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GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Targeting DNA Repair Defects for Precision Medicine in Prostate Cancer

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Abstract

Purpose of Review Genomic studies of localized and metastatic prostate cancer have identified a high prevalence of clinically actionable alterations including mutations in DNA repair genes. In this manuscript, we review the current knowledge on DNA repair defects in prostate cancer and provide an overview of how these alterations can be targeted towards a personalized prostate cancer management.

Recent Findings Twenty to 25% of metastatic prostate cancers harbor defects in DNA repair genes, most commonly in the homologous recombination genes. These defects confer increased sensitivity to platinum chemotherapy or poly (ADP-ribose) polymerase (PARP) inhibitors. Recent trials also support a synergistic effect of combining these therapies with androgen receptor-targeting agents. Identification of mismatch-repair defects could result in defining a prostate cancer population who may benefit from immune checkpoint inhibitors. These data have implications for family testing and early diagnosis, as many of these mutations are linked to inherited risk of prostate cancer.

Summary The DNA damage repair pathways are clinically relevant in prostate cancer, being a target for precision medicine; combination with standard-of-care androgen receptor (AR)-targeting agents may be synergistic.

Keywords DNA damage repair · Prostate cancer · PARP · BRCA1/2 · Androgen receptor · Genomic alterations · Personalized medicine

Introduction

The androgen receptor (AR) signalling axis is the predominant driver of prostate cancer genesis and progression. However, a better understanding of the genomic landscape of prostate cancer has identified other commonly dysregulated biological pathways that may be relevant not only in determining the course of the disease but also for designing more precise therapeutic strategies for patients.

In recent years, different DNA damage repair (DDR) pathways have been recognized to be frequently altered in advanced stages of prostate cancer. Promising preliminary clinical data on DNA damaging agents and targeted drugs against the DNA repair machinery suggest that DNA repair in defective prostate cancer represents one (or more than one) of the clinically relevant disease subsets. Additionally, as many of the DDR gene alterations are linked to inherited mutations, their identification has implications towards screening for prostate and other cancer types in patients' relatives.

In this manuscript, we review how alterations in DDR pathways could impact patient stratification for personalized management of early and late stage disease. Additionally, we discuss emerging clinical trial data on the use of DNA-damaging agents and targeted drugs against the DDR pathways for prostate cancer, either alone or in combination with AR-targeting strategies.

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Evidence Summary

An Overview of DNA Repair Mechanisms and Cancer

DNA molecules in every cell are constantly suffering from damage, either as a result of endogenous processes (cell division, metabolism, and DNA replication) or from external factors (e.g., UV light exposure, ionizing radiation (IR), X-rays, and chemical mutagens). All these different sources have deleterious effects on DNA, causing single- (SSB) or double-strand breaks (DSB) [1].

To cope with these insults, different repair mechanisms get activated and correct the damaged DNA. If the repair is not successful, programmed cell death process is activated to sacrifice faulty cells in order to preserve genomic integrity [2]. Tolerance for survival of cells with an unrepaired DNA leads to the accumulation of mutations and genomic instability, which is one of the hallmarks of cancer [3].

Different pathways collaborate towards optimal repair of DNA damage. While there are certain degrees of overlap, specific genes, proteins, and pathways will be activated depending on the exact type of insult to DNA. DSB generated by IR, reactive oxygen species (ROS), replication errors, and dysfunctional telomeres can be resolved by two processes homologous recombination (HR) and non-homologous end-joining (NHEJ). HR is the preferred mechanism due to its error-free characteristic (Fig. 1).

HR is activated during S/G2 phase of the cell cycle and requires a sister chromatid as a template to restore the genomic sequence of the broken ends. Upon damage, DSBs are recognized by the Mre11-Rad50-Nbs1 (MRN) complex. Two related kinases are mainly activated after sensing DSBs: ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related protein (ATR). ATM phosphorylates histone H2AX inducing a signalling cascade that involves mediator proteins such as checkpoint kinase 2 (Chk2), among others [4]. On the other hand, RPA recognizes single-stranded DNA (ssDNA) and recruits ATR thus activating an additional cascade that includes ATR substrates such as Chk1 and other effector proteins [5]. The final execution of the HR-mediated repair involves the formation of RAD51 foci that together with BRCA2, BRCA1, and PALB2 drives the homology search and strand invasion steps [2, 6]. Importantly, the formation of RAD51 foci is a marker of a HR proficiency [7]. Following strand invasion, the sister chromatid is used as a template for the synthesis and ligation of the new DNA strand.

