The Oncologist®

Genitourinary Cancer

PARP Inhibitors and Prostate Cancer: To Infinity and Beyond *BRCA*

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Poly(ADP-ribose) polymerase inhibitor • Prostate cancer • Olaparib • Rucaparib • *BRCA* • DNA damage repair • Homologous recombination repair • Mismatch repair • Mutation • Biomarker

Abstract

The U.S. Food and Drug Administration recently approved two poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors, olaparib and rucaparib, for treatment of biomarker-positive metastatic castrate resistant prostate cancer. The benefits of PARP inhibition have been well characterized in patients who have *BRCA1* and *BRCA2* mutations in several forms of cancer. *BRCA1* and *BRCA2* occupy key roles in DNA damage repair, which is comprised of several different pathways with numerous participants. Patients with mutations in other key genes within the DNA damage repair pathway may also respond to treatment with PARP inhibitors, and identification of these alterations could significantly increase the percentage of patients that may benefit from PARP inhibition. This review focuses on the potential for synthetically lethal interactions between PARP inhibitors and non-*BRCA* DNA damage repair genes. ***The Oncologist*** 2021;26:e115–e129

Implications for Practice: The treatment potential of PARP inhibition has been well characterized in patients with *BRCA1* and *BRCA2* mutations, but there is compelling evidence for expanding the use of PARP inhibitors to mutations of other non-*BRCA* DNA damage repair (DDR) genes. This could increase the percentage of patients that may benefit from treatment with PARP inhibitors alone or in combination with other therapies. Understanding the significance of PARP inhibitor-sensitizing alterations in other common non-*BRCA* DDR genes will help guide clinical decisions to provide targeted treatment options to a wider population of patients.

Introduction

Until the U.S. Food and Drug Administration's (FDA's) recent approval of two poly-adenosine diphosphate (ADP) ribose polymerase (PARP) inhibitors, rucaparib and olaparib, the treatment armamentarium for men with metastatic-castration resistant prostate cancer (mCRPC) included first-generation androgen receptor (AR) axis-targeting agents (flutamide, bicalutamide, and nilutamide), next-generation AR axis-targeting agents (abiraterone, enzalutamide, apalutamide, darolutamide), taxane-based chemotherapies (docetaxel, cabazitaxel), and the radiopharmaceutical radium-223 (for bone metastases), as well as immunotherapy with Sipuleucel-T [1, 2]. Although these therapies have considerably improved outcomes over the past decade, prostate cancer remains the second most common cause of cancer-related mortality in American men [3]. The approval of pembrolizumab for solid tumors designated as microsatellite instability-high (MSI-H) or those with mismatch repair deficiencies served as the first tumor-agnostic treatment regimen that ushered in the era of precision medicine for mCRPC. PARP inhibitors, which take advantage of DNA damage repair (DDR) germline and somatic mutations, introduce a new genetically stratified approach to treating prostate cancer and have previously been approved for treatment of certain forms of breast and ovarian cancers [4, 5]. PARP inhibitors are most often associated with pathogenic alterations of the DDR genes *BRCA1* and *BRCA2*, but there is compelling evidence for expanding the use of PARP inhibitors beyond BRCA to mutations of other non-BRCA DDR genes, which could increase the percentage of patients that

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may benefit from treatment with PARP inhibitors. There is also increasing evidence to suggest that certain DDR mutations do not confer sensitivity to PARP inhibition, and understanding when to not prescribe PARP inhibitors is also critical for physicians as they make clinical decisions. This review will highlight non-BRCA DDR gene alterations that may increase patient sensitivity to PARP inhibition alone or in combination with other therapies.

DNA Damage Repair and PARP Inhibition

PARPs form a large class of 16 enzymes. PARP1 and PARP2 respond to DNA damage and facilitate the cell's DDR response [6]. In healthy cells, PARP1 recognizes and binds to DNA at the site of single-strand breaks (SSBs) and double-strand breaks (DSBs). A series of structural allosteric changes of PARP1 follow, which allows for the recruitment of acceptor proteins and production of a negatively charged poly(ADP-ribose) branched polymer composed of NAD^+ that links the damaged site to surrounding chromatin in a process known as PARylation [7, 8]. The negative charge repulses PARP1 from the complex and acts as a target for DDR proteins and polymerases, including XRCC1, POLβ, and LIG3, for continuation of the damage repair response [8]. Should the SSB repair process fail, an accumulation of SSBs leads to replication arrest, followed by potentially lethal DSB formations at collapsed replication forks. DSBs can also occur independently from failed SSB repair, as they are commonly the result of harmful ionizing radiation damage to the cell. Healthy cells have the ability to recognize and repair DSBs via one of the four main DSB repair pathways: homologous recombination (HR), nonhomologous end joining (NHEJ), alternative NHEJ, or single-strand annealing [9]. In addition to SSBs, PARP1 can recognize DSBs and competes with the Ku protein complex and the MRN complex for localization at free DNA ends. Depending on the phase of the cell cycle, either the Ku protein complex or PARP1 will carry out NHEJ or alt-NHEJ, respectively [10].

Classic NHEJ requires that the Ku protein complex activates and recruits the catalytic subunit of DNA-PK (DNA-dependent protein kinase) to the site of damage, thereby forming the DNA-PK complex, which can be phosphorylated by a number of factors, including ATM, a protein linked to the HR DSB repair pathway [11]. XCCR4 stabilizes the complex, whereas Artemis and other repair and ligation factors are recruited to complete repair. PARP1 has been implicated in the stabilization of the Ku protein complex in some cases [10]. In the absence of the Ku protein complex, PARP1 can induce alt-NHEJ, which operates similarly to SSB repair, with XRCC1 and LIG3 filling key roles for repair [12, 13].

Recognition of DSB damage by the MRN complex, composed of MRE11, RAD50, and NBS1, initiates the HR repair pathway, which provides a homology-directed, high-fidelity repair of DSBs through various subpathways, depending on cell cycle stage and molecular competition [14]. Following recognition by the MRN complex, ATM is recruited to the site of damage to activate the MRN-ATM signaling axis. Together with ATR, the MRN-ATM signaling axis recruits and activates a number of downstream targets, including

