Review Article



# Prostate cancer in the era of "Omic" medicine: recognizing the importance of DNA damage repair pathways

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**Abstract:** Data from recent high-throughput studies analyzing local and advanced prostate cancer have revealed an incredible amount of biological diversity, which has led to the classification of distinct molecular tumor subtypes. While integrating prostate cancer genomics with clinical medicine is still at its infancy, new approaches to treat prostate cancer are well underway and being studied. With the recognition that DNA damage repair (DDR) mutations play an important role in the pathogenesis of this disease, clinicians can begin to utilize genomic information in complex treatment decisions for prostate cancer patients. In this Review, we discuss the role of DDR mutations in prostate cancer, including deficiencies in homologous repair and mismatch repair (MMR), and how this information is revolutionizing the treatment landscape. In addition, we highlight the potential resistance mechanisms that may result as we begin to target these pathways in isolation and discuss potential combinatorial approaches that may delay or overcome resistance.

**Keywords:** Prostate cancer; genomics; DNA damage repair (DDR)

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## Introduction

Prostate cancer remains one of the most commonly diagnosed cancers for men in the Western world and a leading cause of cancer-related deaths worldwide (1). Despite the progress in prostate cancer screening and in the management of localized disease, metastatic prostate cancer is invariably fatal. In the United States alone, the National Cancer Institute estimates that over 26,000 men will have died from prostate cancer in 2017 (2).

Since Huggins and Hodges discovered the effectiveness of hormonal therapy in treating prostate cancer more than 75 years ago, androgen deprivation therapy (ADT) has remained the backbone of systemic prostate cancer treatment. Unfortunately, many patients with hormone-sensitive prostate cancer will eventually develop progressive disease despite castrate levels of serum androgens, a disease state known as castrate-resistant prostate cancer (CRPC). In addition, the clinical risk posed by advanced prostate cancer is also determined by whether tumor cells have colonized other organs, a process known as metastasis, which can occur in both the hormone-sensitive setting, or more commonly, in CRPC.

Although metastatic CRPC is incurable, several current treatments extend overall survival. Currently approved therapies in the United States include second-generation anti-androgens (e.g., enzalutamide and abiraterone), radium-223, immunotherapy (sipuleucel-T) and chemotherapy (docetaxel,

cabazitaxel and mitoxantrone) (3-8). However, each of these therapies prolongs overall survival by only a few months. In addition, unlike cancers where molecular alterations inform treatment decisions [for example, using EGFR inhibitors for certain forms of EGFR-mutated non-small cell lung cancer (9)], treatment for prostate cancer is still largely administered without consideration of the underlying genomic alterations within each individual patient's tumor.

Recently, a number of collaborative studies have further defined the molecular landscape of advanced prostate cancer (10-12). [For the purposes of this review, we will focus on androgen receptor (AR)-positive prostate adenocarcinomas, which comprise the vast majority of prostate cancers; while emerging evidence suggests that there are several other distinct phenotypic entities including small cell, neuroendocrine prostate cancer (NEPC) as well as AR-null, non-NEPC prostate cancer, the molecular characteristics of these less common subtypes are still being defined (13-15)]. Efforts to sequence and understand the genomes, exomes, epigenomes and transcriptomes have revealed common aberrations in genes such as the AR, ETS (E26 transformation specific) gene fusions, *TP53* and *PTEN*, as well as perturbations in pathways involving WNT/β-catenin signaling, cell cycle regulation and DNA repair. In addition, prostate cancer can be molecularly grouped into luminal and basal subtypes, which are prognostic and associated with differential response to ADT (16). Furthermore, genomic predictors can identify patients whose tumors might have enhanced responses to post-operative radiation therapy (17). Taken together, these molecular studies demonstrate that different prostate tumor subtypes harboring different molecular mutations have varying responses to current therapeutic interventions. Therefore, identifying dysregulated pathways in each individual patient's tumor and choosing an appropriate therapy may enhance responses and improve survival. However, there are no trials to date that show a survival benefit of using prostate cancer genomics to guide treatment trajectory.

The DNA damage repair (DDR) response, integral in maintaining genomic stability and integrity, has recently emerged as an important contributor to prostate cancer pathogenesis (18). Many of the key components of the DDR are tumor suppressors, which prevent the formation and propagation of mutations and copy-number alterations. The DDR system includes multiple distinct pathways, two of which are homologous recombination (HR), which relies on BRCA1, BRCA2 and ATM, and mismatch repair (MMR), which involves MLH1, MSH2, MSH6 and PMS2 (*Figure 1*). When genes involved in DDR are mutated, genomic instability and increased mutational burden can occur, which can contribute to continued tumor growth. However, we are beginning to learn that these DDR mutations can also be the "Achilles' heel", rendering the cancer cells more sensitive to alternative approaches and targeted therapy. In this Review, we summarize our current understanding of DDR deficiencies in prostate cancer, and discuss how this is changing the treatment landscape of the disease. We highlight several ongoing studies targeting DNA repair deficiency in prostate cancer and propose future studies that may open additional opportunities for targeted approaches. Finally, we highlight the resistance mechanisms that may emerge as we begin to target these pathways individually and discuss potential combinatorial approaches that may delay or prevent resistance, as our knowledge of tumor biology continues to grow.

