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PARP inhibitors for Homologous Recombination- Deficient Prostate Cancer

Eric S. Christenson and Emmanuel S. Antonarakis*

Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, MD

Abstract

Introduction: Prostate adenocarcinoma represents a leading cause of cancer-related mortality. Increased emphasis on understanding the molecular basis of prostate cancer has identified a substantial burden of homologous recombination (HR) pathway mutations, which are enriched in castrate-resistant disease. This discovery has yielded novel therapeutic opportunities.

Areas covered: We will discuss the treatment of castrate-resistant prostate cancer (CRPC), with a focus on the use of poly (ADP-ribose) polymerase (PARP) inhibitors in this space. Evidence for use in HR-deficient patients will be outlined with discussion of the mechanism of action for this drug class, pathways of resistance, and approaches for expanding PARP inhibitor use to non-HR-deficient prostate cancer subgroups.

Expert Opinion: PARP inhibition represents an exciting tool for management of HR-inactivated CRPC. With rapid adoption of next-generation sequencing technologies and other molecular techniques, the number of patients in this category is likely to increase. Ongoing and future investigations will be critical for improved understanding of the promise and appropriate treatment sequencing of PARP inhibition and optimal options for HR-proficient and -deficient prostate cancer populations. Questions remain about the clinical significance of monoallelic *vs.* biallelic HR mutations, the relevance of germline *vs.* somatic-only mutations, and the importance of mutations in non-canonical HR genes.

Keywords

PARP inhibitors; DNA Repair; Homologous Recombination Deficiency; Castrate Resistant Prostate Carcinoma; Olaparib; Rucaparib; Niraparib

*Corresponding Author: Emmanuel S. Antonarakis, M.D, Associate Professor of Oncology and Urology, Johns Hopkins Sidney Kimmel Cancer Center, CRB1, Room 1M45, 1650 Orleans St, Baltimore, MD 21287, eantona1@jhmi.edu.

Declaration of interest

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1. Background:

Prostate carcinoma represents a significant cause of morbidity and mortality among American men. An average of 120 per 100,000 men are diagnosed with prostate cancer every year leading to 20 deaths per 100,000 men.[1] According to the American Cancer Society, this will amount to approximately 161,360 new cases and 26,730 deaths in the year 2017, making it the most common non-cutaneous cancer diagnosis among men and third leading cause of death behind only lung and colon cancers.[1] Given the predominance in older individuals, prostate cancer is likely to represent an increasing healthcare burden as the US population continues to age.

However, it must also be noted that there is a wide discrepancy between the incidence and mortality of prostate adenocarcinoma, which likely relates to the extreme clinical and genetic heterogeneity of this disease and the different patient populations afflicted by it. This diverse nature warrants careful consideration when determining the optimal treatment approach that will minimize both disease morbidity/mortality and toxicity of therapy. Accordingly, there is significant enthusiasm for improved stratification of which patients have an aggressive form and are likely to develop progressive metastatic disease, versus those who have an indolent form and will experience minimal morbidity and mortality even in the absence of intervention.

Some genomic biomarkers may assist in disease stratification. Patients with homologous recombination (HR) pathway deficits represent a cohort noted to be at elevated risk for both prostate cancer occurrence and a more aggressive disease course. For example, germline *BRCA2* carriers have a 5.0 to 8.6-fold increased risk and a 15% absolute risk of developing prostate carcinoma.[2, 3] Once patients with inherited *BRCA2* (or *BRCA1*) mutations develop prostate cancer, they also have higher rates of progression from localized to systemic disease as demonstrated in a recent patient cohort, which included 79 patients with germline *BRCA1/BRCA2* mutations. In this sample, patients with germline *BRCA1/2* mutations had a 23% local failure rate in contrast to only 7% among non-carriers.[4] Other studies have corroborated the association between increased aggressiveness and germline *BRCA1/2* lesions; these patients present with higher Gleason scores, have shorter metastasis-free survival and reduced overall survival compared to non-carriers.[5–7] Such patients therefore represent an unmet medical need.

In this article, we will discuss the treatment of prostate carcinoma particularly following its progression to castrate-resistant prostate carcinoma (CRPC) with a focus on the use of poly ADP-ribose polymerase (PARP) inhibitors in this space. The evidence for use in HR-deficient patients will be examined with discussion of the mechanism of action for this class of chemotherapeutics, pathways of resistance, and approaches for expanding this class of medications to other prostate cancer subgroups.