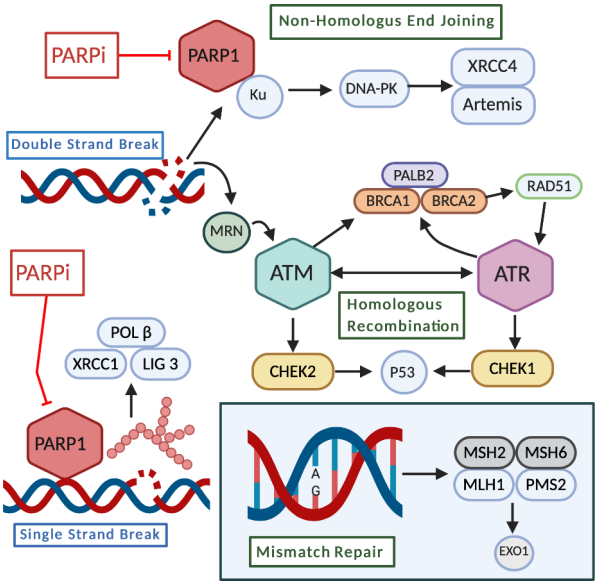

Figure 1. DNA damage repair mechanisms. Single-strand break (SSB) repair: PARP1 detects single-strand DNA breaks and facilitates the formation of a negatively charged, branched polymer that recruits XRCC1, LIG 3, and POL β to the site of damage for ligation and repair. Inhibition of PARP1 at this stage leads to an accumulation of SSBs that ultimately results in DSBs [7, 8]. Double-strand break (DSB) repair: nonhomologous end joining–DNA ends are bound by Ku proteins, which are stabilized by PARP1, and form the DNA-PK (DNA-dependent protein kinase) complex following recruitment of DNA-PKcs (catalytic subunit of DNA-PK). XCCR4 and Artemis are recruited, which stabilize and recruit other repair factors to the site of damage [9–11]. Homologous recombination: damage is detected by the MRN complex, which recruits and activates ATM. ATM can activate the PALB2, BRCA1, and BRCA2 complex, ATR, or CHEK2, depending on cell cycle phase. RAD51 is activated and conducts a search for a homologous template used for repair, which activates other factors necessary for repair. Ultimately, P53 is stabilized by either CHEK1 or CHEK2 and proofs the repair [12–20]. Mismatch repair: a MSH2/MSH6 heterodimer recognizes and localizes mismatched base pair errors and forms a complex with MLH1 and PMS2. This complex recruits the exonuclease EXO1 as well as other repair and ligation factors [21–24].
Figure was created using BioRender.com.
Abbreviations: PARP, poly(ADP-ribose) polymerase; PARPi, PARP inhibitor.

BRCA1, BRCA2, PALB2, CHEK1, CHEK2, RAD51, and P53 [12–20].

Another form of DNA damage repair concerns the resolution of mismatched nucleotides that arise from replication errors, repair errors, or chemical damage. Mismatch repair (MMR) is initiated following recognition of an error by either MutSα (MSH2/MSH6) or MutSβ (MSH2/MSH3), depending on the size of the error: MutSα preferentially repairs smaller indels, whereas MutSβ localizes to larger tracts of base errors. Depletions in MutSα are more deleterious; however, as larger errors can be repaired through other pathways, should the function of MutSβ be hindered [21, 22]. Following recognition and localization by either MutSα or MutSβ, MutLα (MLH1/PMS2) is recruited to form a tetrameric complex that forms DNA incisions [23]. Exo1, and a number of other polymerases and ligation proteins, are recruited to

complete the repair [10, 24]. These DNA repair mechanisms are summarized in Figure 1.

Due to the significant roles that PARP1 fulfills in mediating the cell's DDR response, PARP inhibitors emerged as a potential therapy to sensitize tumor cells to conventional DNA damage-causing cancer treatments. Nicotinamide analogs were shown to inhibit poly(ADP-ribose) polymer formation and to increase tumor cell sensitivity to dimethyl sulphate [25], and further drug development led to the first-generation clinical introduction of veliparib, rucaparib, olaparib, niraparib, and second-generation talazoparib. There is some variation in size and structure among available PARP inhibitors, but generally, the inhibitors bind to active sites of PARP1, preventing PARylation and the ability of bound PARP1 to release from DNA-chromatin structures. This process has been described as "PARP trapping," and available PARP inhibitors vary in how effectively PARP can be trapped [26]. Approved prostate cancer (PCa) PARP inhibitors, rucaparib and olaparib, are relatively similar in their ability to trap PARP. Talazoparib has been shown to bind chromatin, DNA, and PARP to around a 100-fold greater degree than olaparib and rucaparib, but this cannot be directly correlated to clinical efficacy [27]. Studies investigating head-to-head PARP inhibitor efficacy, target, and toxicity comparisons are ongoing [25, 28–32].

In 2005, PARP inhibitors were implicated as a possible means of treatment for patients with cancer with germline *BRCA1* and *BRCA2* mutations [33, 34]. Patients possessing germline mutations in DNA damage repair genes have a higher risk of developing certain cancers, including prostate, breast, and ovarian cancers [35–37]. There is also evidence suggesting germline mutations in DNA damage repair genes are more likely to be associated with aggressive disease types. Cells harboring these heterozygous mutations often lose the wild-type functioning allele during tumorigenesis and are rendered unable to repair DSBs via the HR repair pathway, thus driving carcinogenesis and the emergence of a tumor that is genetically distinct from the normal tissues around it. Treating patients possessing these DDR genetic mutations with PARP inhibitors offers a combinatory approach that introduces errors in DNA damage detection and takes advantage of the preexisting malfunctioning HR pathway within the tumor microenvironment, likely resulting in tumor cell death. This exploitative approach is known as "synthetic lethality," in which two normally nonlethal events synergistically produce a fatal effect [30]. The capability to induce lethal events confined to tumor tissue harboring loss-of-function mutations in essential DNA damage repair genes poses great therapeutic potential across many types of cancers [33, 38]. In 2014, the FDA approved olaparib as a monotherapy treatment of advanced ovarian cancer in patients with deleterious germline *BRCA* mutations, with approvals of other PARP inhibitors in other cancers following [39]. FDA approvals of PARP inhibitors are listed in Tables 1 and 2.

Table 1. FDA approvals for poly(ADP-ribose) polymerase inhibitors in all cancers

Disease and drug	Treatment	Approval date
Ovarian cancer		
Olaparib	Advanced ovarian cancer	12/19/2014
	Ovarian cancer maintenance therapy	08/17/2017
	First-line maintenance therapy in BRCA-mutated advanced ovarian cancer	12/19/2018
	First-line maintenance therapy with bevacizumab for HRD-positive advanced ovarian cancer	05/08/2020
Rucaparib	Advanced ovarian cancer	12/19/2016
	Maintenance therapy of recurrent ovarian cancer	09/16/2018
Niraparib	Recurrent ovarian cancer	03/27/2017
	Late-line treatment of recurrent ovarian cancer	10/23/2019
	First-line monotherapy for platinum-responsive advanced ovarian cancer regardless of biomarker status	04/29/2020
Breast cancer		
Olaparib	Germline BRCA-mutated metastatic breast cancer	01/12/2018
Talazoparib	Germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer	10/16/2018
Pancreatic cancer		
Olaparib	First-line maintenance therapy in BRCA-mutated metastatic pancreatic cancer	12/30/2019
Prostate cancer		
Rucaparib	Monotherapy for BRCA1/2 mutant mCRPC	05/15/2020
Olaparib	HR repair gene mutated mCRPC	05/20/2020

Abbreviations: FDA, U.S. Food and Drug Administration; HR, homologous recombination; HRD, homologous recombination deficient mCRPC, metastatic castration-resistant prostate cancer.