## Homologous repair deficiencies in prostate cancer

HR is one of two pathways that eukaryotic cells use to repair DNA damage when double-stranded breaks (DSBs) occur. This process, which occurs during the synthesis, or S phase, of the cell cycle, involves using the sister chromatid as the template for DNA synthesis to repair DSBs. HR depends on multiple proteins (including BRCA1, BRCA2, ATM, RAD51, and PALB2 and others) to (I) detect DSBs, (II) resect the 3' ends near the break, (III) promote pairing and invasion of the homologous double helix, and (IV) synthesize the corresponding DNA sequence (19). As this process relies on the sister chromatid to provide the "good" copy, HR is characterized by a low mutation rate and maintains fidelity. Alternatively, cells can utilize another pathway to repair DSBs, a process called non-homologous end joining (NHEJ). Unlike HR, NHEJ is much more error-prone, and is characterized by frequent insertions and deletions in the damaged region of the genome, leading to increased genomic instability (20,21). Deficiencies in HR are the most common DDR defects found in prostate cancer, and without a functioning HR pathway, tumor cells rely exclusively on NHEJ (10). Accordingly, *Brca1* or *Brca2* deficiency in mouse models leads to a mutational signature characterized by deletions followed by tandem repeats (20-22). Interestingly, BRCA1, BRCA2, and RAD51 also have HR-independent functions that help to prevent genomic instability and tumorigenesis (23).

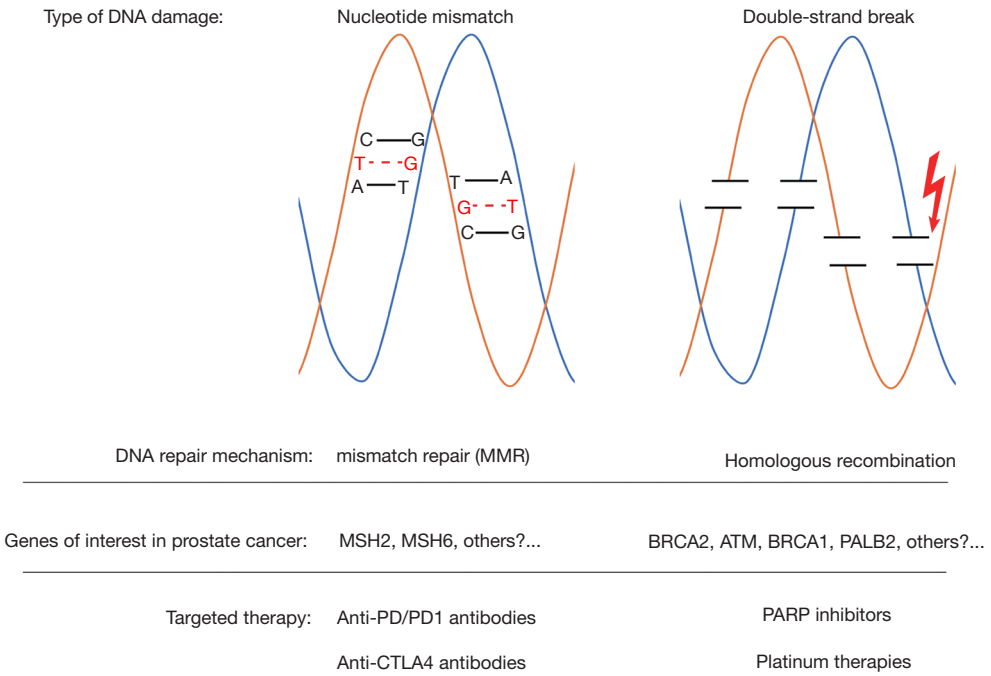


**Figure 1** DNA damage repair pathways in prostate cancer.

Loss of function mutations in DDR genes (both germline and somatic) have been increasingly recognized in the progression and pathogenesis of aggressive prostate cancer. Recent studies demonstrate an increased prevalence of HR mutations in metastatic castration resistant prostate cancer (mCRPC), with approximately 20–25% of patients with metastatic disease having germline or somatic mutations in BRCA2, ATM, or BRCA1 compared to <10% found in primary prostate tumors (10,11,18,24). This enrichment in metastatic CRPC patients points towards an important role of HR deficiency in the development of advanced disease. Accordingly, familial inherited mutations in *BRCA2* and *BRCA1* confer an increased risk of developing aggressive prostate cancer. For example, heterozygous germline *BRCA2* mutations confer an 8.6-fold increased risk of prostate cancer in men less than 65 years old, while germline *BRCA1* mutations confer a 3.75-fold increased risk (25,26). In addition, men with deleterious *BRCA2* germline mutations are diagnosed at a younger age, have more advanced tumor stage and grade at diagnosis, experience shorter median overall survival, and have increased risk of prostate cancer specific mortality (27). Therefore, it is important to systematically identify these patients, and refer them to genetic counselors as appropriate to discuss implications for their family members.

