions in mCRPC vs. primary prostate cancer.

Data is now also emerging regarding the prevalence of *germline* mutations in DNA repair genes in patients with prostate cancer [17]. When examining a subset of 20 genes involved in one of several DNA repair pathways in a cohort of 692 men with metastatic prostate cancer, 11.8% of subjects were found to harbor an underlying inherited germline mutation. The most commonly mutated genes in these men were *BRCA2* (5.4%), *CHEK2* (1.9%), *ATM* (1.6%), and *BRCA1* (0.9%). There were 2 cases (0.3%) of mutated genes involving mismatch repair pathways (*MSH2, MSH6*). Furthermore, germline DNA repair gene mutations were more common in patients with metastatic prostate cancer (11.8%) when compared to a cohort of patients with localized prostate cancer (4.6%) and compared against the general population (2.7%). The high prevalence of germline gene mutations in the homologous recombination repair pathway was confirmed in a subsequent study examining subjects who died from metastatic prostate cancer. In a series of 313 patients with lethal prostate cancer, the carrier rates for germline mutations in *BRCA2, ATM,* and *BRCA1* was cumulatively 6%, with rates of 3.5%, 1.9%, and 0.6% for the individual genes, respectively [18]. Finally, a more recent study evaluating inherited DNA repair mutations in 319 mCRPC patients receiving abiraterone or enzalutamide, found that 24 men (7.5%) harbored germline lesions in DNA repair genes; the most commonly implicated genes in that study were *BRCA2, PALB2, ATM* and *CDK12* [19]. Therefore, the prevalence of germline DNA repair gene mutations in mCRPC is likely between 8–12%, which is much higher than previously anticipated.

Table 2 summarizes the relative prevalence of somatic inactivating DNA repair alterations in populations ranging from localized disease to mCRPC.

## 3. Treatment opportunities for Homologous Recombination-Deficient (HRD) Prostate Cancer

The most common DNA repair defects present in both localized and metastatic prostate cancer involve genes regulating the homologous recombination pathway. The pathway of error-free homologous recombination is normally employed after the introduction of double-strand DNA breaks in cells. A variety of genes are critical to this pathway, including *BRCA2, BRCA1, PALB2, ATM* and most of the Fanconi anemia (*FANC*) genes. Cells that have deficiency in homologous recombination are prone to introduction of errors into the cellular genome as the result of faulty double-strand DNA repair, especially resulting from ionizing radiation. While this feature likely explains the higher cancer risk for patients who are carriers of these genes, it also is important as it is also represents a potential susceptibility to specific therapy that can lead to ‘synthetic lethality’ [20].

### 3.1 Radiation therapy for localized disease

The prognosis for a localized prostate cancer with HRD may be worse than for similar cancers without HRD [21,22, 23]. The optimal treatment strategy for these tumors is not known, as there are no prospective studies comparing outcomes for patients specifically with HRD for primary treatment with surgery versus radiation therapy. Currently, most patients with localized prostate cancer are offered local therapy based upon multiple clinical and pathologic factors, including disease risk, patient age, and anatomic details of the cancer. Genetic profiling has not been used to date to steer patients to a specific modality (such as radiation therapy vs surgery). Newly identified homologous recombination gene defects in primary prostate cancers may offer unique treatment opportunities for these patients in the future.

Currently, patients who undergo definitive radiation therapy for intermediate- or high-risk localized prostate cancers are typically offered concurrent hormonal therapy, which results in superior outcomes compared to radiation therapy alone. The mechanism by which androgen deprivation therapy synergizes with radiation therapy is thought to be due to impairment of nonhomologous end joining double-strand DNA repair [24, 25]. In a similar fashion, tumors with inherent defects in DNA repair genes may be particularly susceptible to radiation therapy, even in the absence of concurrent hormonal therapy. In fact, preclinical models have demonstrated that defects in HRD (such as BRCA2) result in increased sensitivity to radiation damage when compared to tumors without such defects, ability to repair DNA damage caused by radiation therapy [26].

Localized treatment of HRD tumors with radiation also offers an opportunity to combine other agents targeting the homologous recombination pathway to synergize with radiation or combat resistance. Future trials may combine PARP inhibitors and other agents with radiation therapy. Given the theoretical sensitivity to radiation therapy and potential to combine targeted agents with radiation therapy, genotyping primary cancers (or using other biomarkers #32 evans) may eventually guide physicians to recommend a specific local treatment modality.

