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Review Article

Development of PARP inhibitor combinations for castration resistant prostate cancer unselected for homologous recombination repair mutations

Taylor Ryan McFarland, Adam Kessel, Umang Swami, Neeraj Agarwal

Division of Oncology, Department of Internal Medicine, Huntsman Cancer Institute, University of Utah, Salt Lake, UT, USA

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Abstract: Genetic instability is a hallmark of cancer and, with the introduction of poly (ADP-ribose) polymerase (PARP) inhibitors, is a targetable feature of many tumors. Currently, two PARP inhibitors, olaparib and rucaparib, have received approval as monotherapy by the Food and Drug Administration for the treatment of men with castration resistant prostate cancer with selected mutations involving the homologous recombination (HR) pathway. However, it is currently debated whether an HR mutation is a prerequisite for response or if patients with HR-proficient mCRPC may also benefit from their use when combined with other targeted or immunotherapeutic agents. Several large phase III trials of PARP inhibitors with novel androgen axis inhibitors in groups of unselected patients are underway. Additionally, there are several early phase trials combining PARP inhibitors with radioligands or immunecheckpoint inhibitors. Here we discuss the currently ongoing or recently concluded trials of PARP inhibitor based combinatorial therapies in unselected patients with mCRPC, the rationale behind these trials, and how these may impact the treatment paradigm in men with mCRPC.

Keywords: Metastatic prostate cancer, PARP, BRCA, immunotherapy, olaparib, rucaparib, talazoparib, androgen receptor

Introduction

Two inhibitors of poly (ADP-ribose) polymerase (PARP), olaparib and rucaparib, have recently received single-agent Food and Drug Administration approval for patients with metastatic castration resistant prostate cancer (mCRPC) harboring mutations in the homologous recombination (HR) genes [1]. Specifically, rucaparib is approved for treatment of patients with mCRPC who have been treated with androgen receptor (AR) directed therapy and a taxane-based chemotherapy and have a deleterious germline and/or somatic BRCA mutation [2]. Olaparib was approved for patients with mCRPC who have progressed on a novel hormonal therapy (NHT; abiraterone or enzalutamide) based on the PROfound trial, which required patients to have a deleterious germline or somatic HR mutation (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D or RAD54L) [3].

Both of these drugs currently require an HR mutation to be present, meaning that the majority of patients with mCRPC are not eligible for their use. In the PROfound trial, only 28% of the screened population had a qualifying mutation [4]. Expanding the benefits of PARP inhibitors to a broader group of patients, i.e., to those with HR proficient tumors, is an area of active investigation in several phase II and III clinical trials (**Table 1**). Herein, we discuss the role of the DNA repair pathway in mCRPC, PARP inhibitor's mechanisms of action, and the evidence and rationale for developing various combinatorial regimens for treatment of unselected patients with mCRPC.

Mechanisms of action of PARP inhibitors

PARP inhibitors were the first example of a clinical drug that took advantage of synthetic lethality [5]. Originally described almost a century ago, synthetic lethality is where two deficiencies - both tolerable in isolation-combine and

Table 1. PARP inhibitor clinical trials that are not selecting for or including patients without an HR mutation