## Targeting homologous repair defects

An encouraging development in the last decade has been the identification of novel therapeutic strategies to treat tumors with HR deficiency (28,29). Although detecting HR deficiency with enough sensitivity and specificity remains difficult, there is a clear distinct genomic phenotype that can be observed (30). Importantly, tumors deficient in HR have increased sensitivity to agents that lead to DSBs such as platinum-based chemotherapies and poly-ADP-ribose polymerase (PARP) inhibitors (31-34). Platinum-based chemotherapy such as cisplatin and carboplatin are DNA cross-linking agents that halt the progression of replication forks whereas PARP inhibitors prevent the normal release of the DNA repair protein PARP1 from DNA, leading to replication fork stalling and eventual DSBs. Without a functioning HR pathway, the accumulation of dsDNA damage renders cells non-viable.

In other cancer types, there is evidence that *BRCA1* and *BRCA2* mutations sensitize tumors to treatment with platinum-based chemotherapies (35-37). Several phase II combination therapy trials in prostate cancer have been performed to study the efficacy of carboplatin with docetaxel, paclitaxel, everolimus, and etoposide (38-41). These studies showed a $PSA_{50}$ (i.e., reduction of PSA by

**Table 1** Ongoing trials of platinum-based chemotherapy in DDR-deficient prostate cancer

| Name of trial | Identifier | Drug | Phase/design | Eligibility | Primary endpoint | Status |
|---|---|---|---|---|---|---|
| The BARCODE 2 Study—The Use of Genetic Profiling to Guide Prostate Cancer Treatment | NCT02955082 | Carboplatin | Phase 2 single-group assignment (n=450) | mCRPC with DNA damage repair deficiency | PSA response rate/ radiographic response rate | Recruiting |
| Single Arm Open Label Phase II Pilot Study of Carboplatin Patients With mCRPC and PTEN Loss and/or DNA Repair Defects | NCT02311764 | Carboplatin | Phase 2 single-group assignment (n=25) | mCRPC and progression on AR therapy and taxane | PSA response rate | Recruiting |
| A Pilot Study of Docetaxel and Carboplatin for Treatment of Patients With mCRPC Containing Biallelic Inactivation of Genes in the BRCA1/2 Pathway | NCT02598895 | Docetaxel and carboplatin | Phase 1 single-group assignment (n=14) | mCRPC and progression on at least 1 prior chemotherapy treatment (enzalutamide, abiraterone, and/or docetaxel) with deleterious biallelic HR mutations | PSA response rate | Recruiting |

DDR, DNA damage repair; mCPPC, metastatic castration-resistant prostate cancer; PSA, prostate specific antigen.

50%) response rate ranging from 18–26% in mCRPC patients. Although tumor sequencing was not performed to identify patients with DDR deficiencies in this population, this frequency is close to the observed rate of HR deficiency observed in metastatic CRPC (41-43). Although it is entirely speculative, this suggests the possibility of positive responses to platinum in HR-deficient metastatic CRPC patients (44). In particular, non-specific DNA-damaging agents such as platinum agents may prove to be a promising treatment modality for HR-deficient CRPC patients, as they are reasonably well-tolerated, inexpensive, and their efficacy does not rely solely on disrupting a single mechanism of DNA repair. Indeed, several ongoing trials are investigating platinum-based chemotherapy in prostate cancer patients with known DDR defects (*Table 1*).