### 3.2 PARP Inhibition

Poly(ADP) ribose polymerase (PARP) inhibitors are the most developed class of drugs that specifically treat tumors with HRD. In preclinical models, tumors with HRD were shown to be susceptible to inhibition of the PARP1/2 enzymes, through a process termed ‘synthetic lethality’ [27, 28]. PARP functions in the DNA repair pathway by serving in base excision repair of DNA single-strand breaks. In the absence of PARP functionality, cells are unable to repair single-strand DNA breaks. Persistent single-strand breaks are converted to double-strand breaks during subsequent DNA replication. Cells typically would then employ the homologous recombination repair pathway to address such double-strand defects. However, deficiencies in the homologous recombination pathway enzymes exacerbates double-strand strand breaks, leading to chromosomal instability and eventually cell death due to catastrophic genomic damage. Thus, the intrinsic homologous recombination deficiencies lead to susceptibility to PARP inhibition. Importantly, since the proteins regulating homologous recombination are tumor suppressors, only bi-allelic inactivation leads to loss

of protein function (and results in subsequent sensitivity to PARP inhibition), while mono-allelic homologous recombination gene mutations do not generally induce loss of protein function and therefore do not generally sensitize to PARP inhibitors [28].

While a small number of prostate cancer patients were included in early clinical studies of PARP inhibitors [29], the first dedicated study of a PARP inhibitor for advanced prostate cancer was a 50-patient trial of patients with mCPRC [30]. This study was not only the first extensive investigation of PARP inhibition in prostate cancer, but it furthermore served as a proof-of-concept that prostate cancer may be treated with therapy targeting specific genetic defects. Olaparib—which was the first FDA-approved PARP inhibitor and carries an indication for recurrent *BRCA-mutated* ovarian cancer [31]—was tested in men with mCRPC that was resistant to prior taxane chemotherapy. All patients had received multiple lines of therapy for mCRPC, and nearly all patients had received prior abiraterone. Patients were treated with 400mg of olaparib twice daily. Eleven of 49 evaluable patients (22%) had a 50% or greater PSA decline ($PSA_{50}$ response) using olaparib. Six patients (19%) had a radiographic partial response by RECIST 1.1 criteria (out of 32 with measureable disease).

A panel of genes related to the homologous recombination repair was tested in the patients to determine a possible biomarker of response for olaparib for mCRPC. These genes included *BRCA2, BRCA1, ATM, PALB2, CHEK2,* and *FANCA*. Of these 11 patients with a $PSA_{50}$ response in the trial, 10 of the responders had tumors with HRD as defined by a deleterious alteration in this panel of genes. Also, 5 of the 6 radiographic responders had HRD tumors. Overall, 16 patients (32%) on the trial had tumors with HRD, and those patients had an 88% composite response rate. Those tumors that were deemed biomarker-positive had a median radiographic progression-free survival of 9.8 months and a median overall surviv 13.8 months, compared to significantly inferior clinical outcomes among biomarker-negative patients. Olaparib produced a radiographic response and a $PSA_{50}$ response in just one biomarker-negative patient. The $PSA_{50}$ response rate for tumors without HRD was 6%, and these biomarker-negative patients had shorter median progression-free survival (2.7 months) and overall survival (7.5 months). Importantly, previous trial using other PARP inhibitors in unselected prostate cancer populations did not show significant efficacy in the mCRPC setting [32, 33].

Based upon these striking data and the high response rate in HRD tumors, the field has exploded with trials investigating PARP inhibition in prostate cancer. The FDA has also recently granted ‘breakthrough designation’ status for olaparib for the treatment of castration-resistant prostate cancer with mutations *BRCA1, BRCA2,* or *ATM* with progression after prior abiraterone and/or enzalutamide. As a result, olaparib will now be tested in the randomized phase III setting (compared against abiraterone or enzalutamide) in men with mCRPC who harbor germline and/or somatic mutations in *BRCA1/2* or *ATM,* and will stratify by whether or not prior taxane chemotherapy was used (NCT02987543). Approximately 10–12% of patients may be candidates for olaparib or other PARP inhibitors, if restricted to this gene signature. A second randomized cohort from this same phase III trial of olaparib will also permit enrollment of patients with mutations in 12 other HRD genes, probably accounting for another 10–12% of mCRPC patients. Many additional trials are investigating PARP inhibition as a single-agent in progressive mCRPC. Rucaparib, the

other FDA-approved PARP inhibitor with an indication for the treatment of resistant ovarian cancer with mutations in *BRCA1* or *BRCA2,* is also currently being tested in prostate cancer in a pivotal phase III trial. Ongoing or pending trials of PARP inhibitors for prostate cancer with HRD are listed below.

