# DNA Repair in Prostate Cancer

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Prostate cancer (PC) is the second most common neoplasm among men. According to Cancer Research United Kingdom (UK) (, accessed on 26 May 2021) it is the second leading cause of cancer- related death in the UK. Locally advanced disease is curable, although metastatic disease has limited therapeutic options.

Keywords: prostate cancer ; DNA damage repair ; PARP ; BRCA ; next-generation sequencing

## 1. Introduction

Prostate cancer (PC) is the second most common neoplasm among men [1][2]. According to Cancer Research United Kingdom (UK) (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero, accessed on 26 May 2021) it is the second leading cause of cancer- related death in the UK [3]. Locally advanced disease is curable, although metastatic disease has limited therapeutic options. Androgen Receptor (AR) signaling represents still the most important pathway to target for developing new and more effective therapies, and androgen deprivation therapy (ADT) is still the cornerstone of management of PC patients. Resistance development to ADT defines the status of metastatic castration resistant prostate cancer (mCRPC) still associated with dismal clinical outcome, poor prognosis and limited therapeutic options [2][4][5].

## 2. DNA Repair Mutations in Prostate Cancer

The incidence of germline mutations in DDR genes among men with mCRPC varies between 11–33% making it significantly higher than that of localized disease [6]. As previously mentioned, the commonest DDR aberration is *BRCA2*, followed by *CDK12*, *ATM*, *CHEK2*, *BRCA1*, *MSH2*, *FANCA*, *MLH1*, and *RAD51* [2]. The most frequent somatic genomic aberrations include *AR* (62.7%), *ETS* family (56.7%), *TP53* (53.3%), and *PTEN* (40.7%) [4].

The breast cancer genes 1 and 2 (*BRCA1* and *BRCA2*) are located at chromosome 17q21 and 13q12, respectively [7]. They are large genes consisting of 100 and 70 kb, respectively [8]. They have an autosomal dominant inheritance pattern with incomplete penetrance [9]. They are part of an HR DNA repair pathway usually utilized for DSB repair. *BRCA* dysfunction determines HR deficiency, which is usually compensated by NHEJ, an error prone repair system [8]. In any case of impairment of HR, synthetic lethality induced by poly (ADP-ribose) polymerase (PARP) inhibition occurs and may target tumor tissue selectively. The synthetic lethality could even represent the therapeutic strategy of cancers with *BRCA*-like properties, known as “BRCAness” [10]. This is based on the observation that deficiency in genes beyond *BRCA* that are also implicated in HR may confer sensitivity to PARP inhibitors. Consequently, alterations in DDR genes, particularly in those involved in HR repair, are predictors of response to PARP inhibition [5].

Structurally speaking, although both *BRCA* genes have a nuclear localization sequence, their functional domains hardly display homology. The *BRCA2* gene has eight internal repeats also known as BRC repeats and a DNA binding domain which interact with *RAD51* and *DSS1* (deleted in split-hand/split foot protein 1) respectively, both of which are HR-related proteins. *BRCA1* has three domains: RING, coiled coil, and BRCT which interact with BARD1 (*BRCA1*-associated RING domain), PALB2 (partner and localizer of *BRCA2*), *ABRA1* (abraxas), *CtIP* (CtBP interactive protein), and *BRIP1* (BRCA1-interacting protein *C*-terminal helicase 1). Hence *BRCA1* is a major component of the HR, but apart from that, is also involved in DNA damage sensing, cell cycle regulation, E3 ubiquitin ligase activity and chromatin remodeling [8].

Incidence of germline *BRCA* mutations in newly diagnosed PC is 1.2–2% [11]. *BRCA1/2* carriers can have around 4- and 8-fold risk of developing PC, respectively [9]. Moreover, *BRCA* mutation carriers with localized PC have worse outcomes than those who are wild type, regardless of the local treatment they have previously undergone. Indeed, *BRCA* carriers have the worst prognosis, higher Gleason Score (8+), increased rate of lymph node involvement, earlier onset of distant metastasis, and shorter survival [11]. Patel et al. identified no statistically significant associations between *BRCA1*

pathogenic sequence variants (PSVs) and elevated PC risk. However, *BRCA2* showed a PC Cluster Region (PCCR), specifically c.756–c1000 and c.7914+ with PSVs linking to elevated risk of disease [12].

A dearth of consensus pertaining to screening high-risk PC patients was prevalent [10]. To mitigate this, the IMPACT Study (Identification of Men with a genetic predisposition to PC: Targeted screening in *BRCA 1/2* mutation carriers and controls) screened and enrolled 1522 PC patients with germline *BRCA 1/2* mutation along with 959 controls [13] with annual prostate specific antigen (PSA) testing and warranting prostate biopsy if PSA >3ng/mL were performed. *BRCA2* carriers (3.3%) showed a higher incidence of PC than their *BRCA1* counterparts (2.6%) and controls (<2%) [9]. More than 67% of *BRCA2* and 61% of *BRCA1* carriers were classified under the intermediate/high-risk category.