Based on the success of PARP inhibitor therapies in breast and ovarian cancer patients with HR deficiency, recent trials have investigated the efficacy of PARP inhibitors in the context of metastatic CRPC patients who carry deleterious HR mutations. PARP is a nuclear enzyme complex that functions in repairing single-strand DNA breaks (SSBs) and coordinating DNA repair through base excision. PARP contains a zinc-finger DNA-binding domain that detects the SSBs and then catalyzes the transfer of ADP-ribose to several protein acceptors involved in DNA metabolism and base excision repair. Therefore, PARP inhibition impairs the base-excision repair (BER) pathway, resulting in the accumulation of DNA damage. The TOPARP-A trial was carried out in the United Kingdom as an open label, single-arm, phase II trial to evaluate the efficacy of 400 mg olaparib twice a day in men with advanced metastatic CRPC (24). Patients were eligible if they experienced clinical progression after one or two lines of chemotherapy (with no prior exposure to platinum, cyclophosphamide, mitoxantrone, or PARP inhibitors). The primary endpoint was a reduction of PSA by 50% or the conversion of circulating tumor-cell count from ≥5 cells/7.5 mL of blood, to <5 cells/7.5 mL of blood. These patients were heavily pre-treated—all participants had received prior docetaxel, 49 of 50 (98%) had received abiraterone or enzalutamide, and 29 (58%) had received cabazitaxel. Fourteen of 16 patients (88%) who responded to olaparib treatment were found to have a DDR gene mutation. All 7 patients with *BRCA2* loss, and 4 of the 5 patients with *ATM* deficiency responded to olaparib. Interestingly, of the patients with *BRCA2* deficiency, 4 patients had bi-allelic somatic loss, while 3 patients had deleterious germline mutations (24). The authors concluded that treatment with

a PARP inhibitor in patients with defects in DNA repair leads to high response rates.

In addition to olaparib, several other PARP inhibitors are currently being tested in clinical trials for prostate cancer. For example, TRITON II and TRITON III are ongoing trials testing the PARP inhibitor rucaparib. TRITON II is a multi-center phase II study evaluating the efficacy of rucaparib monotherapy in patients with metastatic CRPC and HR deficiency who have progressed after taxane treatment and a next generation AR inhibitor. This trial includes patients harboring a deleterious mutation in one of classical DDR genes (i.e., *BRCA1*, *BRCA2*, or *ATM*) as well as those harboring a mutation in an expanded HR deficiency panel (including *BRIP1*, *BARD1*, *CHEK2*, *PALB2*, *NBN* and *CDK12*). Intriguingly, these non-*BRCA1/2* genes may account for up to 35% of inherited DDR mutations in metastatic CRPC patients (18). In contrast to TRITON II, TRITON III is a phase III randomized control trial evaluating the efficacy of rucaparib *vs.* abiraterone, enzalutamide, and docetaxel in patients with a deleterious mutation in *BRCA1*, *BRCA2* or *ATM*. Other trials using PARP inhibitors are summarized in *Table 2*. Importantly, whether a single loss of function mutation is sufficient to confer sensitivity to PARP inhibitors or platinum therapy, or whether loss of the second allele (either through a bi-allelic mutation or loss of heterozygosity), is required for treatment response remains to be determined. As clinicians begin to utilize tumor sequencing more routinely to guide patient management, we will also undoubtedly uncover more variants of unknown significance (VUS) in these DDR genes. As not all mutations within a gene have the same functional consequence or impact on treatment sensitivity, we anticipate that careful annotation of these VUS and cross-referencing with established databases (e.g., ClinVar) will be required to best identify the patients most likely to benefit from these targeted approaches. The current clinical trials will undoubtedly help to answer some of these issues, and generate further hypotheses to test in preclinical models.

## Response and resistance to PARP inhibitors

Unfortunately, most responses to PARP inhibitors are not sustained, and last only approximately 10–18 months (24,45), after which resistance develops. Mutations in PARP itself, the target of the PARP inhibitors, are not commonly found, although the protein levels of PARP and another protein, 53BP1, have been implicated in mediating resistance. In breast and ovarian cancer, *BRCA2* reversion mutations that restore the translated reading frame have been shown to be a primary resistance mechanism to PARP inhibitors (46,47). In an analysis of patients from the TOPARP trial, de Bono and colleagues observed that reversion mutations could also be identified in cell-free DNA (cfDNA) in both patients with deleterious germline and somatic BRCA2 mutations (48). Our group has also identified *BRCA2* reversion mutations in PARP inhibitor treated CRPC patients. Interestingly, these mutations were identified in cfDNA before clinical evidence of progression and resistance to PARP inhibitor therapy was observed, pointing towards the possibility of monitoring PARP sensitivity through the use of serial cfDNA sampling (49). At the University of California, San Francisco (UCSF), we are currently conducting a study sequencing the cfDNA of prostate cancer patients on any PARP inhibitor to characterize the spectrum of mutations that emerge prior to clinical detection of resistance. Similar to the development of PARP inhibitor resistance, *BRCA2* reversion mutations may also represent a mechanism of resistance patients treated with platinum therapies, as was recently described in a case report published by Pritchard and colleagues (50). Taken together, we predict that *BRCA* reversions (and likely other biomarkers) will need to be carefully monitored by serially analyzing cfDNA in patients on single-agent PARP inhibitors or platinum therapies, which may herald the beginning the resistance and trigger the clinician to change therapy.