In contrast to HR, NHEJ is a mechanism normally limited to the G1 phase of the cell cycle. It repairs DSBs by rapidly ligating the broken DNA ends without using a DNA template; this is why, NHEJ is consider an error-prone and potentially inaccurate repair mechanism. During the first step, the Ku70/80 heterodimer senses and rapidly binds DSBs, recruiting and activating the catalytic subunit of the DNA-dependent protein kinases (DNA-PKs). These kinases activate themselves and other substrates to prevent DNA end resection via the stabilization and protection of DSBs [8]. An additional protein involved in the inhibition of end resection step is 53BP1 [9]. After DNA-PK binding, broken ends are

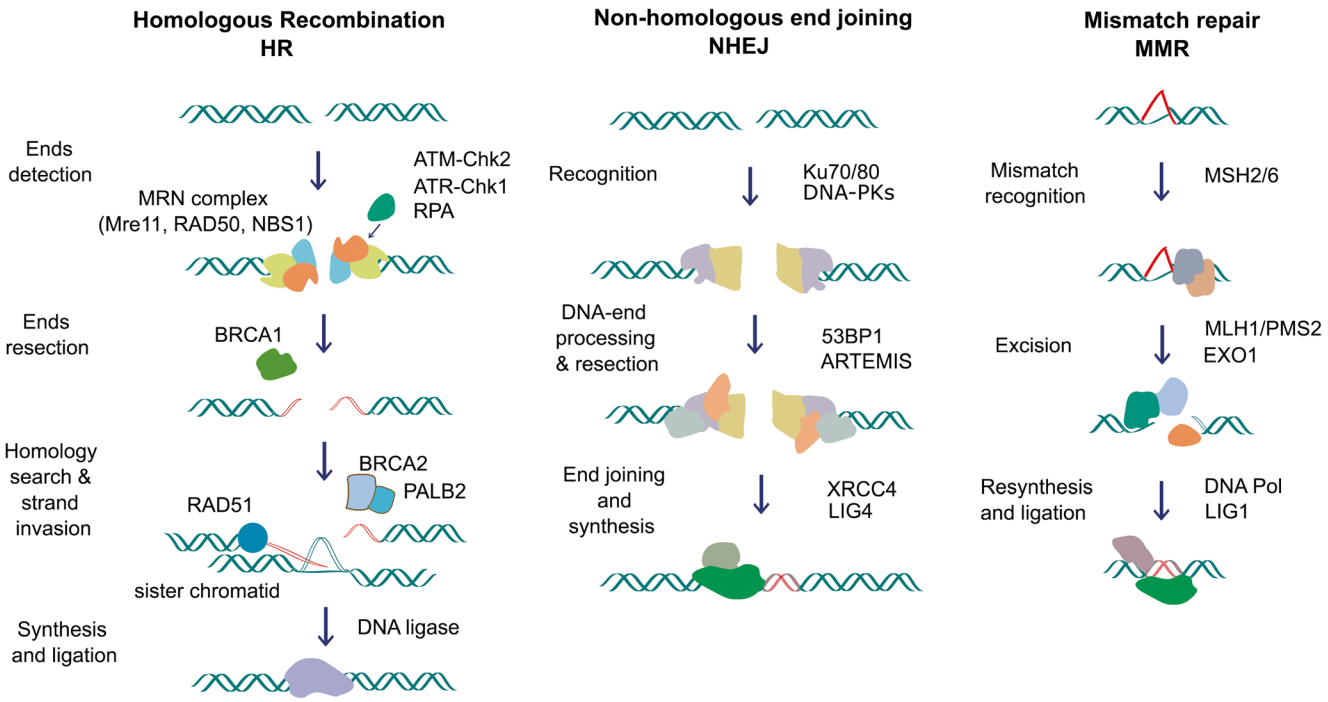

Fig. 1 Overview of DNA repair pathways

processed by the endonuclease ARTEMIS, followed by XRCC4 binding and Lig4-mediated ligation.