NCT ID	Phase	Status	Arms	Primary outcome	N	Study Designs	Start Date	Primary Completion Date	Completion Date
NCT03732820 (PROpel)	III	Active, not recruiting	Olaparib + abiraterone vs. placebo + abiraterone	rPFS	904	Randomized, parallel assignment, quadruple blinding	Oct 2018	Apr 2021	May 2026
NCT03834519 (KEYLYNK-010)	III	Recruiting	Pembrolizumab + olaparib vs. abiraterone or enzalutamide	rPFS, OS	780	Randomized, parallel assignment, open label	May 2019	Apr 2022	Apr 2023
NCT03748641 (MAGNITUDE)	III	Recruiting	Niraparib + abiraterone vs. placebo + abiraterone	rPFS	1000	Randomized, parallel assignment, quadruple blinding	Jan 2019	Jul 2022	Feb 2025
NCT04455750 (CASPAR)	III	Not yet recruiting	Rucaparib + enzalutamide vs. placebo + enzalutamide	rPFS, OS	1002	Randomized, parallel assignment, double blinding	Jan 2021	May 2023	Sep 2026
NCT03787680	II	Recruiting	Olaparib + AZD6738	ORR	47	Non-randomized, single group assignment, open label	Oct 2019	Nov 2021	Nov 2025
NCT03338790 (CheckMate 9KD)	II	Active, not recruiting	Nivolumab + rucaparib vs. nivolumab + enzalutamide vs. nivolumab + docetaxel	ORR, RR-PSA	330	Non-randomized, parallel assignment, open label	Dec 2017	Jan 2021	Nov 2021
NCT03516812	II	Active, not recruiting	Bipolar androgen therapy + olaparib	TEAEs, PSA50	36	Single group assignment, open label	Aug 2018	Mar 2021	Mar 2023
NCT04592237	II	Recruiting	Carboplatin + cabazitaxel + cetrelimab + niraparib vs. carboplatin + cabazitaxel + niraparib	PFS	120	Randomized, parallel assignment, open label	Dec 2020	Dec 2025	Dec 2025
NCT02893917	II	Active, not recruiting	Olaparib + cediranib vs. cediranib	rPFS	90	Randomized, parallel assignment, open label	Dec 2016	Dec 2021	
NCT03431350 (QUEST)	I/II	Recruiting	Niraparib + cetrelimab vs. niraparib + abiraterone	TEAEs, CRR, ORR	140	Non-randomized, sequential assignment, open label	Mar 2018	Jul 2021	Dec 2021
NCT04556617	I/II	Recruiting	PLX2853 + olaparib + abiraterone vs. PLX2853 + olaparib	TEAEs, ORR, RR-PSA	110	Non-randomized, parallel assignment, open label	Sep 2020	Feb 2023	Mar 2023
NCT03317392	I/II	Recruiting	Radium-223 + olaparib vs. radium-223	MTD, rPFS	120	Randomized, parallel assignment, open label	Oct 2018	Nov 2021	Nov 2021

Composite response rate (CRR), maximum tolerated dose (MTD), treatment emergent adverse events (TEAEs), objective response rate (ORR), prostate-specific antigen response rate (RR-PSA), progression-free survival (PFS), radiographic PFS (rPFS), PSA decline of at least 50% below baseline (PSA50).