DDR Mutations and Prostate Cancer

A number of studies have reported the frequencies of somatic and germline mutations in DDR genes at several disease stages of PCa, but whether or not patient mutation status (germline or somatic) indicates clinical benefit has yet to be seen [40]. In 2015, Robinson et al. evaluated 150 cases of mCRPC and found that 22.7% of tumors harbored deleterious DDR germline or somatic mutations in *BRCA1*, *BRCA2*, *ATM*, *CDK12*, *FANCA*, *RAD51B*, and *RAD51C* [41]. Pritchard et al. found that 11.8% of screened patients with mCRPC had at least one germline mutation in a DDR gene [42], and Abida et al., in 2017, found that 27% of screened patients across all stages of PCa possessed germline or somatic alterations in either *BRCA1/2*, *ATM*, and *CHEK2* [43]. The recent PROfound trial screened 4,425 patients with mCRPC for 15 genes with direct or indirect roles in HR. A total of 2,792

Table 2. FDA approvals for poly(ADP-ribose) polymerase inhibitors in prostate cancer

Drug	Approved dose	Treatment group	Side effects	Clinical trials contributing to approval
Rucaparib	600 mg orally twice daily, with or without food	Men with deleterious *BRCA* germline or somatic mutations and mCRPC who have previously been treated with AR-directed therapy and a taxane-based chemotherapy	Fatigue (including asthenia), nausea, anemia, ALT/AST increased, decreased appetite, rash, constipation, thrombocytopenia, vomiting, diarrhea	TRITON2: NCT02952534
Olaparib	300 mg orally twice daily with or without food	Men with deleterious, or suspected deleterious, germline or somatic HR repair mutated mCRPC following disease progression after enzalutamide or abiraterone treatments	Nausea, fatigue (including asthenia), anemia, vomiting, diarrhea, decreased appetite, headache, neutropenia, dysgeusia, cough, dyspnea, dizziness, dyspepsia, leukopenia, thrombocytopenia, and abdominal pain	PROfound: NCT02987543

Abbreviations: FDA, U.S. Food and Drug Administration; ALT, alanine aminotransferase; AR, androgen receptor; AST, aspartate aminotransferase; HR, homologous recombination; mCRPC, metastatic castration-resistant prostate cancer.

Table 3. Frequencies of germline vs. somatic mutations in DNA damage repair genes and evidence-based clinical applications in prostate cancer

Gene	Frequency of somatic mutation,[a] %	Frequency of germline mutation,[b] %	Evidence-based clinical application[c]
ATM	3.7–5	1.6	Modest activity of PARPi as monotherapy (TRITON 2, TOPARP-B, TALAPRO-1). Consideration of PARPi + ATR inhibitor combination.
BRCA1	1	0.9	Clear benefit of PARPi (PROfound, TRITON 2, TOPARP-B, TALAPRO-1, GALAHAD).
BRCA2	6–7	5.4	Clear benefit of PARPi (PROfound, TRITON 2, TOPARP-B, TALAPRO-1, GALAHAD).
BRIP1	0.5	0.2	Limited data of potential activity (TRITON 2). More studies recommended.
CDK12	2.8–10		Modest activity of PARPi as monotherapy (TRITON 2). Consideration of PARPi + PD-1/PD-L1 inhibitor combination.
CHEK2	1–2	1.9	Limited data of potential activity (TRITON 2; TOPARP-B). More studies recommended including PARPi + ATR inhibitor combinations.
FANCA	0.1–3	0.1	Limited data of potential activity (TRITON 2). More studies recommended.
NBN	0.5–1	0.3	Modest activity in limited data. More studies recommended.
PALB2	0.5–2	0.4	Potential benefit of PARPi (PROfound, TRITON 2, TOPARP-B, TALAPRO-1). More studies warranted.
RAD51B	3		Limited data available (TRITON 2). More studies recommended.
RAD51D	2.7	0.4	Limited data available. More studies recommended.

Ongoing clinical trials measuring PARP inhibitor response (classified by select DNA damage repair genes) are listed in supplemental online Table 1.
[a]Sources: [43, 46–47, 60].
[b]Sources: [41–42, 45, 51, 60].
[c]Sources: [44, 48–49, 52–53, 55].
Abbreviations: PARPi, PARP inhibitor; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1.

patients were successfully sequenced, and qualifying alterations were found in 778 of 2,792 (28%) patients [44]. These reported frequencies in sequenced patients have been corroborated by several other studies in mCRPC [45–51], as seen in Table 3.

Due to the benefits seen in breast and ovarian cancers treated with PARP inhibitors, coupled with the frequency of DDR mutations seen in PCa, a number of clinical trials have arisen to evaluate the effects of PARP inhibition when used to treat PCa. The canonical use of PARP inhibitors in PCa offers a molecular-stratified approach that is novel to the PCa treatment regimen, which has thus far lacked targeted treatment options and the associated biomarkers. Accompanying the recent approval of rucaparib and olaparib by

the FDA for the treatment of mCRPC, several trials are examining the effects of other PARP inhibitors when used to treat PCa at different disease stages, some in combination with current standard of care drugs. Summaries of completed and ongoing trials are listed in Table 4.

In 2014, a phase II clinical trial, TOPARP-A (NCT01682772), investigated treatment of mCRPC with olaparib in 50 patients, irrespective of DNA damage repair mutations. Of these patients, 16 had tumor aberrations of DNA-repair genes (*BRCA2*, 7; *ATM*, 5; *BRCA1* or *CHEK2*, 3; and *HDAC2*, 1). Of those 16 patients, 14 had a response to olaparib, as measured by a composite methodology that included declines in circulating tumor cells (CTCs) [52]. These data resulted in olaparib receiving breakthrough therapy designation in prostate cancer from the FDA. To further examine the antitumor effects of olaparib in men harboring DNA damage repair mutations with mCRPC, TOPARP-A was followed by TOPARP-B (NCT01682772), a randomized phase II trial for men with prostate cancer that had progressed to mCRPC. Patients were screened via targeted next-generation sequencing (NGS) of either primary or metastatic cancer biopsies. Those who exhibited a pathogenic mutation or homozygous deletion in a DNA damage repair gene that had previously been associated with PARP inhibition sensitivity were enrolled and separated into two cohorts receiving either 300 mg or 400 mg olaparib twice daily. Of the DDR mutation subgroups, the *BRCA1/2* subgroup saw the most confirmed responses and the longest median radiographic progression-free survival, with 25 of 30 *BRCA1/*2 patients achieving a composite overall response rate (ORR) of 83.3%. However, many of these responses focused on CTC declines rather than prostate-specific antigen (PSA) declines or objective responses. Patients with alterations in *ATM*, *CDK12*, and *PALB2* achieved radiographic objective responses in 1 of 12, 0 of 18, and 2 of 6 patients, respectively. PSA declines of at least 50% were detected in 1 of 19, 0 of 20, and 4 of 6 patients, respectively. These data suggest that *PALB2* mutants may be susceptible to PARP inhibition. Both of the TOPARP trials demonstrated the antitumor effects of olaparib when used to treat men with mCRPC possessing certain DDR genetic aberrations, with evidence that certain patients with non-*BRCA* mutations may benefit from PARP inhibition as well [53]. TOPARP-B, however, demonstrated some of the limitations of obtaining accurate and timely somatic genetic testing, as only 13.7% (98/711) of the screened patients were placed on study.