What about trying to prevent or delay resistance by using drug combinations that target multiple pathways? For example, targeting WEE1, a tyrosine kinase that inactivates CDK1/CDK2 in response to DNA damage, has not only been shown to have activity in *BRCA*-mutated cancer (51) but the combination with PARP inhibitors has also been shown in preclinical pancreatic cancer models to sensitize tumor cells to radiotherapy (52). Other strategies may involve utilizing alternating cycles of PARP inhibitor with taxane therapy, which may help to clear the PARP inhibitor-resistant clones. However, more preclinical studies and clinical trials will be required to determine whether rationale combination strategies will delay the emergence of PARP inhibitor resistance, and whether the side effect profile can be tolerated by patients.

## AR signaling and DDR

AR plays a central role in prostate cancer, both in the

 

**Table 2** Ongoing and completed trials of PARP inhibitors in prostate cancer

| Name of trial | Identifier | Drug | Phase/design | Eligibility | Primary endpoint | Status |
|---|---|---|---|---|---|---|
| A Phase II Trial of Olaparib in Patients With Advanced Castration Resistant Prostate Cancer (TOPARP) | NCT01682772 | Olaparib | Phase 2 single-group assignment (n=89) | mCRPC with progression one or two prior chemotherapies | PSA response rate/ objective response rate | Completed |
| Studying the Effects of Olaparib (± Degarelix) Given to Men With Intermediate/High Risk Prostate Cancer Before Radical Prostatectomy (CaNCaP03) | NCT02324998 | Olaparib +/– degarelix | Phase 1 RCT (n=20) | Intermediate/high risk patients with planned RP | PARP inhibition by change in IHC levels of biomarkers such as PAR, gamma H2AX, pH2A(s129), Rad51 foci, FANCD2 foci, ATM/ ATR/CHK1/2 | Recruiting |
| Olaparib With or Without Cediranib in Treating Patients With Metastatic Castration-Resistant Prostate Cancer | NCT02893917 | Olaparib +/– cediranib | Phase 2 RCT (n=84) | Two prior therapies | Radiographic progression free survival | Recruiting |
| A Study of Rucaparib in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON2) | NCT02952534 | Rucaparib | Phase 2 single group assignment (n=160) | HR deficiency, after taxane and 1–2 next gen AR inhibitors | PSA response rate/ objective response rate | Recruiting |
| A Study of Rucaparib Verses Physician's Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON3) | NCT02975934 | Rucaparib *vs.* abiraterone, enzalutamide, or docetaxel | Phase 3 RCT (n=400) | BRCA1/2/ATM mutation, progression after 1 next gen AR | Radiographic progression free survival | Recruiting |
| An Efficacy and Safety Study of Niraparib in Men With Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies (Galahad) | NCT02854436 | Niraparib | Phase 2 single group assignment (n=160) | DDR anomaly, and progression on AR therapy and taxane | Objective response rate (RECIST criteria) | Recruiting |
| Enzalutamide and Niraparib in the Treatment of Metastatic Castrate-Resistant Prostate Cancer | NCT02500901 | Niraparib + enzalutamide | Phase 1 single group assignment (n=2) | CRPC and progression with 1 prior chemo | MTD | Terminated |
| Olaparib in Men With High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, With Integrated Biomarker Analysis | NCT03047135 | Olaparib | Phase 2 single group assignment (n=50) | Post-RP BCR, +/– prior salvage, non-metastatic disease | PSA response rate | Recruiting |

**Table 2** (*continued*)

**Table 2** (*continued*)

| Name of trial | Identifier | Drug | Phase/design | Eligibility | Primary endpoint | Status |
|---|---|---|---|---|---|---|
| Phase II Study to Evaluate Olaparib With Abiraterone in Treating Metastatic Castration Resistant Prostate Cancer | NCT01972217 | Olaparib + abiraterone *vs.* abiraterone | Phase 2 double-blind RCT (n=159) | Progression on docetaxel for mCRPC | Radiographic progression free survival | Active, not recruiting |
| BRCAAway: A Randomized Phase II Trial of Abiraterone, Olaparib, or Abiraterone + Olaparib in Patients With Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects | NCT03012321 | Olaparib *vs.* olaparib + abiraterone *vs.* abiraterone | Phase 2 crossover assignment (n=70) | mCRPC with HR deficiency | Objective progression free survival | Recruiting |
| A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib *vs.* Enzalutamide or Abiraterone Acetate in Men With mCRPC with HR Gene Mutations (PROfound) | NCT02987543 | Olaparib *vs.* olaparib + enzalutamide/ abiraterone | Phase 3 RCT (n=340) | HR mutation after progression on ADT | Radiographic progression free survival | Recruiting |
| Phase Ib/II Trial of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (mCRPC) | NCT02861573 | Olaparib + pembrolizumab, pembrolizumab +docetaxel + prednisone, pembrolizumab + enzalutamide | Phase 1 parallel assignment (n=180) | Cohort A-after docetaxel, cohort B-after abiraterone/ enzalutamide, cohort c-after abiraterone | PSA response rate | Recruiting |
| Phase IB Trial of Radium-223 and Niraparib in Patients With Castrate Resistant Prostate Cancer (NiraRad) | NCT03076203 | Niraparib + radium-223 | Phase 1 single group assignment (n=6) | Progression on ADT | MTD | Recruiting |
| A Safety and Pharmacokinetics Study of Niraparib Plus Androgen Receptor-Targeted Therapy (Apalutamide or Abiraterone Acetate Plus Prednisone) in Men With Metastatic Castration-Resistant Prostate Cancer | NCT02924766 | Niraparib + apalutamide or abiraterone | Phase 1 single group assignment (n=60) | Progression on AR targeted therapy and docetaxel | MTD | Recruiting |
| A Randomized Gene Fusion Stratified Phase 2 Trial of Abiraterone With or Without ABT-888 for Patients With Metastatic Castration-Resistant Prostate Cancer | NCT01576172 | Veliparib + abiraterone *vs.* abiraterone | Phase 2 RCT (n=148) | Patients with and without ETS fusion with progression on ADT | PSA response rate | Recruiting |