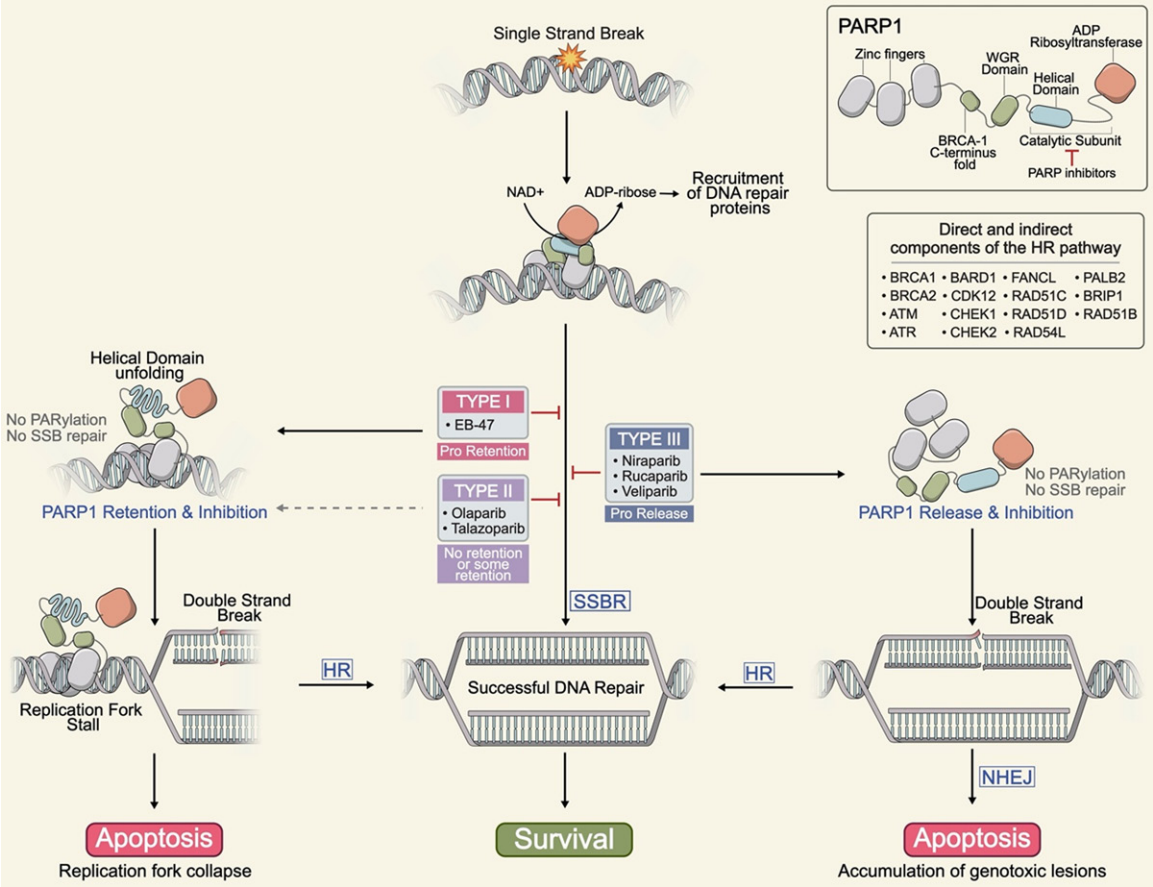

Figure 1. The DNA repair pathway and the mechanisms of PARP inhibitors. Internal and external stress regularly generates single strand breaks. Poly (ADP-ribose) polymerase 1 (PARP1) recognizes these breaks, binds to the DNA, and recruits single strand break repair (SSBR) proteins. All clinical PARP inhibitors block the ability of PARP1 to recruit repair proteins. They can also have allosteric effects promoting retention (type 1), promoting some or no retention (type 2), and promoting release (type 3). Without the homologous recombination (HR) pathway, cells are unable to reconcile replication fork stalling or double strand breaks and rely on the more error prone non homologous end joining (NHEJ) pathway. Shown in the top right boxes are diagram of the domains of PARP1 and a list of direct and indirect members of the HR pathway that have been evaluated in clinical trials.

create conditions that are in-compatible with life [6].

When DNA undergoes a single-strand break (SSB), the damaged DNA structure is quickly recognized by PARP1 [7]. Upon binding to DNA, the catalytic subunit of PARP1 recruits various proteins via PARylation which then repair the break [8]. It is this catalytic subunit where clinical PARP inhibitors compete with NAD^+ for binding [9]. Pharmacologic inhibition of PARP results in the accumulation of SSBs that progress to double-strand breaks (DSBs) after DNA replication (**Figure 1**). Normally, the HR pathway ensures the faithful repair of these DSBs, but this is compromised when cells are deficient in various HR components (i.e., BRCA1/2, ATM, etc.). DSBs are instead repaired by the error prone non-homologous end joining pathway, which has the tendency to generate large-scale replication errors that result in mitotic catastrophe and cell death [9].

While cancer cells with genetic loss of PARP1 or PARP2 are still viable, their inhibition is potentially cytotoxic, even in the absence of HR deficiency. This is because, in addition to preventing catalytic function, PARP inhibitors can have allosteric effects on PARP1 that promote its retention or release from DNA [10]. It has recently been suggested that PARP inhibitors should be classified based on the allosteric effect they have on PARP1; with type 1 promoting retention, type 2 inducing no or mild pro-

retention allostery, and type 3 promoting release [11] (**Figure 1**). Drugs that induce retention of PARP on DNA are thought to be the most cytotoxic, even in HR proficient cells.

A unique relationship exists between the DNA repair pathways and the nuclear hormone receptors. This is most notably manifested in patients with germline HR mutations that have increased incidence of cancers involving the breast and prostate [12]. However, genome profiling studies have revealed that alterations in HR genes occur somatically at a frequency similar to the germline, and together can be found in 19-25% of patients with mCRPC [13, 14]. These tumors tend to have higher Gleason scores, more frequent visceral metastases, and worse rates of survival [15-17]. Interestingly, several reports have identified prostate tumors that lack an HR mutation but have a DNA damage signature similar to that seen in HR deficiency [18, 19] and these may be targetable with PARP inhibitors.