### 3.3 Abiraterone and Novel Hormonal Therapy

There may be other treatment opportunities specifically for tumors with HRD alteration in addition to PARP inhibition monotherapy. Tumors with HRD may be more responsive to agents targeting the androgen/AR axis, such as abiraterone. The possibility of increased sensitivity to abiraterone was raised in an exploratory analysis of subjects in a randomized phase II trial testing abiraterone with or without the PARP inhibitor veliparib [34]. All patients with mCRPC were eligible to join the study, and tumor biopsies performed on study were subsequently analyzed for the presence of mutations in DNA repair genes. Overall, the patients in the trial had $PSA_{50}$ responses of 64–71%, without any significant difference between the two cohorts (*i.e.* abiraterone with or without veliparib). Eighty-seven of the patients had tumors tested for HRD lesions, and 22/87 (25%) had deleterious mutations in either *BRCA2* (n=13), *ATM* (n=5), *BRCA1* (n=1), *PALB2* (n=1), *FANCA* (n=1), or *RAD51* (n=1). Surprisingly, the patients with HRD had *superior* response rates regardless of treatment allocation (combined 89% $PSA_{50}$ response) and median progression-free survival (13.8 months) compared to tumors without HRD (57% $PSA_{50}$ response, and 7.8 month progression-free survival). This analysis perhaps suggests that tumors with HRD may be more responsive not only to PARP inhibition in combination with abiraterone but to abiraterone itself (notably, even in the HRD patients, the addition of veliparib did not significantly improve outcomes however) [34]. Based upon this hypothesis-generating study, a phase 2 study will now examine abiraterone versus olaparib (or the combination) in chemo-naïve mCRPC patients who harbor HRD mutations. However, nother retrospective study in mCRPC patients receiving either abiraterone or enzalutamide suggested an inferior outcome to novel hormonal therapy in men with germline homologous recombination defects compared to germline mutation-negative patients (3.3 *vs* 6.2 months, respectively) [19]. Therefore, the true prognostic impact of DNA repair mutations on sensitivity or resistance to novel hormonal therapy remains obscure at this time [35].

Despite the promising initial data from the patients in the abiraterone/veliparib study regarding responsiveness of HRD tumors to manipulation of the AR axis, the presence of mutations in DNA repair genes was traditionally thought to confer an inferior prognosi compared to tumors without such mutations [21,22, 23]. If in fact therapies like abiraterone are found to have relatively increased efficacy in HRD tumors, the use of such therapies may abrogate this prognostic disadvantage. More studies, including of agents beyond abiraterone such as enzalutamide or other experimental antiandrogens, are needed in mCRPC patients with HRD to resolve this uncertainty.

### 3.4 Platinum chemotherapy

For other malignancies where HRD is common—such as ovarian cancer—many tumors show particular sensitivity to platinum chemotherapy agents [36]. Carboplatin works by binding DNA and forming DNA cross-links that interfere with transcription and replication

[37]. The DNA damaged by the platinum agent is required to be repaired to restore the functionality of the cell, or cell death can result. Epithelial ovarian cancer and triple-negative breast cancer (both of which may be enriched for tumors with HRD) have clinical evidence of increased sensitivity to platinum chemotherapy compared to other chemotherapeutic agents and compared to tumors without mutations in homologous recombination repair pathway genes [38, 39, 40, 41]. Much of the development of PARP inhibition in ovarian cancer has focused on platinum-sensitive tumors, given the observations regarding underlying potential sensitivity to both treatments. In theory therefore, chemotherapy with carboplatin is a potential efficacious treatment options for prostate cancer patients with HRD.

For metastatic adenocarcinoma of the prostate, carboplatin is used particularly for tumors with resistance to taxane monotherapy [42, 43] or for tumors exhibiting features consistent with a neuroendocrine or aggressive-variant phenotype [44, 45]. Carboplatin is typically administered in conjunction with a taxane chemotherapeutic, or with etoposide if a biopsy shows evidence of pure small cell transformation. When used in an unselected population with regard to DNA repair mutation status after progression on docetaxel chemotherapy, platinum plus either docetaxel or paclitaxel produced response rates of 14–26% in prospective single-arm trials [42, 43]. General adoption of combination chemotherapy with platinum for all patients with mCRPC has been limited by lack of significant improvement in efficacy with further additive side effects of the platinum agent.

However, testing platinum in patients specifically with tumors with HRD may present an opportunity to select for increased tumor sensitivity. This concept has been exemplified by several case series. For example, one group has recently reported dramatic and sustained responses to carboplatin and/or cisplatin chemotherapy in three different mCRPC patients with bi-allelic inactivation of the *BRCA2* gene [46]. In a separate report, a patient with aggressive neuroendocrine prostate cancer with a germline inactivating lesion in *FANCA* (and a somatic deletion of the second *FANCA* allele) had an exceptional response to the combination of cisplatin-docetaxel, lasting >12 months [47]. To substantiate these anecdotes, multiple trials have opened testing carboplatin or carboplatin-plus-docetaxel for patients with mCRPC and mutations in *BRCA1, BRCA2, ATM,* or other homologous recombination repair genes (see Table 4.). In addition, a new trial designed by the ECOG-ACRIN cooperative group (EA8152) will randomize docetaxel-pretreated mCRPC patients to receive combination chemotherapy with carboplatin-paclitaxel with or without the addition of veliparib. Although this last trial will not select only patients with HRD lesions, the presence or absence of HRD at baseline will be used as a prespecified stratification factor to evaluate treatment responses in both subgroups.