Repair of SSB is driven by alternative mechanisms, mainly base excision repair (BER), nucleotide excision repair (NER), or mismatch repair (MMR) [10].

MMR is in charge of repairing mispaired DNA bases induced during replication and DNA recombination. The majority of genes involved in this pathway belong to the MSH and MLH family, including several sensor molecules such as MSH2 and MSH6. The first step consists on mismatch recognition by the MSH2/6 heterodimer, followed by the recruitment of MLH1/PMS2. The PMS2 endonuclease activity creates single-stranded nicks near the mismatch, where exonuclease EXO1 starts removing the segment of the DNA strand containing the mismatch [11]. Defects in the MMR pathway result in the accumulation of point mutations. These processes have been identified as clinically relevant for predicting response to immune checkpoint blockade in different tumor types, as we will review later in this manuscript.

Why Targeting DNA Repair Defects in Cancer Medicine?

Cancerous cells defective for DNA repair mechanisms present genomic instability, which usually results in an uncontrolled cell proliferation. However, some of these defects may also render them vulnerable to specific therapeutic approaches. Two main examples of successful development of drugs in this space are poly (ADP-ribose) polymerase (PARP) inhibitors and immune checkpoint inhibitors.

Pharmacological inhibition of PARP enzymes results in suppressing of SSB repair capabilities. Hence, SSB will progress to DSB; although most cells will be able to repair these DSB, some tumors which have lost DSB repair capacities might not be able to cope with the accumulation of DSB resulting from PARP-1 inhibition. This interaction is an example of the biological premise of synthetic lethality: two events which are not lethal per se become unbearable for the cell when they occur together. Over a decade ago, two seminal papers described how preclinical cancer models lacking BRCA1 or BRCA2 proteins, key effectors in DSB repair, could not tolerate PARP inhibition (PARPi) [12, 13]. The identification of inherited mutations of *BRCA1* or *BRCA2* genes in patients with breast and ovarian cancer led to the development of PARPi in the clinics [14, 15]. As the synthetic lethal interaction should only occur in tumor cells but not in normal cells, which would be functionally HR-deficient, PARP inhibitors promised high tumor-specific effect and a wide therapeutic index. Different PARP inhibitors are now approved for the treatment of certain subtypes of breast and ovarian cancer associated to different HR defects [16–20].

Similarly, the use of DNA-damaging agents in patients with DDR defects aims to overload defective tumor cells with levels of DNA damage, beyond the threshold which they can handle. Examples are the high sensitivity to platinum-based chemotherapy or to radiation of HR-deficient tumors.

In recent years, the development of immune checkpoint inhibitors (ICI) has been transformative for the management of several tumor types. Clinical validation of predictive response biomarkers to ICI would contribute towards a more effective use of these therapies. Beyond using the drug target as a predictive biomarker (such as PD-1 expression for PD-1/PDL-1 inhibitors), the association of mismatch-repair defects with responsiveness to ICI have been investigated. The underlying hypothesis is that MMR-deficient, genomically unstable tumors would accumulate non-synonymous mutations and result in an increased expression of so-called mutation-associated neoantigens, which would enhance tumor immunogenicity [21–24].

Prevalence of DNA Repair Gene Defects in Different Stages of Prostate Cancer and Implications for Prognosis

Inherited mutations in *BRCA1* and *BRCA2* are known to increase the risk of prostate cancer. Earlier studies focused in men with primary prostate cancer, where the prevalence of germline *BRCA1/BRCA2* mutations is around 1% and around 2%, respectively, in populations enriched for young age patients at the time of diagnosis and/or significant family history of cancer [25–27].