**Table 2** (*continued*)

**Table 2** (*continued*)

| Name of trial | Identifier | Drug | Phase/design | Eligibility | Primary endpoint | Status |
|---|---|---|---|---|---|---|
| A Pilot Study Combining ABT-888, an Oral PARP Inhibitor, With Temozolomide in Patients With Metastatic Castration Resistant Prostate Cancer Who Have Failed Up to Two Non-hormonal Systemic Therapies | NCT01085422 | Veliparib + temozolomide | Phase 1 single Group assignment (n=35) | mCRPC with docetaxel progression | PSA response rate | Completed |
| Nivolumab in Prostate Cancer With DNA Repair Defects (ImmunoProst Trial) | NCT03040791 | Nivolumab | Phase 2 single group assignment (n=29) | mCRPC after taxane-based chemotherapy progression with DNA repair defects | PSA response rate | Recruiting |
| Phase Ib/II Trial of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer | NCT02861573 | Pembrolizumab + olaparib *vs.* pembrolizumab + docetaxel + prednisone *vs.* pembrolizumab + enzalutamide | Phase 2 parallel assignment (n=180) | mCRPC and either progressed on docetaxel or enzalutamide | PSA response rate | Recruiting |
| Docetaxel, Carboplatin, and Rucaparib Camsylate in Treating Patients with mCRPC with Homologous Recombination DNA Repair Deficiency | NCT03442556 | Induction with docetaxel and carboplatin + rucaparib camsylate maintenance | Phase 2 single group assignment (n=20) | mCRPC and progression on docetaxel, sipuleucel-T, abiraterone, and or cabazitaxel (no prior platinum/PARP) | Radiographic progression free survival | Not yet recruiting |

PARP, poly-ADP-ribose polymerase; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate specific antigen; RCT, randomized controlled trial; RP, radical prostatectomy; PAR, poly(ADP-ribose); ATM, ataxia-telangiectasia-mutated; ATR, ataxia-telangietctasia and Rad3-related; CHK, checkpoint kinase; HR, homologous recombination; AR, androgen receptor; DDR, DNA damage repair; RECIST, response evaluation criteria in solid tumors; MTD, maximum tolerated dose; BCR, biochemical recurrence; ADT, androgen deprivation therapy; ETS, E26 transformation-specific.

hormone-sensitive and castrate-resistant settings (53). In preclinical models of prostate cancer, AR signaling is implicated in DNA damage and DDR (54-58). Androgen signaling promotes TOP2B mediated double-strand breaks, and the co-localization of AR and TOP2B to sites of *TMPRSS2-ERG* genomic breakpoints is essential for the generation of *TMPRSS2-ERG* rearrangements, which are present in more than 50% of prostate cancers (59). These rearrangements result from the fusion of the AR-responsive *TMPRSS2* promoter with the *ERG* transcription factor, which is considered a quintessential driver of aggressive prostate cancer (60,61).