2. Medical Need in Aggressive Disease:

The initial management of prostate adenocarcinoma once it becomes metastatic and no longer amenable to local approaches is the use of androgen deprivation therapy to “starve”

the prostate cancer cells by targeting their dependency on androgen/androgen receptor (AR) signaling. This is accomplished with the use of GnRH agonists or antagonists that inhibit the GnRH → FSH/LH → gonadal testosterone axis. Bilateral orchiectomy is another option, although this approach is rarely pursued in the US. All three options are felt to be equivalent in terms of achieving tumor remissions and can be effective for an extended period time; however, outcomes vary greatly between individuals before castrate-resistant prostate cancer develops.

Ultimately, most prostate cancers progress even in the presence of androgen/AR inhibition, requiring the addition of other agents for disease control. At that time, the disease is termed castrate-resistant prostate cancer (CRPC) and despite improvements in progression-free and overall survival resulting from the various systemic approaches described below in the “Existing treatments” section, it is important to note that none of these options are curative. Hence, there is an unmet need for alternative systemic approaches, especially those that target other genomic vulnerabilities including homologous repair deficiency.

3. Existing Treatments:

Despite the significant mortality associated with prostate adenocarcinoma, there are a limited number of effective therapeutic options available after metastatic disease is no longer responsive to androgen deprivation via GnRH agonism/antagonism, the so-called castrate-resistant state. These approaches include increasing the suppression of the androgen axis via direct receptor blockade with anti-androgens such as enzalutamide, or non-gonadal androgen synthesis inhibitors such as abiraterone, along with a few effective chemotherapy regimens which include the microtubule inhibitors docetaxel and cabazitaxel. Finally, alternative modalities including immunotherapies (sipuleucel-T) and bone-targeting radiopharmaceutical drugs (radium-223) have also entered the armamentarium. These systemic approaches are summarized in Table 1.

Suppression of Androgen/AR Axis Signaling

Abiraterone (a CYP17 inhibitor, used in combination with low-dose prednisone) represents the lone adrenal androgen synthesis inhibitor approved for the treatment of metastatic CRPC. This indication is based on two large randomized trials, one conducted by De Bono et al demonstrating a survival improvement with abiraterone plus prednisone versus prednisone control in docetaxel-pretreated patients, and the second by Ryan et al demonstrating a significant improvement in survival when the combination of abiraterone and prednisone was compared to prednisone in a chemotherapy-naïve group.[8, 9] Of interest, additional newer data suggest that the combination of abiraterone and prednisone may provide a significant survival advantage when utilized in the setting of castrate-sensitive disease together with initial androgen deprivation therapy; this approach has already been readily adopted.[10]

Enzalutamide is a novel anti-androgen approved for use in combination with androgen deprivation in order to gain improved blockade of the androgen receptor (AR) in CRPC, and has largely replaced bicalutamide. Enzalutamide (an agent that antagonizes the AR, prevents its translocation into the nucleus, and inhibits its interaction with DNA promoter/enhancer

motifs) showed improved progression-free survival when compared to bicalutamide in two randomized studies.[11, 12] Enzalutamide's approval in the metastatic CRPC setting is based on the PREVAIL (chemotherapy-naïve) and AFFIRM (docetaxel-refractory) trials that demonstrated overall survival improvements of 35.3 months versus 31.3 months and 18.4 months versus 13.6 months, respectively, when compared to placebo in these two clinical settings.[13, 14] Based on these data, enzalutamide has largely replaced bicalutamide for the treatment of CRPC in the current era. Therefore, enzalutamide and abiraterone/prednisone currently represent the two primary medications utilized for the first-line systemic treatment of mCRPC in modern practice.

Notably, there is felt to be significant cross resistance between androgen blockade and testosterone synthesis inhibition; this has limited the benefit of administering them sequentially.[15] Retrospective analysis suggests that treating with abiraterone prior to enzalutamide might have overall improved efficacy in comparison to sequencing the two agents in the reverse order, although prospective validation of this hypothesis is required.[16, 17]

Chemotherapy options:

Not all CRPC is created equal with some cancer cells being able to grow and proliferate despite androgen deprivation therapy secondary to autocrine/paracrine testosterone production whereas other clones develop constitutive androgen receptor activation allowing for utilization of this growth pathway even in the absence of testosterone. Clones displaying constitutive AR activation are unlikely to respond to additional suppression of the androgen axis, and while there is no perfect mechanism for assessing which category a patient will fall in to, detection of the AR-V7 splice variant is highly suggestive of primary (and secondary) resistance to enzalutamide or abiraterone therapy and may represent a population better suited for a chemotherapy-based approach.[18–21]