The PROfound trial (NCT02987543) was a prospective, randomized phase III trial that examined the efficacy of olaparib in men with mCRPC and DDR mutations in 15 genes associated with HR: *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. The primary endpoint examined was imaging-based progression-free survival (PFS). Patients with alterations in *BRCA1/2* or *ATM* were assigned to cohort A, and patients with alterations in any of the other 12 genes were assigned to cohort B. Within each cohort, patients received either 300 mg olaparib twice a day or a standard of care treatment (enzalutamide or abiraterone) at a 2:1 ratio. In cohort A, PFS was significantly longer in the olaparib group compared with the control (7.4 months vs. 3.6 months; hazard ratio for progression or death, 0.34; 95% confidence interval [CI], 0.25–0.47; $p < .001$), with *BRCA1* and *BRCA2* patients achieving hazard ratios of 0.41 and 0.21, respectively. Of the overall population (cohorts A and B), PFS was significantly longer in the olaparib patients than control patients (5.8 months vs. 3.5 months; hazard ratio, 0.49; 95% CI, 0.38–0.63; $p < .001$). Patients with mutations in *RAD54L* had a 0.33 hazard ratio, suggesting potential benefit outside the realm of *BRCA1/2* [44]. As noted, 4,425 patients were screened, but only 387 of those 4,425 (8.7%) patients were sequenced successfully. Failure of DNA sequencing occurred in approximately 31% of the tumor samples received, highlighting one of the limitations of the study.

Findings from the PROfound trial led to the FDA's recent approval of olaparib for patients with mCRPC with progression after treatment with enzalutamide and/or abiraterone that have deleterious germline alterations in *BRCA1*/*BRCA2* or somatic deleterious alterations in *BRCA/BRCA2*, *ATM*, *BARD*, *BRIP*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.

The TRITON series of clinical trials is currently evaluating the use of rucaparib to treat men with mCRPC that have germline or somatic mutations in DDR genes. The eligibility criteria of TRITON2 (NCT02952534), a phase II trial, included mutations in any HR gene, whereas TRITON3 (NCT02975934), an ongoing phase III trial comparing rucaparib with standard of care treatments, is enrolling only men with mCRPC and mutations in *BRCA1/2* and *ATM*. Rucaparib was granted breakthrough therapy designation by the FDA based on initial efficacy and safety results from the TRITON2 study. Preliminary published data from this study shows promising results, with 43.9% of *BRCA* patients achieving a confirmed radiographic response, with the majority of responses lasting longer than 24 weeks [54]. Analysis of patients with non-*BRCA* DDR genes was conducted, and of 19 evaluable patients with *ATM* mutations, 10.5% had confirmed partial radiographic responses that were ongoing at the time of visit cutoff. No objective responses were observed in those harboring *CDK12* mutations. Of nine evaluable patients with *CHEK2* aberrations, one patient with a co-occurring *ATM* alteration had a confirmed partial response and a confirmed PSA response, and one other patient also achieved a confirmed PSA response. Of 13 patients comprising a group that included mutations in *FANCA*, *PALB2, BRIP1*, or *RAD51B*, 38.5% had an ORR, with one complete response seen in a patient with a *FANCA* mutation and four partial responses seen in patients with *PALB2* ($n = 2$), *BRIP1* ($n = 1$), or *RAD51B* ($n = 1$) [55]. The TRITON2 trial contributed to the FDA's recent accelerated approval of rucaparib to treat patients with mCRPC with germline or somatic *BRCA1/2* mutations.

The TOPARP, PROfound, and TRITON series trials, along with others listed in Table 3, have paved the way for the recent addition of PARP inhibitors to the PCa treatment regimen, which marks the beginning of a new molecular-based approach to treating the disease. However, much remains to be considered, including challenges facing sequencing availability, tissue acquisition, lack of protein ascertainment, and suggested guidelines, as well as the appropriateness of using PARP inhibitors to treat patients with non-*BRCA* mutations in DDR genes.

Table 4. Ongoing clinical trials of poly(ADP-ribose) polymerase inhibitors

Drug and trial no.	Status	Phase	Treatment	Patient population	Primary endpoint	Biomarkers included in eligibility criteria
Olaparib						
NCT03434158 (IMANOL)	Active	II	Olaparib, maintenance	Patients with mCRPC after docetaxel treatment reaching partial or stable response	Progression-free survival	BRCA1, BRCA2, ATM, FANC genes, CHEK2, MLH1, MSH2, MSH6, PMS2, PALB2, RAD51C, MRE11
NCT03432897	Active	II	Olaparib, neoadjuvant	Patients with locally advanced Pca and defects in DNA repair genes	PSA response rate	BRCA1, BRCA 2, ATM, CHEK1, CHEK2, FANCONIS ANEMIA (FANCL), HDAC2, PALB2, BARD1, BRIP1, CDK12, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L
NCT03810105	Active	II	Olaparib + durvalumab	Patients with castration sensitive, biochemically recurrent, nonmetastatic PCa and DDR mutations	Undetectable PSA	BRCA1, BRCA2, ATM, CHEK2, FANCA, RAD51C, RAD51D, PALB2, BRIP1, BARD1, or CDK12
NCT03012321	Active	II	Abiraterone/ prednisone, olaparib vs. abiraterone/ prednisone + olaparib	Patients with mCRPC and DDR defects	Objective progression-free survival	ATM, BRCA1, BRCA2, FANCA, PALB2, RAD51, ERCC3, MRE11, NBN, MLH3, CDK12, CHEK2, HDAC2, ATR, PMS2, GEN1, MSH2, MSH6, BRIP1, FAM175A
NCT03570476	Suspended (COVID-19)	II	Olaparib, neoadjuvant	Patients with localized PCa and DNA repair deficiencies	Pathological complete response rate	BRCA1, BRCA2, ATM, PALB2 (germline) or BRCA1, BRCA2, PALB2, FANCA, ATM (somatic)
NCT02987543 (PROfound)	Active, not recruiting	III	Olaparib vs. enzalutamide or abiraterone	Patients with mCRPC who have failed prior treatment with a new hormonal agent and have qualifying tumor mutation in an HR gene	Radiographic progression-free survival	BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L
NCT03516812	Active, not yet recruiting	II	Olaparib + durvalumab	Nonmetastatic patients predicted to have a high neoantigen load that have received local therapy	Undetectable PSA	CDK12, mismatch repair deficiencies, or HR repair deficiencies
NCT03263650	Active	II	Olaparib following cabazitaxel	Patients with aggressive variant Pca	Progression-free survival	None
NCT03317392	Active	I/II	Olaparib + radium 223	Patients with mCRPC that has spread to the bone	Maximum tolerated dose, progression-free survival	None
NCT03787680 (TRAP)	Active	II	Olaparib + AZD6738	Patients with mCRPC with or without DDR mutations	Complete or partial response in DNA repair proficient patients	General DNA repair deficiency
NCT03047135	Active	II	Olaparib only	Patients with high-risk biochemically recurrent PCa following radical prostatectomy	PSA repsonse rate	None
NCT02893917	Active, not recruiting	II	Olaparib with or without cediranib	Patients with mCRPC	Progression-free survival	None

(continued)

Table 4. (continued)