Interestingly, PARP1 appears to be an important contributor to the tumorigenic effects of *TMPRSS2-ERG*. PARP1 enhances the transcriptional function of AR, is required for tumor growth in xenograft models, and promotes the development of castration resistance (62). PARP1 interacts directly with ERG, and is required for the full activity of ERG. Additionally, ERG-positive xenografts are more sensitive to PARP inhibition (63). These observations led to a clinical trial by Hussain and colleagues to evaluate the efficacy of veliparib plus abiraterone *vs.* abiraterone monotherapy in patients with metastatic CRPC. The investigators hypothesized that ETS-fusion positive tumors would have an enhanced response to veliparib plus abiraterone compared to abiraterone alone. While there was no difference observed in the PSA response rate between the patients with ETS-fusion positive and negative tumors, the 25% of patients with HR deficiencies in both arms of the study had better responses than the patients with HR wildtype tumors. Progression free survival in patients with HR deficient tumors was 13.8 *vs.* 8.1 months in patients with HR wildtype tumors (P=0.0472). HR deficiency was also associated with a significantly better PSA rate response (90% *vs.* 56.7%; P=0.007) (64). In contrast, a study published by Annala *et al.*, which included a cohort of 319 patients who had progressed to metastatic CRPC, demonstrated that DNA repair defects were associated with a shorter median time to castration resistance after initiating ADT (11.8 *vs.* 19.0 months, P=0.031) and median time to progression on abiraterone or enzalutamide (3.3 *vs.* 6.2 months, P=0.01) (65,66). The difference between the Annala *et al.* and the Hussain *et al.* analyses may be accounted for by the fact that Annala *et al.* looked at mutations present in the cfDNA of patients treated with either abiraterone or enzalutamide, while Hussain *et al.* looked at germline and somatic mutations present in primary tumor tissue in patients treated with abiraterone ± veliparib. Given the differences in trial design and the conflicting results, further investigation is needed to determine the prognostic implications of HR deficiency in the setting of treatment with second-generation anti-androgen therapies.

## MMR deficiencies and immunotherapy in prostate cancer

In addition to homologous repair, cells have another DDR system, the MMR pathway, to correct base-base mismatches and insertion-deletion loops, which can also occur during the replication phase of the cell cycle (*Figure 1*). In tumors lacking MMR, long tracks of repeated sequences known as microsatellites are prone to strand slippage, which results in the insertion-deletion loops and the accumulation of mutations in these microsatellite areas. The classic example of MMR deficiency is Lynch syndrome, which is characterized by the germline loss of one of the canonical MMR genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*), and increases the risk of developing colorectal, endometrial and ovarian cancer, as well as prostate cancer (67). Cheng and colleagues previously identified deleterious germline MMR mutations in a small percentage of patients with metastatic prostate cancer (4 of the 692 patients, 0.6%) (18), suggesting that this is not a major pathway contributing to prostate cancer development. However, the combined prevalence of germline and somatic mutations are reportedly higher (approximately 3–12%, depending on the study) (68,69). Interestingly, hypermutated prostate cancers are characterized by complex *MSH2* and *MSH6* structural rearrangements, in contrast to colon cancer, which is often due to *MLH1* epigenetic silencing or inactivating mutations (69). Next generation sequencing (NGS) assays that typically only sequence the exons of target genes may actually miss these MMR gene alterations resulting from intronic or non-coding region rearrangements because they do not typically capture these structural rearrangements. An alternative approach is to use immunohistochemistry (IHC) to detect MMR protein loss. Guedes and colleagues recently used IHC to screen >1,100 prostate cancer patients for MSH2 loss, and found that although MSH2 deficiency was rare in the general cohort (1%), it was enriched in patients with primary Gleason pattern 5 disease (8%) and small cell prostate cancer (5%) (70). This suggests that standard IHC may be an appropriate method to identify prostate cancer patients with MMR deficiency.

 

**Table 3** Ongoing trials of immunotherapy regimens in DDR- and MMR-deficient prostate cancer

| Name of trial | Identifier | Drug | Phase/design | Eligibility | Primary endpoint | Status |
|---|---|---|---|---|---|---|
| Pembrolizumab in Metastatic Castration Resistant Prostate Cancer (mCRPC) With or Without DNA Damage Repair Defects | NCT03248570 | Pembrolizumab | Phase II, open-label study of pembrolizumab (n=50) | mCRPC with or without DNA damage repair defects | Objective response rate | Recruiting |
| Nivolumab in Prostate Cancer With DNA Repair Defects (ImmunoProst Trial) | NCT03040791 | Nivolumab | Phase II, open-label study of nivolumab (n=29) | mCRPC with or without DNA damage repair defects who have progressed on previous taxane chemotherapy | PSA response rate | Not yet recruiting |

DDR, DNA damage repair; MMR, mismatch repair; mCRPC, metastatic castration resistant prostate cancer; PSA, prostate specific antigen.