The two most widely utilized chemotherapy options for prostate carcinoma are microtubule inhibitors (taxane agents), docetaxel and cabazitaxel. Docetaxel supplanted mitoxantrone as the first-line chemotherapy agent of choice on the basis of two phase 3 trials, which demonstrated superiority of docetaxel over mitoxantrone, a drug only associated with an improvement in prostate carcinoma related symptoms but no survival advantage. The TAX327 trial evaluated docetaxel/prednisone versus mitoxantrone/prednisone, demonstrating an improvement in overall survival of 18.9 months versus 16.5 months for the every-3-weeks docetaxel arm. This was confirmed by a second phase 3 trial by Petrylak et al examining docetaxel/estramustine versus mitoxantrone/prednisone, which showed an improvement in overall survival of the docetaxel arm to 17.5 versus 15.6 months.[22, 23]

Cabazitaxel is newer microtubule inhibitor that is approved for use in patients with prostate adenocarcinoma after progression on docetaxel therapy or who are intolerant. This is based on the results of the TROPIC trial, which showed an improvement in progression-free survival (2.8 versus 1.4 months) and overall survival (15.1 versus 12.7 months) of cabazitaxel over mitoxantrone when used in combination with prednisone after prior receipt of docetaxel therapy.[24] A recent first-line chemotherapy trial (FIRSTANA) comparing docetaxel versus cabazitaxel in chemotherapy-untreated CRPC patients failed to show

superiority of cabazitaxel in this setting, while a second study suggested that patients who don't achieve an adequate initial PSA response to docetaxel might fare better if they are immediately switched to cabazitaxel.[25, 26] Thus, cabazitaxel generally remains a second-line chemotherapy option for CRPC at present, while docetaxel is the preferred first-line treatment. In addition, docetaxel added to androgen deprivation has been shown to improve survival in men with metastatic hormone-sensitive prostate cancer with higher initial disease burden, representing a reasonable standard of care for newly-diagnosed metastatic patients who are chemo-fit.[27–29]

Immunotherapy and Radiopharmaceuticals:

Sipuleucel-T and radium-223 are two alternative therapeutic approaches that have been shown to provide a modest improvement in survival in patients without visceral disease.[30, 31] Sipuleucel-T is an individualized prostate cancer vaccine created by harvesting and exposing a patient's own antigen-presenting cells to a fusion peptide composed of prostatic acid phosphatase (PAP) conjugated with GM-CSF. This option is approved for asymptomatic and minimally symptomatic CRPC patients, where it was shown to produce a 4.1 month improvement in median overall survival.[31]

Radium-223 is a radioactive isotope that localizes to areas of bone turnover which in this patient population is often synonymous with sites of bony involvement of prostate carcinoma.[32] Once it has localized to the osteoblastic lesions, radium-223 emits alpha-particle radiation to the surrounding tissue in an effort to reduce metastatic burden. In a landmark phase 3 trial (ALSYMPCA), it was associated with a 2.8 month increase in median overall survival and less symptomatic skeletal events in comparison to placebo plus best supportive care.[30] This radiopharmaceutical agent is approved for CRPC patients with symptomatic bone metastases without bulky nodal or visceral involvement.

4. Need for Further Therapeutic Options

Given the lack of curative intent provided by existing treatment options, there is a significant push for development of novel therapeutic approaches for addressing metastatic castration-resistant disease particularly for those patients whose options may be limited due to rapid progression through currently available AR-directed therapy or a predicted lack of hormonal responsiveness due to AR-V7 detection. One emerging strategy involves the use of PARP inhibitors in patients exhibiting alterations in the HR repair pathway, which are most commonly associated with *BRCA1/BRCA2-deficient* tumors.

PARP inhibitors

The idea of blocking multiple DNA repair pathways to produce irreparable damage to cancer cells' genome with the induction of apoptosis or necrosis was first introduced in two seminal papers, one by Bryant et al and the other by Farmer et al.[33, 34] These manuscripts elegantly demonstrated the concept of "synthetic lethality", whereby cells defective in HR would be less equipped to address any additional dysfunction within DNA repair pathways, specifically when single-strand DNA break repair was inhibited, leading these lesions to progress to double-strand DNA breaks. In this context, if HR was also deficient then non-

homologous end joining would ensue, producing aberrations within key cellular pathways and trigger cell death.[4, 33] These papers demonstrated large therapeutic indexes for PARP inhibitors in HR-deficient cells, which it was hoped could be leveraged into both extremely effective and well tolerated treatment options in this population at elevated risk for a number of malignancies.[33] Given the high incidence and mortality associated with prostate carcinoma, along with the high rate of HR deficits in metastatic CRPC (approximately 20–25% of cases), there is substantial enthusiasm for developing PARP inhibitors for prostate carcinoma.[35, 36]