### 3.5 Bipolar Androgen Therapy

The rationale for treatment of HRD tumors with agents that produce double-strand DNA damage can be extended to the novel concept of high-dose testosterone therapy (also called bipolar androgen therapy, BAT) for patients with mCRPC. In the setting of castrationresistance, prostate cancer cells significantly elevate levels of AR expression as an adaptive mechanism, in order to continue to express the androgen-regulated genes needed

for growth [48]. In the setting of amplified AR levels, flooding the cell with supraphysiological levels of testosterone can paradoxically result in cell-cycle arrest and double-strand DNA breaks [49]. *In vivo* models have shown that tumors can regress with the administration of high-dose testosterone therapy, but eventually tumors re-adapt to the high testosterone environment over time [50]. A series of human trials have been testing the modulation of testosterone levels from supratherapeutic to near-castrate levels (*i.e.* bipolar androgen therapy). In these clinical trials, bipolar androgen therapy has resulted in PSA and even objective responses in a significant subset of patients [51,52], and has been able to re-sensitize some patients to abiraterone and enzalutamide despite prior resistance to these agents. Based on these encouraging preliminary clinical results using this seemingly paradoxical approach, a randomized study has been designed for abiraterone-pretreated mCRPC patients (NCT02286921). Such patients are being randomized (1:1) to receive BAT or enzalutamide, with the primary endpoint being radiographic progression-free survival.

Theoretically, bipolar androgen therapy (through its resultant double-strand DNA damage) may be particularly effective in tumors with HRD. While this treatment is still experimental and trials are ongoing, we have reported on an exceptional responder to this high-testosterone therapy [53]. This exceptional responder underwent germline and tumor sequencing and was found to have HRD, specifically with deleterious mutations in *BRCA2* and *ATM*. We have therefore postulated that men with mCRPC and HRD may be particularly susceptible to bipolar androgen therapy. Indeed, unpublished data from our group has found additional HRD mutations in other exceptional responders to BAT treatment. Further characterization of the underlying DNA mutation profile for responders to this therapy is urgently needed, and further studies of bipolar androgen therapy (either alone or in combination with other DNA-damaging agents) should now be conducted in this patient population. Nonetheless, this therapeutic avenue (*i.e.* BAT) represents a potential additional treatment opportunity for these DNA repair-deficient tumors.

### 3.6 Radium–223

Preclinical studies have demonstrated particular sensitivity of cancer cells with HRD to ionizing radiation [26]. In the same fashion that introduction of double strand breaks via platinum chemotherapy, high dose testosterone, or unrepaired single strand breaks via PARP inhibition, prostate cancer cells with HRD may be susceptible to radiation therapy. In theory, for patients with HRD with metastatic disease concentrated in bone, the use of the FDA-approved therapy radium-223 may result in particularly notable efficacy. Radium-223 is an intravenous alpha-emitting radiopharmaceutical approved for patients with mCRPC with symptomatic bone metastases [5]. While there are no formal studies testing radium-223 specifically in this subgroup of tumors, Steinberger *et al.* have reported on an exceptional responder to radium-223 therapy who underwent tumor sequencing identifying a deleterious frameshift mutation in BRCA2 [54]. The patient had bi-allelic loss of BRCA2 based upon germline and tumor testing. Further study, either through collection of a prospective case series of patients with HRD treated with standard of care radium-223 or via a dedicated clinical trial for such patients, will further define the relative benefit for radium in this specific subpopulation.