Combination of PARP inhibitors with radiation and radiopharmaceuticals

In the 1990's, it was realized that patients with hormone-sensitive prostate cancer had improved responses to radiation treatment when it was combined with androgen deprivation therapy (ADT) [20]. The proposed molecular basis of this was somewhat non-intuitive, and it would later be discovered that AR is activated by radiation-induced DSBs and is able to upregulate several DNA repair genes during treatment [21-23]. Exposure to ADT results in the downregulation of DNA repair genes, prolonged irresolution of damaged foci, and increased tumor-cell death [23, 24]. A consequence of this is that the activity of PARPs is increased which, in addition to their ability to promote cell survival, can also modulate the activity of AR. Thus, it has been proposed that PARP inhibitors would synergize with ADT and radiation-based therapies.

Two early phase trials for unselected patients with mCRPC are underway that combine PARP inhibitors with the radiopharmaceutical radium Ra 223 dichloride (radium-223). The single-arm NiraRad trial (NCT03076203) has been assessing the safety of niraparib and radium-223 among 14 patients with mCRPC that have bone metastases. The larger phase I/II COMRADE trial (NCT03317392) is a randomized parallel alignment trial evaluating radium-223 with or without olaparib in 112 patients with bone metastases. Both are expected to be completed by November of 2021.

Combination of PARP inhibitors with androgen signaling inhibitors

Even with ADT, AR continues to sustain transcriptional activity through a myriad of resistance mechanisms. This is why therapies that further reduce AR signaling, such as the NHTs, have greatly improved survival in patients after the onset of castration resistance [25]. Interestingly, PARPs might be able to disrupt AR activity in a manner that is independent of AR's interaction with androgens. Recent work has suggested that PARP enzymes, PARP1 and PARP2, bind to the pioneering transcription factors GATA2 and FOXA1, respectively, and alter the chromatin landscape of the cell allowing AR to access prostate-cancer-specific enhancer regions (**Figure 2**) [26, 27]. Treatment with PARP inhibitors downregulates AR transcriptional targets, including HR genes [24]. Additionally, constitutively active AR splice variants (AR-Vs) are capable of driving proliferation, restoring the DNA damage response, and are associated with resistance to NHTs [28-31]. Since PARP inhibitors affect AR in a manner that is independent of androgens, it is possible that they could reduce the activity of AR-Vs, and were shown to do so *in vitro* [29]. It is for these reasons that a combination of the two drugs could potentiate each other and improve clinical responses.

Preclinical work suggested that ETS fusions, a genomic event found in around half of patients, enhances susceptibility to PARP inhibitors [32]. Following this, the phase II trial NCI 9012 evaluated the treatment of abiraterone with or without veliparib in all-comers with mCRPC [33]. However, there was no significant improvement in outcome with the addition of veliparib, with regards to PSA response (72.4% vs. 63.9%; P = 0.27) or progression free survival (PFS) (11 vs. 10.1 months; P = 0.99). Although no difference was seen in the outcomes of patients with ETS fusions, other biomarkers such as alterations in the HR pathway, TP53, or PTEN were associated with a significantly longer PFS with addition of veliparib.