These germline mutations in patients with non-metastatic disease, while rare, are clinically relevant, as germline *BRCA2* mutations have been found to be a negative prognostic factor, independent of PSA levels or Gleason score. Carriers with non-metastatic prostate cancer have shorter cancer-specific survival (8.6 vs 15.7 years) and higher risk of developing metastatic disease, based on a large study comparing outcome of 79 mutation carriers vs almost 2000 control cases [28]. In a second study, Castro et al. also noted that worst outcome occurred both in patients receiving radical prostatectomy and radiation therapy with curative intent [29]. Recently, a retrospective analysis of a cohort of over 1000 prostate cancer patients engaged in active surveillance programs showed that *BRCA1, BRCA2, and ATM* mutation carriers experienced more often upgrading of their tumor staging at 2, 5, and 10 years of follow-up and required intervention [30]. Together, these data support incorporating genomic stratification based on, at least, germline *BRCA2* mutations for a more precise management of non-metastatic prostate cancer.

With the advent of more accurate and less costly next-generation sequencing technologies, interrogating the somatic (not inherited) mutational landscape of cancers has become a powerful resource to define tumor subgroups, which then need to be clinically validated for precision medicine strategies [31–33]. The Cancer Genome Atlas Research Network (TCGA) depicted the genomic landscape of 333 cases of non-

metastatic prostate cancer based on whole-exome sequencing of untreated primary tumors. While up to 19% of these tumors were classified as "defective" for DNA repair genes, actually all six cases described as *BRCA2* mutant presented a germline mutation (K3326*) of unclear pathogenic value, and many cases of heterozygous deletions in *FANCD2* did not have loss of the second allele, suggesting that the true rate of significant DNA repair gene defects in non-metastatic, potentially curable, prostate cancer is below 10% [34•].

An enrichment for DNA repair gene mutations has been identified in late stage metastatic prostate cancer (Table 1). In a whole-exome sequencing study of 150 metastatic biopsies, the SU2C-PCF International Consortium identified biallelic DNA repair gene inactivation in 23% of cases, being *BRCA2* mutations and homozygous deletions the most common in 12% of cases [35•]. In a recent whole-genome sequencing descriptive study of metastatic biopsies, additional inactivating events such as *ATM* or *PRKDC* structural rearrangements, which would not have been detected by whole-exome sequencing, were described, suggesting that the prevalence of DNA repair defective metastatic prostate cancer could be even higher. In a follow-up study, whole-exome sequencing data from different published cohorts of primary and metastatic prostate cancer was re-analyzed using standardized pipelines [32, 34•, 35•, 41, 42••], confirming the significant enrichment for DNA repair gene defects in metastatic (27%) vs non-metastatic (10%) prostate cancer.

The SU2C-PCF genomic landscape study [35•] represented at its time of publication the biggest effort to comprehensively characterize metastatic prostate cancer. Beyond the high prevalence of DNA repair gene defects, a significant finding was that many of these events were associated to a germline mutation, more often than expected based on the reported prevalence for inherited *BRCA1/2* mutations in prostate cancer. Based on this observation, a larger cohort of 692 patients receiving treatment for metastatic prostate cancer across seven institutions in the USA and the UK was selected to study the presence of inherited mutations in DNA repair genes [38••]. Samples underwent targeted sequencing using different local panels; a standardized data analysis for 20 DNA repair genes identified pathogenic or suspected pathogenic mutations in 82 cases (11.8%). Consistently, *BRCA2* (5.3%) was again the most commonly inherited mutation. This prevalence was significantly higher than expected when compared to the genetic profiling of the overall population but also compared to the TCGA series of non-metastatic prostate cancers [34•]. The high prevalence of germline mutation carriers among the metastatic prostate cancer population has now been confirmed in other studies, with certain differences resulting probably from different genetic background across distinct populations worldwide [43, 44].

Notably, germline mutation carriers were identified across age subgroups and in patients with and without significant family history of prostate, breast, or ovarian cancer, despite there is some enrichment for germline mutations in tumors from patients with first degree family relatives with cancer. These data suggest screening for germline mutations should not be limited to younger patients with a significant family history. In fact, the NCCN guidelines have now adopted the recommendation of universal germline screening for all men with metastatic prostate cancer and invite to consider testing also in men with high-risk non-metastatic disease [45]. Implementations of such recommendations would be transformative in the management of prostate cancer patients and will have a definitive impact in early identification of families and individuals at risk of developing prostate, breast, ovarian, pancreatic, and colorectal cancer (Lynch syndromes).