Recent studies suggest that the prevalence of germline (inherited) HR mutations among men with metastatic prostate cancer ranges from 8–14%, reflecting a large proportion of men with advanced disease that may benefit from these agents.[37–40] Interestingly, these patients may not only be sensitive to treatment with PARP inhibitors but may perhaps also demonstrate higher sensitivity to AR-directed therapies, although the data are conflicting.[38, 41] Finally, particular histologic characteristics (such as intraductal or ductal morphology) may help to identify patients who are at higher risk of harboring germline HR mutations; in one recent study the prevalence of germline HR mutations was increased to approximately 40% among men with prostatic ductal or intraductal adenocarcinoma.[39, 42]

PARP inhibitors were first tested in an unselected group of prostate carcinoma patients in the TOPARP-A trial (Trial of Olaparib in Patients with Advanced Castrate Resistant Prostate Cancer) in which 49 patients were provided olaparib therapy. Olaparib did not demonstrate particularly impressive activity for the cohort as a whole with only a 32% response rate (defined as either a PSA reduction, objective tumor response, or CTC reduction).[43] However further analysis with next-generation sequencing (NGS) identified DNA repair gene alterations in 16 of the 49 patients that included *BRCA1/BRCA2*, *ATM* serine/threonine kinase (*ATM*), Checkpoint kinase 2 (*CHEK2*), or Fanconi anemia gene alterations. When patients were stratified on the basis of these results, 14 of the 16 with repair pathway mutations had a favorable response to olaparib compared to only 2 of the other 33 patients whose NGS did not reveal a DNA repair-associated mutation.[43] The progression-free survival in this subgroup was 9.8 months with a median overall survival of 13.8 months.[43] For the seven *BRCA2*-deficient patients in this cohort, all 7 were noted to have a greater than 50% drop in their PSA.[43] On the basis of this trial, the FDA has granted a breakthrough designation for the use of olaparib in metastatic CRPC patients with *BRCA1/2* or *ATM* alterations. Notably, previous studies examining PARP inhibitors in unselected CRPC populations also failed to show significant clinical benefits using PARP inhibitors in the absence of HR-deficient genotypes.[44, 45]

These findings led to the design of the phase 3 PROFOUND study, in which patients with abiraterone- and/or enzalutamide-pretreated CRPC will be screened for somatic HR deficiency mutations and will then be randomized to either AR-targeted therapy or olaparib. A second smaller randomized phase 2 study will compare abiraterone vs olaparib vs the combination of the two drugs, among metastatic CRPC patients with germline or somatic HR-deficiency mutations.

In addition, the phase 3 TRITON3 study has been launched which will examine the use of rucaparib (another PARP inhibitor) in a front-line setting for CRPC for individuals with HR-deficient tumors versus physician's choice of the currently approved first-line agents of abiraterone, enzalutamide, or docetaxel.

5. Scientific Rationale:

Single-strand break repair:

Single-strand breaks (SSB) represent a common mechanism of DNA damage that can occur during DNA replication stress, or exposure to carcinogens. Poly ADP ribose Polymerases (PARPs) initiate the repair of this damage through the identification of DNA lesions, recruitment of base excision repair pathway machinery, and coordination of the repair process.[4] After identification, repair of SSBs is mediated through a glycosylate, which removes damaged bases, endonuclease activity that eliminates the deoxyribose backbone, and a DNA polymerase that adds the correct nucleotide, utilizing the opposite strand as its template.[3] When SSBs are not effectively repaired, they can progress to double-strand breaks (DSB) which then accumulate in the cell.