### 3.7 Checkpoint Blockade Immunotherapy

Prostate cancer was the first cancer to have an immunotherapy that prolonged survival, following the approval of sipuleucel-T in 2010 [3]. Given that early success, prostate cancer was initially avidly studied for responses to immune checkpoint blockade (anti-PD1 and anti-CTLA4 strategies). However, while immune checkpoint blockade has transformed the treatment options for many other malignancies, prostate cancer has not been shown to be as responsive to this approach to date. Single-agent anti-CTLA4 (ipilimumab) has been tested extensively in advanced prostate cancer. However, two pivotal phase 3 trials were negative in unselected mCRPC populations, although activity was certainly seen in many individuals. The first of these trials randomized men (n=799) with mCRPC with progression after docetaxel chemotherapy to receive ipilimumab or placebo [55]. There was no difference in overall survival between cohorts (11.2 months vs 10.0 months, HR 0.85, p=0.053). A subgroup analysis suggested that patients without poor-prognostic features (such as elevated alkaline phosphatase or visceral metastases) may have benefited more from ipilimumab. A second phase 3 study then tested men (n=602) with mCRPC that was minimally symptomatic, chemotherapy-naïve, and free from visceral metastases [56]. Despite the selection of a population with more favorable prognostic features, that study was similarly negative, with no difference in overall survival observed (28.7 months vs 29.7 months, HR 1.11, p=0.36). However, even in this second study, about one-quarter of patients had PSA responses and about one-tenth of patients had objective RECIST-responses. The conclusions from these studies was that immune checkpoint blockade may be effective in a subset of prostate cancer patients but had not been shown to be effective for a genetically unselected population.

There is a paucity of data regarding anti-PD-1 therapy in prostate cancer, as just seventeen patients with mCRPC were included on the phase I trial of nivolumab, without any objective reported responses although $PSA_{50}$ responses were seen [57]. However, more recent studies with pembrolizumab have shown occasional anecdotal radiographic and $PSA_{50}$ responses to PD1 inhibition in mCRPC [58, 59]. A signature defining a potential response to anti-PD-1 therapy has not been developed, such as quantifying and correlating PD-1/PD-L1 expression to response or associating response for patients with specific prior treatments. The data regarding expression of PD-1/PD-L1 in prostate cancer is conflicting [60, 61,62]. Furthermore, it is possible that therapy for prostate cancer (such as antiandrogens) results in relative immunosuppression [63] that theoretically may blunt anti-PD-1 response.

In other tumor types, mutations in homologous recombination genes have been associated with a higher mutational load, higher numbers of tumor neoantigens, and PD-expression [64]. It can therefore be postulated that mCRPC tumors with mutations in homologous recombination repair pathway genes may represent a subset of cancers for which immune checkpoint blockade may be effective. Indeed, there is evidence from the melanoma literature that BRCA-deficient melanomas respond more favorably to PD1 inhibition compared to BRCA wild-type melanomas [65]. Based upon this rationale, several phase 2 trials are underway to test immune checkpoint blockade specifically in prostate tumors with HRD (or microsatellite instability [MSI]) (see Table 5). The relationship between DNA

mismatch repair mutations and sensitivity to immune checkpoint inhibitors will be discussed further in the next section.

## 4. Treatment Opportunities for Microsatellite Instability (MSI)-High Prostate Cancer

The mismatch repair (MMR) pathway is responsible for repairing DNA replication errors and DNA damage occurring in DNA single strands. Tumors with mutations in MMR pathway genes (and resultant microsatellite instability) are found most commonly in colorectal and other gastrointestinal malignancies, as well as endometrial and ovarian cancers [66]. However, a small but potentially important fraction of prostate cancers are now understood to harbor these MR mutations. Up to 3% of tumors in the mCRPC sequencing datasets harbor exomic mutations in mismatch repair genes. However, whole-exome or targeted genetic sequencing efforts may perhaps underestimate the true prevalence of MMR alterations in mCRPC. In a recent study using next-generation sequencing to interrogate the four MMR genes (MSH2, MSH6, MLH1, PMS2), the authors found that 5/50 mCRPC patients (10%) from a rapid-autopsy series harbored large-scale and complex genomic rearrangements involving one or more of the MMR genes, primarily MSH2 and MSH6 [67]. Most (but not all) of these cases resulted in MSI-high tumors with multiple unstable satellite regions and accompanied by hypermutation (>10 mutations/Mb of DNA). A more recent publication from this same group suggested that MMR mutations may be enriched in patients with ductal adenocarcinoma histology, where the prevalence of MSI-high tumors may be as high as 30–40% in that subset [59]. Overall, the true prevalence of mismatch repair mutations in advanced prostate cancer will probably be around 5% or so.

Tumors with the high mutational load, such as melanoma and lung cancer, in general have been most the most responsive cancers to immunotherapy [68, 69]. A recent proof-of-concept trial tested the activity of the anti-PD-1 antibody pembrolizumab in tumors that either harbored mismatch repair mutations or those with proficient mismatch repair machinery [70]. In that trial, 21 patients with tumors harboring MSI (11 colorectal and 9 of other gastrointestinal tumors) and 20 patients with microsatellite-stable colorectal cancer were treated with pembrolizumab. The objective response rate for tumors with MSI was 53% (9/17) among evaluable patients, while the objective response rate for tumors without MSI was 0% (0/19). There were significant advantages for the MSI-high group in terms of progression-free and overall survival as well. This success of selecting tumors with MSI for immune checkpoint blockade in multiple histologies, if based upon a hypermutated phenotype, may also be extrapolated to mCRPC.