The impact in clinical outcome and prognosis of DDR defects in metastatic prostate cancer still remains unclear. First, a retrospective study analyzing outcome of 319 patients with metastatic prostate cancer [46] associated germline DDR mutations with a shorter time to progression to standard-of-care abiraterone and enzalutamide treatment (3.3 vs

Table 1 DDR genes frequently altered in prostate cancer

DDR gene	Common aberration types	Primary	Metastatic	Reference(s)
BRCA2	Deletion, mutation	3%	13.3%	[34•, 35•]
ATM	Deletion, mutation	4%	7.3%	[36, 37]
CHEK2	Germline mutation	0%	1.87%	[38••]
CDK12	Mutation	1%	6.9%	[36]
BRCA1	Mutation	1%	0.7%	[35•]
FANCD2	Copy loss	6%	–	[35•]
RAD51C	Copy loss	3%	–	[35•]
RAD51D	Germline mutation	–	0.43%	[38••]
MSH2	Copy loss, mutation, rearrangements	0.3%	2%	[39]
MSH6	Mutation	1.5%	2%	[39, 40]
MLH1	Copy loss, epigenetic silencing	0.3%	0.7%	[35•]

6.2 months, $p = 0.01$). A second report from the same group included somatic next-generation sequencing (NGS) from circulating tumor DNA and also found a link between DNA repair gene defects (in that case either germline or somatic) and faster resistance to abiraterone and enzalutamide [47]. However, these results have not been confirmed in other studies where no different outcome or not even a trend towards improved outcome was observed for patients with germline DDR mutations receiving enzalutamide or abiraterone [48–50]. Reasons for these discrepant results may include different tests being considered (germline vs somatic in ctDNA testing), population enrichment for patients with higher/lower disease burden, and the proportion of patients in each study who received these therapies in the pre- vs post-taxane setting. Along this line, the recent PROREPAIR-B study [51] showed in a prospective setting that g*BRCA2* carriers had an overall more aggressive course of disease in terms of shorter time to development of castration-resistance and in terms of shorter cause-specific (CSS) for metastatic castration-resistant prostate cancer (mCRPC) (hazard ratio 2.11; $p = 0.03$).While these data support g*BRCA2* mutations as a prognostic factor, its predictive role for selecting among standard of care therapies is less clear. Prospective studies will help elucidate the true role of DDR defects in prognosis of metastatic disease; however, it is likely that with the development of targeted agents for this molecularly defined subset of patients, current prognostic impact may not be necessarily the same in a more precise therapeutic setting [51].

Targeting DNA Repair Gene Defects in Advanced Prostate Cancer

A small number of patients with germline *BRCA2* mutations and prostate cancer were included in the first-in-man trials of different PARP inhibitors, providing the first set of evidence of the activity of these drugs in prostate cancer patients [14, 52, 53•].

In a basket phase II study of olaparib for *BRCA1/2* germline mutation carriers, eight patients with prostate cancer were enrolled [54]. Four out of 8 achieved a significant PSA response; however, it should be noted that 3/4 non-responding patients have had platinum-based chemotherapy prior to the PARPi treatment; platinum chemotherapy is not commonly used in prostate cancer and has some degree of cross-resistance with PARP inhibitors [55].