Drug and trial no.	Status	Phase	Treatment	Patient population	Primary endpoint	Biomarkers included in eligibility criteria
NCT03732820 (PROpel)	Active	II	Olaparib + abiraterone vs. placebo + abiraterone	Patients with mCRPC who have received no prior cytotoxic chemotherapy or new hormonal agents	Radiological progression-free survival	None
NCT01972217	Active, not recruiting	II	Olaparib + abiraterone vs. placebo + abiraterone	Patients with mCRPC	Part A: adverse events, dose limiting toxicities; part B: radiological progression-free survival, progression or death	None
Rucaparib						
NCT03413995 (TRIUMPH)	Active	II	Rucaparib only	Patients with mCRPC who have not yet been treated with ADT and germline mutations in DNA damage genes	PSA response rate	BRCA1, BRCA2, ATM, CHEK2, NBN, RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM
NCT03442556	Active	II	Carboplatin and docetaxel followed by maintenance rucaparib	Patients with mCRPC and HR repair deficiency	Radiographic progression-free survival	ATM, BRCA1, BRCA2
NCT03533946 (ROAR)	Active	II	Rucaparib only	Patients with castration sensitive PCa demonstrating "BRCAness"	PSA response rate	ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, ERCC3, FAM175A, FANCA, FANCL, GEN1, HDAC2, MLH1, MRE11, NBN, PALB2, PPP2R2A, RAD51, RAD54L
NCT04253262	Active	I/II	Rucaparib + copanlisib	Patients with mCRPC	Phase I: maximum tolerated dose; phase II: overall response	Phase I: none; phase II: BRCA1, BRCA2, ATM, BARD1, BRIP1, CHEK1, FANCL, FANCA, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L
NCT04171700 (LODESTAR)	Active	II	Rucaparib only	Patients with various solid tumors and with deleterious mutations in HRR genes	Best overall response rate	BRCA1, BRCA2, PALB2, RAD51C, RAD51D, BARD1, BRIP1, FANCA, NBN, RAD51, RAD51B
NCT02952534 (TRITON2)	Active, not recruiting	II	Rucaparib only	Patients with metastatic castration-resistant prostate cancer, and evidence of a homologous recombination gene deficiency	Objective response rate, prostate specific antigen response	ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, or other
NCT02975934 (TRITON3)	Active	III	Rucaparib vs. abiraterone or enzalutamide	Patients with mCRPC and evidence of a homologous recombination gene deficiency	Radiographic progression-free survival	ATM, BRCA1, BRCA2, or other HR gene mutation

(continued)

Table 4. (continued)

Drug and trial no.	Status	Phase	Treatment	Patient population	Primary endpoint	Biomarkers included in eligibility criteria
Talazoparib						
NCT03330405	Active, not recruiting	II	Avelumab + talazoparib	Patients with mCRPC	Dose limiting toxicity, Overall response	ATM, BRCA1, BRCA2
NCT03148795 (TALAPRO)	Active, not recruiting	II	Talazoparib only	Patients with mCRPC and DNA repair defects who have previously received taxane-based chemotherapy and have progressed on at least 1 hormonal agent	Objective response rate	General DNA repair deficiency
NCT03395197 (TALAPRO2)	Active	III	Talazoparib + enzalutamide vs. placebo + enzalutamide	Patients with mCRPC	Dose confirmation, radiographic progression-free survival	None
NCT04332744	Active, not yet recruiting	II	Talazoparib + enzalutamide	Patients with metastatic, castration-sensitive PCa	PSA response rate	None
Niraparib						
NCT04030559	Active	II	Niraparib: neoadjuvant	Patients with localized PCa and alterations in DNA repair pathways	Pathologic complete response	ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCD2, FANCL, GEN1, NBN, RAD51, RAD51C, and other DDR genes
NCT04288687	Active, Not yet recruiting	II	Niraparib only	Patients who have recently received platinum-based therapy	Radiographic progression-free survival	BRCA1/2, ATM, FANCA, PALB2, CHEK2, HDAC2, or BRIP1
NCT02854436 (GALAHAD)	Active	II	Niraparib only	Patients with mCRPC and DNA repair anomalies	Objective response rate	BRCA1, BRCA2, and other DDR genes
NCT04037254	Active	II	Niraparib + ADT	Patients with PCa with a high chance of recurrence	Preferred dose, PSA response	None
NCT03748641	Active	III	Niraparib + abiraterone vs. placebo + abiraterone	Patients with mCRPC	Progression-free survival	None
Other						
NCT04182516	Active	I	NMS-03305293	Patients with selected advanced or metastatic, relapsed, or refractory solid tumors who have exhausted standard treatment options or for whom standard therapy is considered unsuitable	First-cycle dose limiting toxicity	BRCA1, BRCA2

Abbreviations: DDR, DNA damage repair; HR, homologous recombination; HRR, homologous recombination repair, mCRPC, metastatic castration-resistant prostate cancer; PCa, prostate cancer; PSA, prostate-specific antigen.

Targeting Noncanonical DDR Genes

Although the beneficial effects of treating patients with *BRCA1/2* mutations are evident, a wider patient population with mutations in other DDR genes may benefit from treatment with PARP inhibitors. As with *BRCA*, the ideology behind treating patients harboring mutations in non-canonical DDR genes remains rooted in the concept of synthetic lethality: using loss-of-function mutations present in