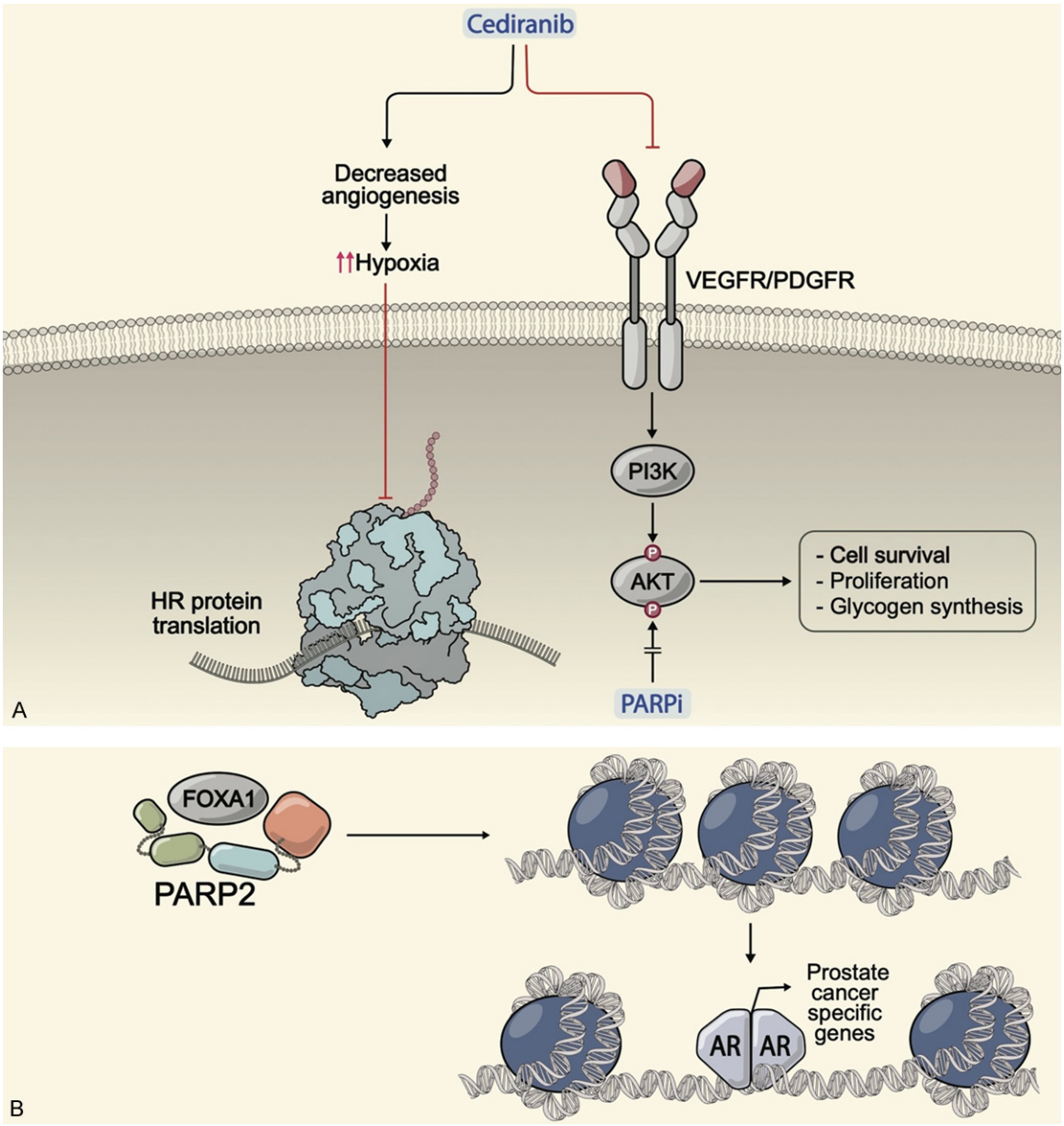

Figure 2. A. Cells treated with Poly (ADP-ribose) polymerase 1 (PARP1) inhibitors (PARPi) have increased activation of the AKT survival pathway. Cederanib is able to decrease the translation of homologous recombination proteins through a hypoxia-dependent mechanism by inhibiting vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDFGFR) signaling. B. PARP1/2 have been shown to bind to pioneering transcription factors and change the chromatin landscape of cells to allow the androgen receptor (AR) to bind to prostate-cancer-specific enhancers.

In a phase II study of 142 post-docetaxel patients treated with abiraterone, the addition of olaparib was associated with an increased radiographic PFS of 13.8 months (95% CI 10.8-20.4) compared to 8.2 months (95% CI 5.5-9.7) with placebo [34]. Combination of the two agents was associated with an increased frequency of grade 3-5 adverse events, notably anemia and neutropenia. However, these were consistent with the known safety profiles of both agents and there were no novel adverse events. This study was not adequately powered for a subgroup analysis based on HR status, and complete genomic information was not available for all patients.

The PROpel trial of olaparib or placebo with abiraterone in the first line setting will be one of

four major phase III trials that will more definitively answer if a PARP inhibitor and NHT combination is effective for unselected patients with mCRPC (NCT03732820). TALAPRO-2, a trial of talazoparib or placebo with enzalutamide as first line therapy after the onset of mCRPC, is also underway assessing efficacy of the combination in both selected and unselected patients (NCT03395197). Similarly, the MAGNITUDE trial will combine niraparib or placebo with abiraterone and will include two cohorts based on the presence or absence of HR alterations (NCT03748641). All have radiographic PFS as the primary endpoint, and include secondary end points assessing the time to the initiation of chemotherapy and all plan on collecting genomic data [35-37]. Additionally, the phase III CASPAR trial (NCT04455750) of enzalutamide with rucaparib or placebo in 1,002 patients recently began recruitment and has a planned completion by September 2026.