The loss of MMR is often associated with an increased mutational load, which is thought to result in increased tumor neoantigens due to changes in the amino acid sequence encoding proteins, which can be presented to immune system and recognized as non-self. This, in turn, has been hypothesized to augment the response to immune checkpoint inhibitors such as pembrolizumab, nivolumab and atezolimumab (71,72). A pivotal study by Le and colleagues showed that responses to anti-programmed death 1 (anti-PD-1) therapy were significantly better in patients with MMR deficiency compared to those without MMR deficiency (40% *vs.* 0%). This has led to the FDA approval of the anti-PD1 agent pembrolizumab in the treatment of patients with unresectable or metastatic MSI-high or MMR-deficiency solid tumors, the first FDA approved cancer therapy irrespective of the tissue of origin. Responders to checkpoint inhibitors may also include those without MMR deficiency or microsatellite instability. Indeed, in a small study of metastatic CRPC patients treated with pembrolizumab, one of the responder patients did not have detectable microsatellite instability (73). Additional work will be required to determine what other subtypes of prostate cancer, besides those with MMR deficiency or microsatellite instability, might benefit from this therapeutic approach. Of particular interest is whether DDR-deficient tumors are also immunoresponsive, which is currently being tested in clinical trials (*Table 3*). Moreover, for MMR-deficient tumors that do not respond to anti-PD1 agents, the combination with ipilimumab, an anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4) monoclonal antibody, may also be considered.

Finally, there has also been considerable interest in combining anti-PD-1/PD-L1 agents with other novel agents to stimulate immunotherapy responses in patients without MMR deficiency. Given that PARP inhibitors may be able to trigger genomic instability, and that tumors with HR deficiencies are already unstable, there has been interest in combining immunotherapy with PARP inhibition in advanced prostate cancer. An ongoing study by Karzai and colleagues using the combination of durvalumab (an anti-PD-L1 agent) and olaparib reported that approximately 40% of patients unselected for HR or MMR deficiency had a documented decline in their PSA. In addition, studies combining nivolumab plus another PARP inhibitor, rucaparib, are also underway, as are immunotherapy combinations with conventional taxane chemotherapy in urothelial carcinoma (i.e., KEYNOTE-395). In addition,

novel agents in combination with checkpoint inhibition are being explored as well. For example, inhibitors of indoleamine dioxygenase (IDO), an enzyme involved in the metabolomic checkpoint, in combination with anti-PD1 therapy are in clinical trials for multiple tumor types, although recent data in melanoma from the ECHO-301/KEYNOTE-252 trial were disappointing. Whether these combinations in particular molecular subtypes of prostate cancer will enhance immunotherapy sensitivity remains to evaluated, and is an exciting area of ongoing investigation.

## Future outlook and conclusions

Over the last several years, we have gained a deeper understanding of the molecular alterations that define prostate cancer. Surprisingly, one of the key hallmarks that emerged from the multiple large-scale sequencing studies was that a significant subset of prostate cancer involves mutations in genes involved in various DNA repair pathways, including HR and MMR. These insights have led to the study and use of new agents to treat prostate cancer, including PARP inhibitors, platinum chemotherapy, and checkpoint immunotherapy. It is important to remember that several other DNA repair pathways exist (e.g., NHEJ), which are regulated and executed by a suite of other unique enzymes, all of which may be potential targets for therapy. This includes drugs targeting DNAPK and ATR, which are currently under clinical testing and development.

With these paradigm shifts occurring in prostate cancer treatment, understanding the genomic features of each individual patient's tumor is becoming increasingly important. Choosing the right treatment for the right patient and integrating genomic information with clinical data to inform treatment decisions continue to be the goal of precision oncology. One outstanding question is whether homozygous mutations or deletions are required for sensitivity to these targeted approaches, or whether hemizygous mutations are sufficient for therapeutic response. In considering HR deficiency, genes such as *BRCA1*, *BRCA2*, and *ATM* are classically considered tumor suppressors. As such it would be expected that loss of both copies would be required for therapeutic sensitivity. However, there is currently a paucity of conclusive data supporting this hypothesis. But as suggested in the TOPARP-A trial, the vast majority of PARP inhibitor responders had homozygous loss of function HR gene mutations or deletions. Ongoing trials such as TRITON II/III only require a single-copy mutation for eligibility, and so this will be a critical issue to address. Similarly, as the field of precision oncology continues to mature, the annotation of VUS will be a crucial element in the development of targeted therapies. To this end, it will be important to have robust functional assays and preclinical models to help predict and evaluate which variants are likely to confer response.

At the same time, we must continue to understand treatment resistance to stay a few steps ahead of the tumor and be able to provide effective treatment options for the patient. This will involve not only setting up the pipeline to perform sequential biopsies of metastatic lesions, but also the pipeline to interrogate the whole genome, exome, transcriptome, and proteome in order to understand the multiple pathways to resistance. In addition, we need to improve the technology to sequence cfDNA and capture circulating tumor cells, or CTCs, in order to allow us to obtain serial liquid biopsies, which are particularly useful in cases where biopsies may not be possible (e.g., of metastatic spine lesions or abdominal lymph nodes). The incorporation of omics in prostate cancer will open new therapeutic opportunities for patients and new areas of investigation for clinical, translational and basic scientists, which may ultimately allow oncologists to achieve cures for patients with metastatic, castrate-resistant disease.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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