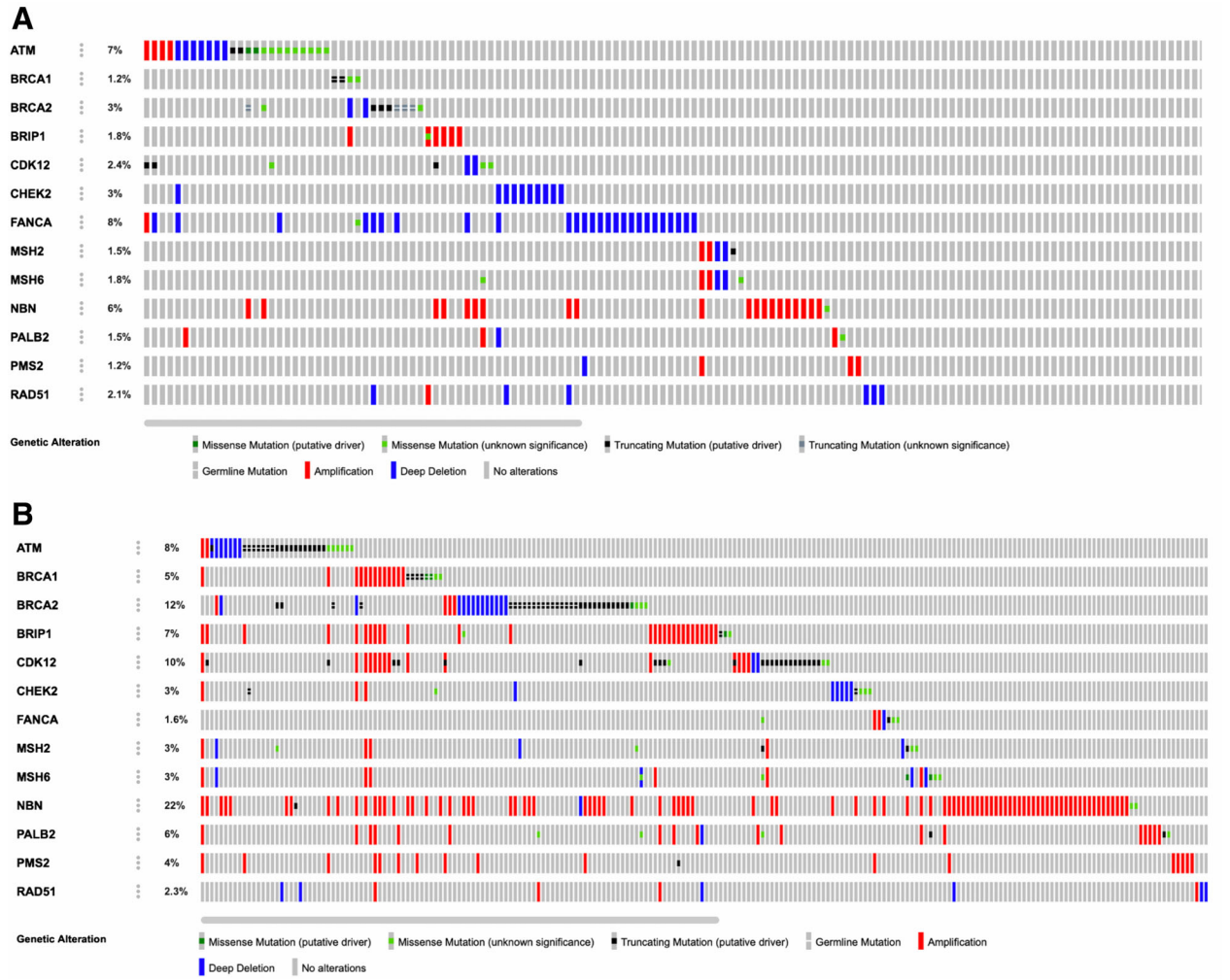

Figure 2. OncoPrints of primary and metastatic prostate cancer samples. **(A):** cBioPortal OncoPrint of queried genes using whole-exome sequencing of 333 primary prostate adenocarcinoma tumor samples analyzed by The Cancer Genome Atlas [59, 61, 62]. **(B):** cBioPortal OncoPrint of queried genes using whole-exome sequencing of 444 metastatic prostate adenocarcinoma samples analyzed by Abida et al. [60–62].

tumors in combination with inhibition of the cell's ability to detect and respond to DNA damage in order to induce a lethal event. Several studies investigating the effects of using PARP inhibitors to treat PCa, including the trials discussed above, have reported responses in patients with mutations in non-*BRCA* DDR genes; however, less attention has been given to these "other" genes. A recent study using unsupervised clustering of whole-genome sequencing data found that 7 of 22 patients clustered in a HR-deficient category did not have a biallelic *BRCA* inactivation [56]. Although individual mutation frequencies may be low, understanding which genes and mutational subtypes most benefit, as well as the mechanisms by which these noncanonical DDR genes respond to PARP inhibition, would considerably increase the patient population considered for PARP inhibitor treatment across other types of cancer.

ATM

ATM, together with ATR and DNA-PKcs, is recruited to DSB sites and works to repair the damage via both NHEJ and HR [57, 58]. According to whole-exome sequencing data available on the cBio Cancer Genomics portal (Fig. 2), alterations in *ATM* were observed in 7% of primary prostate samples [59] and in 8% of tumor samples from patients with metastatic PCa [60–62]. Although patients with *ATM* mutations have not reliably responded in several landmark PARP inhibitor clinical trials in PCa, emerging evidence suggests treating *ATM*-altered patients with both a PARP inhibitor and an ATR inhibitor may have a more efficacious result compared with PARP inhibition alone [63]. Cells proficient in *ATM* that were treated with olaparib and ATR inhibitors, both alone and in combination, did not experience significant cell death [64, 65]. Several clinical trials are examining the combinatory

effects of treating patients with PARP inhibitors and ATR inhibitors in different forms of cancer. The TRAP trial (NCT03787680) is an ongoing phase II trial comparing the responses of patients with mCRPC with DDR mutations to those of mCRPC patients without DDR mutations. Patients in both groups receive olaparib and the ATR inhibitor AZD6738 [63]. Use of PARP inhibitors as a monotherapy has been disappointing to date in terms of either radiographic responses or PSA responses when used to treat patients with *ATM* alterations.

CHEK2

CHEK2 plays an active role in many cellular processes, including cell cycle regulation, apoptosis, and DNA repair. CHEK2 is activated by ATM and ATR in response to DSBs, and its activated monomers activate TP53, serine 988 of *BRCA1*, and other cell cycle checkpoints responsible for DSB reparations [66–68]. *CHEK2* variants are well characterized and often associated with poor prognoses in several forms of cancer, including PCa, in which alterations were found in around 3% in both primary tumors and metastatic sites [59–62, 69, 70]. Because of the key role of CHEK2 in DDR, PARP inhibition is a possible treatment approach for patients with *CHEK2* aberrations. However, representation of men with PCa and alterations in *CHEK2* was low in the TOPARP, PROfound, and TRITON2 trials [44, 54]. In TOPARP-B, one patient with a *CHEK2* alteration achieved a PSA decrease of 50%, and preliminary TRITON2 data report one patient achieving a radiological response and a PSA reduction, with another also achieving a PSA reduction [55]. Without higher participation of these patients, it will be difficult to draw conclusions [53]. More studies in patients with *CHEK2* mutated tumors are warranted.

NBN

NBN encodes the protein Nibrin (NBS1), a participant of the MRN complex that functions in DSB end processing and HR [71]. Amplifications in *NBN* have been associated with olaparib and veliparib resistance in ovarian cancer and occur in over 40% of patients across 16 cancer types [72–74]. Alterations in *NBN* were found in 6% of primary tumors and 22% of metastatic samples, almost all of which were amplifications in both data sets [59–62]. A small phase II study of olaparib and durvalumab in mCRPC reported one responder (with ongoing responses of more than 12 months) having a deleterious mutation in *NBN* [75]. More data are needed to assess the potential benefit of PARP inhibitor treatments in those with *NBN* mutations.

FANCA, PALB2, and RAD51

FANCA, PALB2, and *RAD51* occupy roles in the Fanconi anemia (FA)/BRCA HR pathway for repair of DSBs. Data concerning PARP inhibitor treatment of patients harboing each of these mutations are provocative but limited. FA is an autosomal recessive disease that is characterized by congenital abnormalities and hypersensitivity to DNA cross-linking agents [76]. This observation led investigators to identify the FA class of genes as important mediators in DSB repair that ultimately activate and aid BRCA1 and BRCA2 in repair [77].

FANCA is a component of the FA core complex responsible for the activation of interstrand crosslink repair [78, 79]. FANCA and the seven other FANC essential proteins in the FA core complex activate the FA/BRCA repair pathway through monoubiquitination of FANCD2 and FANCI. *FANCA* is the most commonly altered FA gene [80], and its significant role in DDR implies patients with mutations in *FANCA* could benefit from PARP inhibition treatment plans. *FANCA* aberrations were found in 8% of primary tumors analyzed by The Cancer Genome Atlas (TCGA), the majority of which were deep deletions [59, 61, 62]. In the preliminary TRITON2 data, one patient with a monoallelic truncating mutation (of 4 patients with *FANCA* alterations) had complete radiographic and PSA responses [54, 55]. One patient with a nonsense *FANCA* mutation achieved a PSA response in the TOPARP-B trial [53].