Double-strand break repair:

There are two major pathways for DSB repair, homologous recombination repair and non-homologous end joining. Of these processes, the higher-fidelity approach is HR where the sister chromatid acts as a template to guide accurate repair of the lesion site. BRCA1 and the ATM protein work in combination to initiate this process with binding of broken ends via Replication protein A (RPA). RPA is subsequently replaced by RAD51 with the assistance of BRCA2 with recruitment of a sister chromatid to serve as a template for DNA repair.[3] Of note, this process is only possible during the S and G2 replication periods due to the need for a readily accessible sister chromatid that acts as a genetic blueprint.[4]

When HR is not possible due either to a deficiency in one of the HR repair enzymes or if the damage occurs outside of the S and G2 replication periods, non-homologous end joining is pursued. This repair process is accomplished by joining the ends of double-stranded DNA fragments via DNA-dependent protein kinases. This restores DNA integrity but does nothing to address any nucleotides lost during the initial break.[3]

6. Market Review:

In the year 2009, there were an estimated 36,100 new cases of metastatic CRPC that occurred in the United States.[46] Given the increasing age of the US population, this number is likely to grow further moving forward. Prostate carcinomas exhibiting HR pathway mutations, either somatic or germline alterations, are at elevated risk for rapid disease progression, as evidenced by the enrichment for these alterations in CRPC compared to localized prostate cancer.[35] The overall prevalence of *BRCA2* mutations in individuals under the age of 65 with prostate carcinoma is only 1.2%, but increases dramatically to 12.7% (germline or somatic *BRCA2* alteration) when considering only patients with CRPC. [47] This number increases even further to 20–25% when *BRCA1* and *ATM*, two additional genes within the HR pathway are also included (*i.e.* >7000 HR-deficient CRPC cases per

year in the US).[35] This substantial population of men would derive benefit from PARP inhibitor-related strategies at the current juncture. If combination approaches, as discussed below, prove effective in expanding the effective use of olaparib to the general CRPC population or the adjuvant setting, then this number is likely to grow even further.

7. Current Research Questions:

Given the limited (i.e. non-curative) and heterogeneous duration of responses noted with the currently available therapeutic options for castrate-resistant prostate carcinoma, there is significant interest for employing combination strategies including the incorporation of novel agents to maximize the durability and depth of these responses as well as determining subgroups (i.e. mutational profiles) that might benefit from specifically tailored approaches.. PARP inhibition represents one class of agents that may prove valuable in this endeavor with specific current research questions centering on two fundamental principles: (1) Can the benefit of PARP inhibition be expanded to patients with intact HR, either through the identification of additional subgroups with increased sensitivity or employing combination approaches that will increase the vulnerability of cancer cells to PARP inhibition? (2) Are there adjuncts to PARP inhibition that can be used to improve the degree and duration of response in patients with tumors exhibiting HR deficits?

Expansion of PARP Inhibitors through Combination Approaches

One observation that inspires enthusiasm for the use of PARP inhibitors in combination with other active agents is the finding that HR pathway proteins are upregulated in CRPC cells. [36, 48] This upregulation could hinder the efficacy of PARP inhibition in HR-proficient CRPC and explain in part its poor efficacy in unselected populations. Enzalutamide has been noted to suppress the expression of these DNA repair genes in prostate cell lines, potentially recapitulating the HR-depleted state noted in individuals with *BRCA1/2* mutations.[36] Therefore one strategy that has been postulated is the use of enzalutamide (or abiraterone) in combination with PARP inhibition, which may prove complementary in allowing for the expansion of PARP inhibition to the HR-proficient CRPC population. This approach is currently being testing in an ongoing phase 1 trial by Mathew et al, who are evaluating enzalutamide in combination with niraparib in the treatment of unselected CRPC patients. Furthermore, the use of AR antagonists in HR-deficient prostate cancers (even when given alone) may lead to particularly effective therapy due to a type of synthetic lethality, as proposed in recent preclinical studies.[49]

Another combination approach that has engendered enthusiasm is the use of PARP inhibition as a sensitizing agent with radiation therapy, either for high-risk localized disease or for metastatic lesions. This is based on the observation that radiotherapy induces prostate cancer death through the production of oxygen free radical species that leads to double-strand DNA damage. PARP inhibitors would be predicted to amplify this effect by preventing the repair of radiation-induced DNA damage. This is reflected in cellular models, where PARP inhibitors and radiation have been shown to have a synergistic impact on cell death.[50] Moreover, a recent case report suggested very pronounced activity of radium-223 in a patient with a germline *BRCA2* mutation and a second somatic hit (i.e. biallelic *BRCA2*

inactivation), implying that men with HR-deficient CRPC may be very sensitive to alpha-particle radiopharmaceutical treatment.[51]