Although studies of PD-1 blockade in prostate cancer are few to date, a trial recently reported preliminary findings that included a remarkable response in mCRPC with MSI. In a phase II trial adding pembrolizumab to enzalutamide for patients with mCRPC progressing on enzalutamide, 3 of the first 10 patients accrued exhibited complete biochemical responses and some also had objective responses [58]. Two of these patients had baseline tissue biopsies that were analyzed for PD-L1 expression and MSI status. One extreme responder was found to have MSI as well as tumoral PD-L1 expression. A second patient with MMR-

deficient prostatic ductal adenocarcinoma from a separate report also demonstrated a favorable response to pembrolizumab monotherapy [59]. Further investigation on the role of immune checkpoint blockade in microsatellite-unstable (MSI-high) advanced prostate cancer is ongoing (Table 5)

## 5. Conclusions

Efforts to systemically catalog the genomic landscape of prostate cancer, from primary prostatectomy specimens to metastatic castration-resistant disease, have shed light on common underlying genetic alterations. HRD is present in a significant minority of advanced prostate cancer patients (20–25%), and clinical trials specifically targeting patients harboring these mutations are ongoing with PARP inhibition, platinum chemotherapy, abiraterone, and immunotherapies. MSI is rare in prostate cancer (perhaps 5% of mCRPC); however, if identified presents a potential opportunity specifically for immune checkpoint blockade therapy. Future studies of prostate cancer natural history and therapies are likely to incorporate association with underlying genetic alterations, and this work may lead to selection of specific therapies for subsets of patients most likely to gain significant benefit. In part, this is now underway with regard to HRD in prostate cancer. The genomic revolution in prostate cancer is upon us.

## 6. Expert Commentary: Future Integration of genetics into routine clinical practice and integration of targeted therapies with other approved therapies

Given the significant prevalence of DNA repair mutations in metastatic prostate cancer and the potential therapies that may specifically be effective for tumors harboring these utations, it is rapidly becoming the standard-of-care to obtain targeted next-generation sequencing of tumor tissue in patients with mCPRC. Many questions remain about optimal tissue to send for genomic sequencing. A fresh biopsy is often the optimal sample to obtain—it has the advantage of representing the current tumor, accounting for the entire evolutionary history of the cancer including changes as the result of selective pressure from treatment. However, biopsies require patients to undergo an invasive procedure, and for patients with inaccessible tumor locations, or bone-only disease, the yield from the procedure may be low. Patients with mCRPC will often have available archival tumor tissue, from either a prostate biopsy or prostatectomy specimen. While this tissue can be analyzed, it is an open question about whether fresh tissue is needed to capture the entire evolution of mutations from initial diagnosis of prostate cancer through the development of castration-resistant disease. Specifically considering the detection of DNA repair mutations, the prevalence of these mutations is significantly enriched in samples taken from metastatic sites in patients with mCRPC (particularly with respect to *BRCA2*) compared to primary prostatectomy specimens. The degree to which tumors become enriched in DNA repair mutations as the result of resistance to therapy is not fully understood. Studies examining multiple samples from primary prostate cancer tissue to metastatic tissue in setting of castration-resistance are needed to define this. Another question is the utility of plasma-derived circulating-tumor DNA (ctDNA) for patients with mCRPC and whether this technology may eliminate the

need for tissue biopsy or archival tissue analysis. Indeed, one additional advantage of ctDNA analysis is the theoretical ability to capture genomic information representing the full complement of tumor clones and mutational events that may be present throughout multiple tissues and organs in the patient's body [71]. Notably, commercial clinical-grade platforms to interrogate ctDNA are now available.

Another unknown question is whether all DNA repair mutations are created equal, or not. For example, is it possible that mutations in *BRCA2* might portent a better or worse prognosis (or a more favorable or less favorable) response to a particular therapy than mutations in other omologous recombination genes? In addition, what is the prognostic and therapeutic impact of germline *vs* somatic DNA repair mutations? Our speculation would be that patients who harbor germline homologous recombination mutations may respond more favorable to PARP inhibitors than those with somatic-only lesions, as has been demonstrated in ovarian cancer [72], but this remains to be determined in prostate cancer. Finally, will therapeutic benefit only be observed in cases with bi-allelic DNA repair gene inactivation, as initially postulated in the 'synthetic lethality' hypothesis; or will certain genes (*e.g.* perhaps *ATM*) be characterized by haplo-insufficiency by which a single-copy mutation may be enough to inactivate the tumor suppressor protein? Or will there be specific clinical situations where synthetic lethality can occur despite proficient genotypes [73], such as in chronically hypoxic tumors that have reduced expression of homologous recombination genes resulting in functional HRD? These and other questions will puzzle translational prostate cancer researchers for the next several years.