PALB2 (partner and localizer of BRCA2) is recruited by BRCA1 to the site of DNA damage, where PALB2 then recruits BRCA2. PALB2 and BRCA2 facilitate the formation of the RAD51 nucleoprotein filament that is responsible for homology search of the intact sister chromatid. The homologous template found is used for accurate DNA synthesis and repair of the DSB [81, 82]. Mutations in *PALB2* were found in approximately 1.5% of primary tumors analyzed by TCGA and in approximately 6% of metastatic sites analyzed by Abida et al. [59–62]. Patients with *PALB2* mutations achieved composite overall responses in four of seven cases, and four of six achieved PSA responses in the TOPARP-B trial, indicating potential benefit from PARP inhibition [53]. In TRITON2, two of two patients with *PALB2* alterations experienced PSA responses. One patient also achieved a partial radiographic response. The other patient had a 47% reduction in tumor volume, but as of the preliminary data release, a follow-up had not occurred, and response has not been confirmed [55].

RAD51 works together with BRCA2 to maintain replication fork stability and independently to promote fork reversal in the process of repairing DSBs. Because of its key role in DDR, deficiencies in *RAD51* are detrimental for genome maintenance, although overexpression of *RAD51* also contributes to an unstable genome, as high levels of RAD51 can lead to aberrant replication fork reversal [16, 83]. Both deletions and amplifications of *RAD51* were found in 2.3% of metastatic samples and 2.1% of primary tumors [59–62]. Participation of patients with *RAD51* mutations in completed PARP inhibitor clinical trials in PCa has been low, but breast cancer studies have determined that lack of RAD51 nuclear foci implies PARP sensitivity [84]. Although potentially promising, more data is needed to determine the effects of PARP inhibitors when used to treat *RAD51*-altered men with PCa.

RNASEH2B

RNASEH2B is one of three genes composing the ribonuclease H2 complex responsible for cleavage of single ribonucleases that have mistakenly been incorporated into DNA [85]. *RNASEH2B*-deficient cells lead to increased incidence of genome-embedded ribonucleotides, the repair of which relies on the topoisomerase 1 excision repair pathway and recruitment of PARP1, indicating a potentially synthetically lethal relationship involving PARP inhibitors separate from

HR and MMR [86]. Zimmermann et al. found that loss of the ribonuclease H2 complex induced PARP sensitivity both in vitro and in vivo, with talazoparib having the greatest effect [87]. *RNASEH2B* loss occurred in 35% of mCRPC tumors analyzed in one study [88], suggesting potential clinical benefit for these patients not previously considered for treatments involving PARP inhibitors.

Mutational Burden and MMR Deficiency

PARP-based therapies inhibit single-strand DNA repair, leading to not only DNA damage but also increased tumor mutational burden (TMB), which enhances the efficacy of immune checkpoint inhibition. Defective HR and MMR mechanisms can also result in higher TMB. Recently, the FDA approved pembrolizumab for the treatment of adult and pediatric patients with TMB-high (≥10 mutations per megabase) solid tumors. This follows prior FDA approvals for MSI-H and MMR-deficient patients. Several clinical trials are investigating PARP inhibitor and immune check point inhibitor combinations, as mutational burden can increase following PARP inhibition treatments [89, 90].

CDK12

CDK12, a kinase frequently mutated in a number of cancers, is most often associated with its role in elongating RNA polymerase II, thereby mediating transcription and translation of several protein-coding genes and contributing to genome stability. Through this mechanism, the transcription of several DDR repair genes, including *BRCA1* and *ATR*, is CDK12 dependent [91, 92]. *CDK12* was altered in 2.4% of primary prostate tumors examined by the Cancer Genome Atlas, with 5 of 8 mutations determined to be either truncating or deep deletions [59]. In contrast, 10% of mCRPC metastatic sites (lymph node, bone, or liver) examined by Abida et al. showed abnormalities in *CDK12*, with 23 of 41 mutations evaluated as either truncating or deep deletions [60–62]. Bi-allelic inactivation of *CDK12* in PCa results in accumulation of focal tandem duplications, gene fusions, and elevated neoantigen burden [93, 94]. Because of CDK12's central role in DDR gene transcription and translation, loss-of-function mutations of CDK12 were determined to imply PARP inhibitor sensitivity in a genome-wide screen [95]. In the TOPARP-B trial, however, no patients (0/20) had a PSA or radiographic objective response. In the PROfound trial, a hazard ratio of 0.74 for rPFS with wide confidence limits was noted for patients with *CDK12* alterations treated with olaparib [44, 53]. Studies of other PARP inhibitor treatments in patients with CDK12 mutations are similarly disappointing, and alternative agents are needed in this subset of patients [44, 53].

Some studies have shown *CDK12*-deficient tumors to be phenotypically and genetically distinct from other PCa HR-deficient tumors, with high levels of inflammatory gene activation, presence of chemokines, and abnormal levels of T cell infiltration in *CDK12* mutant tumors. This suggests that patients harboring *CDK12* mutations may benefit from checkpoint inhibitor immunotherapy [93]. In a retrospective study of men with alterations in *CDK12* and PCa at various stages, Antonarakis et al. found that three of nine patients who received a programmed cell death protein 1 (PD-1) inhibitor had a PSA response, with median progression-free survival of 5.4 months [96]. Patients with PCa with MMR deficiencies have been reported to respond to checkpoint inhibitor immunotherapy in the past [97], and Wu et al. described responses seen in patients with PCa with *CDK12* inactivating mutations when treated with anti-PD-1 monotherapy [93]. This is relevant to PARP inhibition, as upregulations in programmed death ligand 1 are often seen in patients with both DDR mutations and MMR mutations, particularly following treatment with PARP inhibitors [89, 90]. Combinations of PD-1 inhibitors and PARP inhibitors are being tested in ongoing clinical trials in several forms of cancer known for presence of DDR mutations. An ongoing phase III clinical trial (NCT03834519) in men with mCRPC is evaluating the combination of pembrolizumab and olaparib compared with abiraterone or enzalutamide. Data will help elucidate the possibility of synergistic properties of this combination, particularly in those with *CDK12* inactivation mutations and *MMR* deficiencies. Recent data suggest platinum-based regimens may also be effective in these patients [98].

MSH2 and MSH6

MSH2 and *MSH6* are two key genes involved in MMR, an excision-based mechanism for DNA repair of mismatched nucleotides that escape polymerase detection. These errors can occur during replication and recombination [15]. Disruption of the function of MMR genes can lead to aberrant point mutations throughout the genome, the effects of which can vary widely. Germline mutations in any of the mismatch genes is most often associated with hereditary colorectal cancer and accounts for 2%–5% of all colorectal cancer cases [99]. In PCa, alterations in *MSH2* and *MSH6* were found in approximately 4% of primary PCa tumors and around 6% of metastatic samples [59–62], although around 12% of metastatic prostate tumors have elevated rates of single nucleotide mutations, likely arising from deficient MMR genes [100]. Like *CDK12* deficiencies, MMR-deficient patients are known to respond favorably to checkpoint inhibitors. Combinations of PARP inhibitors and check point inhibitors are being explored, but PARP inhibitors are not indicated in MMR deficiencies.

Other Synthetically Lethal Opportunities

PARP inhibition exists as an attractive complement to current prostate cancer therapies, regardless of genetic DNA damage repair mutation presence, because of PARP1's cooperation with the AR and AR signaling. PARP1 has been shown to be recruited to sites of AR action within the cell and to facilitate AR chromatin occupancy in both castration sensitive and resistant cancer cell types. PARP1 has also been shown to promote ligand-independent AR activation, suggesting a role in treatment resistance and disease progression to mCRPC [101].