## 3. Immunotherapy in Prostate Cancer

Immune checkpoint therapies have recently revolutionized the treatment approach of several solid tumors including melanoma, and non-small cell lung cancers. Efficacy of these agents in PC has been disappointing so far. The two most validated immune checkpoint targets are cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD1) and its ligands (programmed death-ligand 1/2, PD-L1/L2). CTLA-4 is currently targeted by ipilimumab while PD1/PD-L1 by pembrolizumab, nivolumab, atezolizumab, and durvalumab. Beer et al. did a randomized, double-blind phase III trial where patients were randomly assigned to two groups: ipilimumab 10 mg/kg vs. placebo every 3 weeks for up to 4 doses. 399 patients were treated with ipilimumab, and 199 patients were treated with placebo. Median PFS and OS in ipilimumab arm were 5.6 and 28.7 months whereas in the placebo arm they were reported to be 3.8 and 29.7 months, respectively. OS, being the primary endpoint, was therefore not impacted but progression of disease was delayed [14]. The IMbassador250 phase III trial randomized 759 patients with mCRPC who underwent prior progression on abiraterone and docetaxel, or in whom ADT was not administered to atezolizumab (atezo) and enzalutamide (enza) ($n$ = 379) vs. enza alone ($n$ = 380). Primary endpoint was improvement in OS; median OS for atezo + enza vs. enza alone were 15.2 vs. 16.6 months, respectively, thus not meeting the primary endpoint [15].

Resistance to approved checkpoint inhibitors is currently believed to be related to the evidence that mCRPC tumors are inevitably immunologically “cold” probably due to their lower somatic mutation tumor burden with consequently reduced tumor-infiltrating T-cells. Combination therapy using multiple checkpoint inhibitors have been proposed to mount a potent T-cell response in PC and to potentially overcome intrinsic resistance to single agent checkpoint inhibition. The Checkmate 650 trial combined CTLA-4 (ipilimumab 3 mg/kg) and PD-L1 (nivolumab 1 mg/kg) in 90 patients with 45 each in cohort 1 (pre-chemotherapy) and cohort 2 (post-chemotherapy). The ORR, median PFS, median OS were 25%, 5.5 months, 19 months and 10%, 3.8 months, 15.2 months in cohort 1 and 2 respectively [16]. Results were promising as compared to the monotherapy counterparts. In line with other tumor types, MMR-deficient mCRPC patients have shown response to immune-checkpoint inhibitors, due to the accumulation of somatic mutations, and consequently, the high neoantigen burden. Pembrolizumab was approved by the FDA in 2017 for solid metastatic MMR-deficient tumors and can be used in MMR-deficient PC patients [17]. The KEYNOTE-199 study recruited 258 patients with prior progression on docetaxel and targeted endocrine therapy to receive pembrolizumab. Median OS was 9.5, 7.9, and 14.1 months in three cohorts of patients with PD-L1 positive, negative, and bone-predominant regardless of PD-L1 expression disease, respectively [18]. Ongoing and future biomarker studies from KEYNOTE-199, including gene expression profiles and tumor mutational burden, will define molecular markers of response to pembrolizumab. Loss-of-function alterations of tumor suppressor protein CDK12 was found in approximately 5–7% of PC. Translational studies demonstrated that *CDK12* mutations may delineate an immuno-responsive subgroup of PC with increased levels of T-cell infiltration and neoantigens. Based on that, *CDK12*-mutated tumors might constitute a separate subgroup of PC in which immunotherapy may be effective [19][20][21]. So far, the largest cohort of *CDK12*-inactivated PC patients treated with immunotherapy has been provided by two independent retrospective multicenter series. They have described the outcomes of 112 *CDK12*-mutated tumors in total [22][23]. Among them, 28 received diverse immunotherapy regimens and favorable responses were achieved even by some heavily pretreated cases. Several key conclusions can be made at that stage. These patients often present with high-risk features, including Gleason grade group 4–5, T3–T4 disease, and de novo metastases. Regardless of the biochemical response, the PFS on AR-signaling inhibitors was generally short. Moreover, responses to immune checkpoint blockade seem to be enriched in less heavily pretreated patients. Finally, recent correlate analysis of mCRPC biopsies revealed *CDK12*-mutated mCRPCs were enriched in immunosuppressive CD4+FOXP3- cells [24].

There are no FDA approved indications for immune checkpoint inhibitors for treatment of castrate-sensitive PC; however, their use is being evaluated in clinical trials. A phase III trial is underway to evaluate pembrolizumab plus enzalutamide plus ADT versus enzalutamide and ADT alone [NCT04191096]. Multiple phase I and phase II trials are evaluating immune checkpoint inhibitors in combination with treatments such as abiraterone and cabozantinib [NCT04477512], radiation therapy [NCT04262154, NCT03795207], and an experimental IL-8 directed monoclonal antibody [NCT03689699]. In

addition, perioperative ipilimumab in combination with castration prior to radical prostatectomy has demonstrated feasibility with longer follow-up ongoing [25].

## References


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