In a small single-arm phase II study of the PARPi olaparib among patients with heavily pre-treated mCRPC [38••], the TOPARP-A study, responses to olaparib (defined in the protocol as radiological responses, PSA falls, or CTC count conversions) were observed in 33% of the overall population. Retrospective molecular characterization of trial tumor biopsies identified a strong association between responses and presence of germline or somatic DDR gene alterations. Indeed, 8/8 patients with *BRCA1/2* mutations responded to olaparib; many of these responses were long-lasting, the longest being a patient who benefited for over 3.5 years. Some responses were observed among patients with *ATM* mutations (two PSA responses and two additional CTC conversions among six patients) [56] or alterations in other genes such as *PALB2*. The second part of this study (TOPARP-B), currently ongoing, aims to validate these data in a population selected based on a prospective program of NGS for detection of DDR gene defects. Recently, preliminary results for the first 85 patients recruited in a phase II trial evaluating the efficacy of the PARPi rucaparib in mCPRC were reported (TRITON2) [57•]. The TRITON2 study population was preselected based on the presence of DNA repair genes alterations in tumor or ctDNA using a commercial targeted sequencing panel. Out of the first 85 patients (the trial is ongoing), confirmed PSA and confirmed radiographic responses were reported in 48% and 45% of patients harboring germline or somatic *BRCA2* defects. No confirmed PSA or confirmed radiological responses were seen among patients with *ATM* or *CDK12* mutations, albeit the study needs yet to be completed. Based on these data, both olaparib and rucaparib have been granted breakthrough designation by the FDA for expedited review for indication in mCRPC. Currently, several randomized phase III trials of PARPi aim to confirm these findings in molecularly defined populations.

The use of platinum-based chemotherapies in prostate cancer has never been part of the standard of care therapeutic armamentarium, and their development was deprioritized since a randomized phase III trial of the orally available drug satraplatin failed to increase survival in a non-molecularly selective population [58]. However, the emerging knowledge on the role of DDR defects in prostate cancer progression has raised interest in the potential benefits of using platinum-based chemotherapies in metastatic prostate cancer. Indeed, combinations of taxanes and chemotherapy seem to be active particularly in populations with poorly differentiated, arguably less AR-dependant tumors [59]. As single agents, metastatic prostate cancer responses to platinum salts have been associated with DNA repair gene defects, primarily *BRCA2* and *ATM* mutations, in small series of patients [60–62].

The prevalence of MMR gene aberrations in prostate cancer is low compared to alterations in other DDR pathways such as HR [39, 42••] but may represent a selected population for the development of ICI, which have been already approved in other tumor types. In two retrospective series of advanced prostate cancer patients, responses to PD1/PDL1 inhibitors were observed among prostate cancers with MMR defects [40, 63]. Beyond MMR defects, tumors with genomic signatures characterized by high number of rearrangements and

small tandem duplications, associated to the presence of CDK12 inactivating mutations, are now in the spotlight, as these tumors express high amounts of neoantigens, present high levels of T cell infiltration, and some responses to ICI have been described among these patients ([36, 64]). Considering the prevalence of CDK12 mutations in advanced mCRPC is 5–7%, these findings could be clinically relevant and deserve further investigation.

In summary, while ICI are not yet part of standard of care prostate cancer management, emerging data is challenging the assumption that these drugs do not work in prostate cancer. Responses to PD1/PDL1 inhibitors in small patient series have been reported and larger trials are ongoing [65–67]; retrospective genomic analysis of such trials may help to better understand the clinical actionability of MMR defects and other DDR alterations in prostate cancer using ICI.

How to Exploit Therapeutically the Interplay Between AR Signalling and DDR in Prostate Cancer

The AR pathway drives prostate cancer progression. Development of resistance to androgen deprivation therapy is due primarily by adaptive mechanisms that enable persistent AR signalling. Even after progression to new generation treatments (abiraterone and enzalutamide), the presence of mutations, amplifications, and splice variants forms of AR promote the oncogenic signalling. Interestingly, ADT has a synergistic effect with radiation therapy for prostate cancer [68]. This observation can be explained, in part, by the induction of AR upon DNA damage, what favors damage resolution thus conferring resistance to cancer cells [69]. Indeed, additional data shows that AR regulates transcription of several sets of DNA repair genes [10, 69, 70]. Different studies in preclinical models associate AR blockade with downregulation of HR gene transcription [71, 72]. Lastly, it has also been shown that PARP-1 can act as an AR co-factor [73], able to modulate its activity and function in DNA damage, and that PARP-1 expression levels increase throughout the disease progression and are upregulated in exposure to antiandrogen therapy [72, 74]. These data provided the rationale for developing PARP inhibitors in combination with AR-targeting agents beyond the metastatic prostate cancer population with DDR gene defects.