Another major issue regarding the management of patients with tumors with HRD or MSI is how best to integrate experimental therapies into the use of existing standard therapies available for treatment of mCRPC. For a patient experiencing progression after first-line abiraterone therapy, for example, is the best option a clinical trial with PARP inhibition or platinum chemotherapy? Is the response of a PARP inhibitor likely to be significantly higher if used before chemotherapy rather than after? If chemotherapy is chosen first, should platinum-taxane combination chemotherapy be front-line, or should platinum be reserved as salvage in the setting of taxane resistance for an HRD tumor? Based upon comparisons between the activity of abiraterone and enzalutamide when used either before or after chemotherapy (or before or after the alternative agent), the clinical activity appears to be significantly reduced after a patients has already experienced progression on other agents. Most of these questions remain currently unresolved. We speculate that therapies such as immunotherapy or PARP inhibition may best be employed early in the treatment sequence for mCRPC, rather than reserving their use for heavily-pretreated tumors.

Furthermore, combination strategies that include standard therapy and targeted therapy or immunotherapies may result in additive efficacy to produce long-term remissions. While patients may experience prolonged survival with mCRPC via the currently available therapies, in general there are not long-term survivors to any one of these therapies. For tumors with oncogenic addition to AR signaling and also harboring HRD, will combining first-line AR targeted agents with PARP inhibitors result in long-term remissions? These are the trials that need to be performed in coming years to truly advance the field and to best serve patients.

Lastly, while this review has focused on the treatment opportunities for patients with mutations in DNA repair pathways specifically in the setting of castration-resistance, another avenue to consider is whether tumor genomic analysis has a role in determining the need for primary therapy or screening approaches. If the presence of these DNA repair mutations is an indicator of likelihood or progression to metastatic disease, initial screening based in-part on genomics, in addition to PSA and physical exam criteria, may select for a group where benefit can be demonstrated.

## 7. Five-Year View

In the coming years, further work that more precisely defines the incidence of underlying DNA repair abnormalities and understands how these alterations develop and change from initial carcinogenesis to end-stage resistant metastatic disease will be required. Although the published genomic studies have given us a first glimpse at the somatic genetic landscape underlying prostate cancer, the total number of patients for which comprehensive genomic analysis has been performed is still relatively small. This is even more true of germline genetic defects, where thousands of prostate cancer patients will need to be systematically screened before the true prevalence of inherited DNA repair mutations can be uncovered. Opportunities remain for expanding the number of patients who have tumors sequenced in a systematic fashion. Just as the past 5 years have seen the emergence of multiple new therapies that rapidly were adopted for standard-of-care use in CRPC, we are hopeful to see further developments and approval of novel genomically-targeted agents in the coming years. The benchmark for understanding the potential impact of these novel agents in part should be set as to whether these therapies provide a novel mechanism of action for all patients, or provide extraordinary benefit in a selected population. The opportunity for the treatment of tumors with HRD and MSI is that extraordinary benefit may be achieved through the above mentioned agents and others to come.

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## List of Abbreviations

| | |
|---|---|
| **AR** | androgen receptor |
| **PARP** | poly(ADP) ribose polymerase |
| **TCGA** | The Cancer Genome Atlas |
| **mCRPC** | metastatic castration-resistant prostate cancer |
| **HRD** | homologous recombination-deficient |
| **BAT** | bipolar androgen therapy |
| **MSI** | microsatellite instability |

| | |
|---|---|
| **MMR** | mismatch repair |
| **ctDNA** | circulating-tumor DNA |

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Papers of special note have been highlighted as:

* of interest

** of considerable interest


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**8.**

### Key Issues

- Mutations of genes regulating DNA repair pathways occur in a significant number o mCRPC tumors, with estimates ranging between one-fifth and one-fourth of patients. About half of these patients will also harbor inherited germline mutations in these same genes.
- PARP inhibition is the most promising targeted therapy in tumors harboring homologous recombination DNA repair pathway defects, with multiple phase 2 and phase 3 trials underway testing PARP inhibition, either alone or in combinations, in mCRPC patients. Olaparib has received ‘breakthrough’ designation by the FDA for *BRCA1/2*- and *ATM-mutated* CRPC tumors.
- Cancers with HRD may be particularly sensitive to certain available therapies, including platinum chemotherapy and perhaps abiraterone.
- While immune checkpoint blockade has not been proven to be very effective in unselected prostate cancer patients to date, PD-1 inhibition specifically for HRD or MSI tumors may identify the susceptible subset of prostate cancer tumors that may respond.
- Future work is needed to define optimal tissue sampling to detect actionable mutations, and to identify the best strategies to integrate experimental therapies into standard treatments for both localized prostate cancer and mCRPC.