Based on previous data in other cancer types that suggest increased sensitivity of HR-deficient tumors with the use of alkylating agents, there is enthusiasm for combining these agents with DNA repair inhibition via PARP inhibitors. This tactic may overwhelm the HR pathway and increase cancer cell apoptosis. With these principles in mind, a phase 2 trial examining the utilization of veliparib in combination with temozolomide was pursued. This regimen was well tolerated but showed minimal anti-tumor effects, suggesting a modification to this approach is necessary and perhaps will not be successful in a biomarker-unselected population.[45]

Immunotherapy-based approaches consisting of PD-1 or CTLA-4 inhibitors have been increasingly utilized in a number of cancer types. However these drugs have not yet proven effective as a monotherapy for prostate carcinoma despite the observation that enzalutamide-resistant prostate carcinomas express PD-L1.[52] This has given plausibility to the notion that the increased DNA damage induced by PARP inhibition might promote the formation of tumor-specific neoantigens and therefore augment the antitumor activity of anti-PD-1/PD-L1 agents. This approach is being piloted in a small cohort in an ongoing trial at the NCI.[53]

Other Prostate Cancer Subgroups that may benefit from PARP Inhibitors

As discussed above, PARP inhibition has demonstrated efficacy in patients with CRPC who exhibit mutations in *BRCA1*, *BRCA2*, and *ATM* on the basis of the TOPARP-A trial. However, it is unclear if there are additional subgroups that might derive benefit from PARP inhibitor monotherapy. One potential candidate is TMPRSS2-ETS which has been noted to exhibit alterations in 50% of prostate cancers found in Caucasians.[54] Given the proposed involvement of PARP1 in the formation of a fusion gene between a transcription factor in the ETS family and the androgen responsive gene TMPRSS2, there was suggestion that this might represent a cohort likely to have increased sensitivity to PARP inhibition outside of its role in DNA repair through prevention of this interaction.[55] This is supported by the pre-clinical observation that olaparib inhibits growth of ETS mutated cell lines.[55]

A phase 2 trial was launched to explore this question, utilizing a combination of PARP inhibition with veliparib plus abiraterone.[56] This trial by Hussain et al randomized 148 patients to abiraterone +/- veliparib, stratified by their ETS gene fusion status to assess whether the addition of veliparib to abiraterone provided a progression-free survival benefit to patients with a particular focus on whether ETS status modified response rates. This trial did not demonstrate any modification in response based on ETS status, but did indicate an improvement in PFS and PSA response rate to PARP inhibition in patients with the DNA repair deficiencies, PTEN loss, TP53 inactivation, and PIK3CA activation with a trend towards improvement in the overall cohort, suggesting potential future molecular based investigations. Most intriguingly, this study also suggested an improvement in PFS using abiraterone (irrespective of PARP inhibition) in men with HR-deficient prostate cancers, supporting the preclinical hypothesis of synthetic lethality when using AR inhibition in HR-deficient cells.[49]

8. Mechanisms of Resistance

While PARP inhibitors have proven effective in CRPC with HR deficiencies, the duration of response has been suboptimal. There is active investigation into the mechanisms by which this loss of response occurs, but it appears to result from a heterogeneous group of secondary events outlined in Table 2. One of the more common of these is the development of reversion mutations within the HR pathway that restore function and allow for double-strand breaks to undergo this less destructive repair pathway.[57, 58] Intriguingly, these reversion mutations that restore the open reading frame of HR genes (e.g. *BRCA2*, *PALB2*) have been observed not only in the setting of somatic HR mutations but also apply to germline mutations as well. By reverting to wild-type, such cancer cells become HR-proficient meaning that they are no longer susceptible to synthetic lethality despite ongoing PARP inhibition.

Another mechanism of resistance actually leads to the loss of the second path of DSB repair. As discussed earlier, cells with *BRCA1* deficits undergo increased non-homologous end junction repair which leads to worsening mutational burden. In contrast, the loss of a key regulatory protein within the non-homologous end junction repair pathway, 53BP1, promotes the increased utilization of HR.[59] If both of these deficits occur in concert, then partial *ATM*-dependent HR repair proceeds in *BRCA1*- but not *BRCA2*-deficient cells.[59, 60] Of note, this escape mechanism has been identified clinically in *BRCA1/2*-associated breast cancer but may also mediate a proportion of prostate cancers that become resistant. [60]

The third proposed mechanism of PARP inhibitor resistance, which is particularly applicable to the HR-proficient population, is the increased expression of *BRCA1*, *RAD54L*, and *RMI2* proteins within the HR pathway. This resistance mechanism may allow cancer cells to better compensate for the increased DSBs seen during PARP inhibition.[36]