Combinations of PARP and immune checkpoint inhibitors

Prostate cancers have demonstrated a remarkable intrinsic resistance to immune checkpoint inhibitors (ICIs) [38]. These tumors are considered to be immunologically cold, containing one of the lowest immune cell infiltrates of any tumor in an analysis of data from the Cancer Genome Atlas [39]. Thus, agents that "heat up" the tumor microenvironment may improve outcomes when combined with ICIs.

A series of experiments in breast, lung, and ovarian cancer have shown that treatment with PARP inhibitors can induce a considerable amount of replication stress, even in HR proficient cells. Because of this stress, genetic material can leak into the cytosol or form highly permeable micronuclei [40-42]. The ectopic DNA is then recognized by the cGAS/STING signaling axis, which triggers the transcription of a type I interferon response [43]. Though this can induce a potent immune response, it also upregulates immune checkpoints like programmed death-ligand 1 (PD-L1) [44]. These discoveries were paired with exciting results from preclinical models that showed a synergistic effect of ICIs and PARP inhibitors. However, some clinical insight can be gained from a genomic analysis of tumors from the TOPACIO trial of niraparib and pembrolizumab in ovarian cancer. Two factors, a HR-deficient mutational signature and elevated presence of exhausted CD8+ T-cells prior to treatment, were capable of predicting all objective responses [45].

In a trial of olaparib and durvalumab in 17 unselected post-NHT patients, nine (52.9%) had a PSA decline of ≥50% and four (23.5%) had a partial radiographic response. Seven of the nine PSA responders had genomic data available which showed all had some alteration in BRCA2, usually an indel or deletion. Patients with HR mutations had a significantly greater probability of achieving a PFS of at least 12 months as compared to those without (83.3% vs. 36.4%, P = 0.031). Several biomarkers were indicative of response including an increase in dendritic cells, a higher amount of Ki-67$^+$/PD-1$^+$/CD8$^+$ T-cells, and a decrease in circulating tumor cells after treatment [46].

The phase Ib/II trial KEYNOTE-365 (NCT02861573) is currently evaluating the effect of the PD-1 inhibitor pembrolizumab in combination with olaparib on 84 post-docetaxel patients who progressed after at least two lines of NHT. No patients had a detectable HR mutation, but a preliminary report demonstrated that five of 39 (13%) had a PSA response and two of the 28 (7%) with measurable disease had a partial response of longer than 12 months [47]. Grade 3-5 adverse events occurred in 51% of patients, the most common being nausea, fatigue, and anemia. Two patients died of treatment related adverse events. The phase III trial KEYLYNK-010 (NCT03834519) will follow up on these results and is planning to recruit 780 patients who have been treated with a taxane chemotherapy and NHT (abiraterone or enzalutamide). They will be randomized 2:1 to treatment with either pembrolizumab plus olaparib or an alternative NHT agent which they have not received previously [48].

The recent results of another phase I trial (NCT03572478) [49], describe rucaparib plus nivolumab in seven unselected patients with mCRPC who had progressed on at least one line of NHT. Only one patient had a PSA response to treatment and was found to have a pathogenic BRCA2 mutation. Pre-clinically, profiling of the patient's tumors and concurrent experiments on Myc-driven murine prostate cancer models found that PARP inhibitors were insufficient to produce a STING-dependent

immune response. Interestingly, a combination treatment of rucaparib with the phosphoinositide 3-kinase (PI3K) inhibitor, buparlisib, greatly increased macrophage-dependent anti-tumor immune activation. The authors showed that PARP/PI3K inhibition in the mouse models resulted in release of DNA-DSB-containing microvesicles from tumor cells that triggered cGAS/STING activation of nearby macrophages, which then induced potent anti-tumor immunity. These results suggest that PARP inhibitors may have a limited ability to increase responses to ICIs in prostate cancer alone but PARP/PI3K inhibition could augment ICI (discussed further in the following section).

Checkmate 9KD (NCT03338790) is a non-randomized three-arm phase II trial examining the combination of nivolumab with enzalutamide, rucaparib, or docetaxel in 330 patients with mCRPC. This study will give a better indication whether or not PARP inhibitors are capable of improving responses to immunotherapy relative to other combination regimens.