Previous prostate cancer studies have shown the benefits of treating locally advanced disease with radiotherapy in combination with androgen deprivation therapy (ADT) [102]. The positive effects seen in these trials are likely due to the synergistic consequence of radiological-induced DNA damage along with ADT impairment of HR and DNA damage repair mechanisms [103]. Resistance to this combination

therapy has been observed and could be explained by reports showing an increase in PARP activity following ADT, thus allowing DNA damage repair to persist [104]. These findings, along with the benefits of PARP inhibition in prostate cancer that have already been discussed, have influenced the use of olaparib and other PARP inhibitors in combination with current standard of care therapies in a number of clinical trials.

A recent study investigating mechanisms of cancer treatment resistance supports a potentially synthetically lethal relationship between PARP inhibition and the mTOR signaling pathway, which orchestrates stress-induced mutagenesis in response to stress that increases cell-to-cell variability, enabling adaptation in response to selective pressures, such as cancer therapies [105]. Although some treatments, such as those involving radiation, are pointedly genotoxic, others are not, and yet an accumulation of DSBs is still observed. Cipponi et al. found that DSBs were a common early response to nongenotoxic treatments in eventually resistant colonies. As *MTOR* inhibition has previously been shown to impair DDR response, it has been hypothesized that the repression of *MTOR*, or of genes regulated by *MTOR* (*PTEN*, *AKT1*, and PIK3s), results in disrupted DDR. This allows for mutagenesis and the fostering of resistant clones in the presence of selective pressures [105–107]. Because of *MTOR*'s affiliations with DDR, specifically HR, Cipponi et al. proposed a synthetically lethal relationship that could be targeted through a combination of targeted cancer therapy and drugs that target DDR (PARP inhibitors). This was tested with rucaparib and palbociclib (a CDK4/CDK6 inhibitor) in a pancreatic cancer cell line, and antitumor effects were more drastic in the combination model compared with either agent alone ($p < .0001$) [105]. This proposed mechanism may explain the clinical benefit observed for PARP inhibitors in the mCRPC setting (in the PROfound and TRITON2 trials) that could potentially extend to DDR genes beyond BRCA1/2.

Challenges of PARP Inhibition

Although PARP inhibition is at the forefront of a new precision-based era of the PCa treatment regimen, there are challenges associated with necessary DDR mutation detection methods, interpreting sequencing data itself, and resistance.

Costs and time required to perform NGS have reduced, but limitations still exist. NGS requires high quality, undamaged samples to be successful. Such rigorous thresholds are oftentimes not met, which limits the power and reliability of studies relying on NGS. In the TOPARP-B trial, 119 of 711 patients that consented to the trial were unable to be screened via NGS because of lack of sample or insufficient tissue, or because they had samples that failed quality assessments [53]. In the PROfound trial, only 69% of acquired tumor samples were successfully sequenced [44]. There are other methods of mutation detection, however, and some studies are using investigational NGS methods that use DNA extracted from circulating tumor cells found in blood samples. As liquid NGS technology improves to become more sensitive and precise, preserved tissue NGS will likely become the inferior option, and the concerns associated with tissue preservation and quality will no longer be relevant. Questions still remain, however, concerning the frequency that patients should be sequenced to capture and address somatic modifications or clonal variations that occur in response to treatment or disease progression.

Even as sequencing methods continue to improve and become more available in the clinical setting, questions exist surrounding the significance of many detected mutations and effects on protein expression and function. NGS findings do not reflect epigenetic changes that could result in disruption of protein function. Although NGS might relay a normal genetic sequence, there could be methylation patterns present that result in the silencing of a certain protein. This could result in missed actionable opportunities. Protein-based assessment methods may help to assess the limitations of NGS.

Furthermore, guidelines for genetic screening are not necessarily in agreement. The National Comprehensive Cancer Network's updated 2020 guidelines state that patients with strong family history of cancer or family history of known germline variants, including *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, should consider germline testing. Somatic testing for *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12* is recommended for men with mCRPC or regional PCa. The Philadelphia Prostate Cancer Consensus Conference in 2019 encouraged all patients with familial and metastatic PCa to be screened for mutations *BRCA1/2* and MMR gene deficiencies. Wider screens are encouraged for clinical trial participation [108]. Although these guidelines are in place, a study in 2018 found that NGS testing is only performed in 1.4% of PCa cases [109]. Similarly, the clinical benefits of germline profiling across several forms of cancer from 2015 to 2019 were assessed, and Stadler et al. found that 50.9% of patients with advanced cancer with BRCA1/2 germline mutations received targeted therapy. As drug development and identification of actionable mutations advance, the percentage of patients receiving the option of targeted treatment is expected to grow [110]. Understanding the significance of germline and somatic mutations of non-*BRCA* genes, as well as optimal treatments and combinations for each, will allow for streamlined guidelines and increased sequencing practices for the treatment of a wider patient population [111].

Finally, as with most treatment options, resistance to PARP inhibition is inevitable in many patients. Of initially HR-deficient ovarian cancers, 50% acquire HR proficiency as a result of PARP inhibition resistance, and similar figures may be seen in PCa [112]. Mechanisms of resistance in prostate cancer can be driven by HR pathway restoration that occurs through reversion mutations [113]. Resistance can also occur with upregulations of replication fork stability genes (most commonly those in the ATR/CHK1 pathway). ATR inhibitors are currently being investigated as a potential therapy for PARP inhibitor resensitization [114]. Persistent DDR transcriptional activity of CDK12 can also contribute to resistance mechanisms [115]. Mechanisms of PARP inhibitor resistance within the realm of PCa is not yet well understood, but understanding the effects of different combinations of PARP inhibitors, checkpoint inhibitors, and classic AR-targeting therapies will aid in clinical decisions anticipating delayed resistance.

Conclusion

The FDA's recent approval of olaparib and rucaparib for biomarker-positive mCRPC marks a new era of PCa treatment, which thus far has lacked targeted treatment options and the reliable biomarkers necessary for molecular-stratified approaches. The effects of germline and somatic mutations of *BRCA1* and *BRCA2* and potential for PARP inhibitor treatments are well characterized across several forms of cancer, but treatment options for alterations in other DDR genes have yet to be realized. Further inquiries into potential synthetically lethal interactions between mutations in these "other" DDR genes, PARP inhibitors, and PARP inhibitor combinations could significantly increase the percentage of patients that might benefit from these treatments. Efforts must also be made to further understand sequencing results, as well as to streamline national and institutional screening guidelines and recommendations.

Acknowledgments

This work was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health (ZIA BC 010547).

The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organization imply endorsement by the U.S. Government.

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Disclosures

Oliver Sartor: Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Inc., Bavarian Nordic, Bristol Myers Squibb, Clarity Pharmaceuticals, Clovis, Constellation, Dendreon, EMD Serono, Fusion Pharmaceuticals, Janssen, Myovant, Myriad, Noria Therapeutics, Inc., Novartis, Noxopharm, Progenics, POINT Biopharma, Pfizer, Sanofi, Tenebio, Telix Pharmaceuticals, and Theragnostics (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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