9. PARP inhibitor data from other disease types

Breast Carcinoma

PARP inhibitors have gained wide recognition as a potential treatment strategy in a variety of tumor types with a specific focus on the utilization in tumors noted to display HR deficiencies. Breast carcinoma represented an obvious early choice for testing these drugs given its high overall population prevalence and enrichment of *BRCA1/2*-positive tumors. Olaparib was assessed in a phase 2 trial by Tutt et al; this study was comprised of heavily pre-treated (median three previous chemotherapy regimens) women with advanced staged stage breast cancer that demonstrated efficacy as monotherapy. The response rate was 41% in the 27 patients who received 400mg twice daily.[61] A recent phase 3 study in metastatic breast cancer patients with germline *BRCA1/2* alterations compared olaparib vs chemotherapy, and found a significant PFS benefit favoring the olaparib arm. [62] This trial has lead to the FDA approval of olaparib for germline HR-deficient advanced breast cancer.

Ovarian Carcinoma

Kaye et al explored the use of olaparib compared to pegylated liposomal doxorubicin for patients with recurrent ovarian carcinoma with germline *BRCA1/2* mutations, which demonstrated a median PFS of 8.8 months for olaparib 400mg compared to 7.1 months for liposomal doxorubicin.[63] Success with this approach led to FDA approval of olaparib in 2014 for ovarian carcinoma patients with germline *BRCA1/2* mutations who have progressed on at least three lines of systemic therapy. This was followed by the approval of niraparib in a similar space of patients with recurrent ovarian carcinoma with germline mutations who had progressed after two or more lines of prior therapy.[64] Niraparib and rucaparib maintenance therapy have also shown promise for recurrent ovarian carcinoma although in distinction the demonstrated benefit occurs in patients irrespective of the presence or absence of a germline BRCA mutation.[65, 66]

A number of combination trials have also been pursued with the hope that PARP inhibition will provide an additional benefit to ovarian cancer patients undergoing standard chemotherapy. In this context, phase 2 trials have evaluated the benefit of adding olaparib to carbopla chemotherapy as induction and maintenance therapy in patients with relapsed ovarian carcinoma.[67] This study demonstrated an improvement in progression free survival of 12.2 months versus 9.6 months in the chemotherapy alone arm, which was accentuated in the 38% of patients noted to have a *BRCA1/2* mutation.[67] The benefit of adding olaparib in a maintenance context was confirmed by Pujade-Lauraine et al in a cohort of 295 *BRCA1/2* positive patients with platinum-sensitive disease who had achieved a response on second-line treatment with chemotherapy.[68] This trial demonstrated a 19.1 month progression-free survival with olaparib compared to 5.5 months with observation, strongly suggesting a role as maintenance therapy in this patient population.[68]

In the area of relapsed disease, Kummar et al looked at PARP inhibitors as an adjunct to chemotherapy, specifically cyclophosphamide +/- veliparib, in a cohort of 72 patients with ovarian, peritoneal, or fallopian tube carcinoma. In this trial, veliparib that did not augment median PFS compared to cyclophosphamide alone.[69] A second trial for relapsed disease by Liu et al. demonstrated more promising results with an improvement in progression free survival of 17.7 months versus 9.0 months with the addition of cedirinib to olaparib when compared to olaparib alone for recurrent platinum-sensitive disease.[70] While this study was not designed to directly assess the impact of olaparib given its incorporation into both arms, subset analysis did demonstrate that the added benefit of cedirinib was primarily seen in the HR-proficient population, suggesting the dual VEGF and PARP inhibition approach might be useful in other disease subtypes.

Basket Trials

In addition to disease-specific trials, there have been several basket trials that sought to assess the impact of PARP inhibition on HR-deficient tumors agnostic of the underlying disease histology. In a cohort evaluating olaparib 400mg in 193 patients with gynecologic malignancies, 62 patients with breast carcinoma, 23 patients with pancreatic carcinoma, and 8 with prostate carcinoma who had received prior chemotherapy, the authors sought to answer how effective PARP inhibitor monotherapy was across HR-deficient disease

subtypes.[71] This trial demonstrated an overall response rate of 26.2% which broke down to individual response rates for the various histologic subtypes of 31.1%, 12.9%, 21.7%, and 50% for ovarian, breast, pancreatic, and prostate carcinomas, respectively.[71] In addition, another 41.6% of patients achieved stable disease for at least 8 weeks, including 40.4% for ovarian, 46.4% for breast, 34.8% for pancreatic, and 25% and for prostate carcinoma.[71] A second basket trial focusing on ovarian and breast carcinoma patients showed similar differential response rates with 41% of ovarian carcinoma patients exhibiting at least a partial response with no objective responses in the 8 triple-negative breast carcinoma patients; five of the 8 (63%) demonstrated stable disease lasting >8 weeks.[72]