Combinations of PARP inhibitors and kinase inhibitors

Components of the cellular growth pathway, such as the receptor tyrosine kinase vascular endothelial growth factor receptor (VEGFR) and the downstream serine/threonine kinases AKT and PI3K, are frequently dysregulated in cancer and can be targeted by several FDA approved small molecule inhibitors. Their combination with PARP inhibitors has shown pre-clinical and early phase promise. Mechanistic investigations have shown that PARP inhibition induces the activation of the PI3K/AKT pathway which promotes cell survival [50]. Inhibition of VEGFR was also found to downregulate BRCA1/2 (**Figure 2**) [51]. Interestingly, in a trial of ovarian cancer, patients with wild-type or unknown BRCA1/2 status saw the greatest benefit with the addition of cediranib, a VEGFR inhibitor, to olaparib compared to those with BRCA1/2 mutated tumors [52].

A recently concluded phase II trial (NCT02893917) randomized 90 men with mCRPC to either cediranib plus olaparib or olaparib alone. Early results showed that the addition of cediranib was associated with an increased rPFS of 11.1 months verses 4 months on olaparib monotherapy (hazard ratio 0.54, 95% CI 0.317-0.928, P = 0.026) [53]. Notably, grade 3 or 4 adverse events were seen in 77% verses 58% of patients in the respective treatment arms. Results on correlation of objective response with respect to the HR status are expected in the near future. Another small phase Ib trial is evaluating a combination of rucaparib with the AKT inhibitor, ipatasertib, in an unselected group of breast, ovarian, and prostate cancer patients (NCT03840200).

Conclusions and future directions

Several other agents that might have synergy with PARP inhibitors are currently in early-phase clinical trials. A phase II trial of the ATR inhibitor AZD6738 and olaparib began recently in 47 patients with mCRPC who had progressed on first-line therapy (NCT03787680). The development of ATR inhibitors for prostate cancer will also allow for a multi-faceted targeting of the DNA damage response pathway.

Laboratory research in mCRPC will need to expand beyond the cellular effects of PARP inhibitors and also examine their modulation of the tumor microenvironment. Additionally, other clinical and molecular biomarkers of efficacy and toxicity to combination treatments are needed. The recently developed radiolabeled small-molecule inhibitor [^{18}F]FluorThanatrace allows for *in vivo* measurements of PARP1 expression via positron emission tomography [54, 55]. A phase I trial is currently underway which will evaluate its ability to assess PARP expression in prostate cancer (NCT03334500). Further research correlating this imaging technique to PARP inhibitor response may someday provide real-time information to aid in decision making on candidacy for treatment with PARP inhibitors, possibly independent of HR status.

PARP inhibitors are usually very well tolerated, with a side effect profile dominated by grade 1-2 nausea, fatigue, and anemia. Another advantage is that these are oral agents. The developments of myelodysplastic syndrome or acute myeloid leukemia are rare complications of their use which have been seen in the treatment of other malignancies [56]. Though more long-term safety data are needed, this appears to occur less frequently in prostate cancer [4, 34, 57]. This complication has been associated with previous treatment with platinum agents [56], which are commonly used for treatment of ovarian cancer and not of prostate cancer.

While those with HR mutations derive the greatest benefit, PARP inhibitors are a class of drugs with enormous potential to be effi-cacious in a larger proportion of men with mCRPC in combination with other agents such as ICIs, targeted therapies, and radiation therapy. The key will be to develop predictive biomarkers of response, beyond just the presence or absence of an HR mutation, to these combinatorial therapies to maximize benefit and minimize toxicities. Altogether, the results of the phase III trials of PARP inhibitor combinations with NHT are waited on with much anticipation, the application of PARP inhibitors outside the setting of HR deficiency will likely remain a thriving area of prostate cancer research long after they are complete.

Disclosure of conflict of interest

Umang Swami is a consultant for Seattle Genetics. Neeraj Agarwal is a consultant for Astellas, AstraZeneca, Aveo, Bayer, Bristol-Myers Squibb, Calithera, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Gilead, Janssen, Merck, MEI Pharma, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics. Taylor Ryan McFarland and Adam Kessel has nothing to disclose.

Address correspondence to: Neeraj Agarwal, Division of Oncology, Department of Internal Medicine, Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope Drive Suite 5726, Salt Lake, UT 84112, USA. Tel: 801-213-5658; E-mail: neeraj.agarwal@hci.utah.edu

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