Two randomized phase II clinical trials investigated the combination of abiraterone acetate and PARPi in the mCRPC stage. In the NCI9012 study, 148 patients were randomly assigned to receive abiraterone plus prednisone with or without veliparib. The primary endpoint was the response rate (PSA or radiological), with a preplanned stratified analysis according to the presence of E26 transformation-specific (ETS) fusion based on preclinical data suggesting an interaction between the recombinant TMPRSS2:ERG protein and PARP-1 [75]. Overall, no significant differences were observed in PSA response rate (72% combination vs 64% abiraterone alone; $p = 0.27$) or median PFS (11 months combination vs 10.1 months abiraterone alone; $p = 0.99$). The presence of ETS fusions was not associated with increased sensitivity in the clinic, in line with retrospective analysis of single-arm olaparib and niraparib studies [53•, 76••]. In contrast to these findings, a randomized phase II trial of olaparib in combination with abiraterone acetate ($n = 142$, patients randomized to abiraterone, steroids and olaparib vs abiraterone, steroids and placebo) reported an improved median radiographic progression-free survival (rPFS) for the abiraterone and PARPi combination arm (13.8 vs 8.2 months, $p = 0.03$) [77•]. In both trials, germline or somatic DNA repair gene defects associated with increased responsiveness. However, the benefit in rPFS for the combination of abiraterone and olaparib was observed across patients with or without genomic DDR defects; these data have led to ongoing phase III trials combining PARPi with AR-targeting agents without prospective molecular stratification.

With the recent data supporting the use of abiraterone and enzalutamide in the hormone-naïve metastatic setting [78, 79], it is envisioned that upcoming trials will challenge these combinations in the earlier space in the near future.

Conclusions and Future Perspectives

Molecular stratification of prostate cancer based on clinically relevant and genomically defined subsets of the disease offers the opportunity for a more precise patient management. With an increased understanding of the role of DDR defects in prostate cancer progression and the enrichment for such alterations in lethal forms of the disease, it is expected that the development of targeted agents in this space will result in personalized therapeutic approaches for these patients.

The degree of evidence acquired in the last decade for germline *BRCA1/2* mutations in the fields of ovarian and breast cancer vouches for embracing genomic stratification in prostate cancer. Germline *BRCA1/2* mutations have been demonstrated to be relevant in determining the risk of prostate cancer, determining prognosis of non-metastatic prostate cancer, and are a suitable therapeutic target in advanced disease.

The role of other germline mutations and other somatic DDR gene defects remains yet to be fully understood. A subset of these defects seems to associate also with responses to specific therapies, but the biomarker suite yet needs to be refined. Intra-patient tumor heterogeneity, genomic tumor evolution, and standardization of tumor and ctDNA NGS assays need to be better addressed to facilitate the incorporation of genomic stratification of prostate cancer in patient care. Molecular profiling beyond mutation calling may offer certain advantages for stratifying patients; non-gene-specific biomarkers currently in clinical development include mutational

patterns or signatures associated with HR defects [80], genome-wide evaluation of copy number and loss of heterozygosity (LOH) changes [81], and protein-based markers of HR proficiency [82].

Despite these challenges, the implementation of genomic stratification of prostate cancer based on DNA repair defects promises to impact therapeutic strategies; the use of PARPi or platinum therapies in genomically defined subsets of prostate cancer will probably represent the first fruit of these precision medicine approaches. Moreover, we envision that in the near future, precision medicine will have wider implications for the management of both metastatic (combination with AR-targeting agents, newer agents such as ATR/CHK inhibitors) and non-metastatic (more precise selection of curative treatments, opportunities for adjuvant treatment strategies) prostate cancer.

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Compliance with Ethical Standards

Conflict of Interest Alejandro Athie declares that he has no conflict of interest.

Sara Arce-Gallego declares that she has no conflict of interest.

Macarena Gonzalez has received compensation from Roche for service as a consultant/advisor and has received reimbursement for travel/accommodation expenses from Astellas, Bayer, and Lilly.

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- • Of importance
- •• Of major importance

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