**Table 1.**

DNA Repair Pathways and Selected Critical Genes.

| Repair Pathway | DNA Damage Mechanism(s) | Selected Critical Genes |
|---|---|---|
| Mismatch Repair | ssDNA base errors from DNA replication & recombination | *MSH2, MSH6, MLH1, PMS2* |
| Nucleotide Excision Repair | ssDNA damage from UV light, polycyclic aromatic hydrocarbons | *XPA-XPG, ERCC1/2/3, CSA/B, RPA, RAD23A/B* |
| Base Excision Repair | ssDNA damage from alkylation, oxidative stress, deamination | *PARP1/2/3, POLB, MUTYH, XRCC1, MBD4* |
| Homologous Recombination | dsDNA damage from ionizing radiation | *FANC* genes, *BRCA1/2, ATM, PALB2, RAD51, NBN, GEN1* |
| Non-Homologous End Joining | dsDNA damage from ionizing radiation | *XRCC4/5/6, LIG4, DCLRE1C, PRKDC, NHEJ1, POLL/M* |
| Trans-lesional DNA synthesis | dsDNA damage requiring repair without DNA template | *POLH, POLI, POLK, PCNA, REV1/3* |

**Table 2.**

Relative prevalence of DNA repair mutations in prostate cancer patients.

| | Localized PCa [10,13] | Metastatic PCa [15,16] |
|---|---|---|
| **Homologous Recombination Pathway** | | |
| *BRCA2* | 2–3% | 7–8% |
| *ATM* | 2–4% | 5–6% |
| *PALB2* | <1% | 1–2% |
| *BRCA1* | 1% | 1% |
| *CHEK2* | <1% | 1–2% |
| *RAD51* | 1–2% | 3–4% |
| *CDK12* | 1–2% | 5–6% |
| **Mismatch Repair Pathway** | | |
| *MLH1* | <1% | 1% |
| *MSH2* | <1% | 2–3% |
| *MSH6* | <1% | 1% |
| *PMS2* | <1% | <1% |
| **Overall** | 8–10% | 20–25% |

**Table 3.**

Pending Phase 2 or Phase 3 trials of PARP inhibition in Prostate Cancer with HRD.

| ClinicalTrials.Gov # | Phase | Investigational Agent | Population |
|---|---|---|---|
| NCT02987543 | 3 | Olaparib vs Standard Treatment (Enzalutamide or Abiraterone) | mCRPC with HRD, second-line therapy |
| NCT03012321 | 2 | Olaparib plus Abiraterone vs Olaparib vs Abiraterone | mCRPC with HRD, first line therapy |
| NCT02975934 | 3 | Rucaparib vs Standard Treatment (Physician's Choice) | mCPRC with *BRCA1, BRCA2,* or *ATM* mutation; second-line therapy |
| NCT02952534 | 2 | Rucaparib | mCRPC with HRD, third- or fourth-line therapy |
| NCT02854436 | 2 | Niraparib | mCPRC with HRD, third-line or beyond therapy |
| NCT02987543 | 2 | Talazoparib | mCRPC with *BRCA1* or *BRCA2* mutation, third-line therapy |
| NCT03047135 | 2 | Olaparib | Biochemically recurrent prostate cancer, hormone-naïve |

**Table 4.**

Pending trials of platinum chemotherapy in Prostate Cancer with HRD.

| ClinicalTrials.Gov # | Phase | Investigational Agent | Population |
|---|---|---|---|
| NCT02311764 | 2 | Carboplatin | mCRPC with HRD, post-docetaxel therapy |
| NCT02985021 | 2 | Carboplatin plus Docetaxel | mCPRC with BRCA1, BRCA2, or ATM germline mutation; second-line or beyond therapy |
| NCT02598895 | Pilot | Carboplatin plus Docetaxel | mCPRC with HRD, second-line or beyond therapy |
| pending | 2 | Carboplatin plus Paclitaxel vs Carboplatin plus Paclitaxel plus Veliparib | mCRPC, post-docetaxel therapy |

**Table 5.**

Pending trials with immunotherapy in Prostate Cancer with DNA repair defects.

| ClinicalTrials.Gov # | Phase | Investigational Agents | Population |
|---|---|---|---|
| NCT03040791 | 2 | Nivolumab | mCRPC with HRD or MSI, post-chemotherapy |
| NCT03061539 | 2 | Ipilimumab plus Nivolumab | mCRPC with HRD or MSI, mCPRC (all-comer), second-line therapy |