Another trial looking specifically at 16 patients with pancreatic carcinoma with *BRCA1/2* or *PALB2*-mutated tumors demonstrated no significant improvement in outcomes with the use of veliparib.[73]

10. Competitive Environ

As outlined above in the “Existing therapies” section, there are a number of treatment options available for the management of CRPC that came into prominence in the last 5–7 years. These agents will be integral to the management of prostate carcinoma going forward, but their optimal sequencing and potential synergy in combination approaches will likely help to define the field in the upcoming years.[15]

In addition, immunotherapy has become increasingly prominent in the treatment paradigm of a number of disease processes. There is active investigation into the best way to utilize these agents in prostate carcinoma with phase 2 trials ongoing which examine the use of ipilimumab plus nivolumab in CRPC.[74] In addition, promising preliminary data have emerged using the PD-1 inhibitor pembrolizumab in metastatic CRPC patients.[75] Based on this encouraging preliminary activity, a large phase 2 study (KeyNote199) examining pembrolizumab monotherapy in PD-L1 positive and PD-L1 negative CRPC has recently completed accrual, and results should be forthcoming in the next 6 months.

The optimal method for incorporating PARP inhibitors into this treatment schema remains to be determined. Ongoing research will be key to providing patients with the optimum treatment strategies and outcomes. If PARP inhibitors become FDA-approved for metastatic HR-deficient CRPC, they will likely be first used as monotherapy in patients who have received at least one of abiraterone and/or enzalutamide, predominantly in the pre-chemotherapy space. These agents may also be preferentially indicated in patients who demonstrate primary resistance to novel AR-directed agents, those who have a short duration of benefit to first-line AR-targeting therapy, or those who have biomarker criteria (e.g. AR-V7) that may be associated with primary/acquired AR-therapy resistance. Since PARP inhibitors may induce myelosuppression, their use in the post-chemotherapy setting will be more limited, particularly in patients who have received both docetaxel and cabazitaxel in whom the risk of further myelosuppression might be too great. PARP inhibitors will also need to be used with caution in patients who have previously received radium-223 due to a potentially higher risk of myelodysplasia and acute myeloid leukemia in this setting.

11. Potential Development

PARP inhibitors have shown encouraging efficacy in patients with CRPC exhibiting HR deficiencies, but have not yet demonstrated compelling evidence for extending their use to patients outside of this selected population. It remains to be seen whether further investigation into combination approaches will help to expand the utility of PARP inhibition to other broader (biomarker-unselected) prostate cancer populations. Another untapped opportunity is the potential use of PARP inhibitors in hormone-sensitive (*i.e.* castration-naïve) non-metastatic or metastatic prostate cancer. To this end, our group is currently conducting a clinical trial (NCT03047135) using olaparib as a monotherapy (in the absence of androgen deprivation) for patients with biochemically-recurrent prostate cancer following radical prostatectomy. This has initially been designed as a biomarker-unselected trial, with a built-in futility assessment with conversion to a biomarker-selected design if there are inadequate responses in the first 20 unselected patients. It is intriguing to consider the possibility of a similar trial for men with metastatic hormone-sensitive prostate cancer, although no such studies are currently ongoing.

With its acceptable therapeutic index in HR-deficient cancer populations, PARP inhibitors are generally well tolerated. In the TOPARP-A trial, the reported Grade-3 or 4 drug-related events were largely related to hematologic toxicity noted at 20% for anemia, 12% for fatigue, and 6% for neutropenia.[43] However there have been reports of the development of myelodysplasia and acute myelogenous leukemia in other diseases with PARP inhibitor usage, although because these patients often have prior exposure to chemotherapy and/or radiotherapy defining a truly causative relationship has been challenging.[76] Were PARP inhibitors shown to lead to high incidences of MDS/leukemia with expanded use, it would lead to a dampened enthusiasm for its use except in the most advanced cancer settings.

12. Conclusions:

The expansion of access and decreasing costs of molecular diagnostics and tumor DNA sequencing has led to an opportunity for the increased utilization of personalized approaches for the treatment of cancer. Germline deficits within HR pathways increase the risk of prostate cancer development and denote a more aggressive phenotype with poorer response to localized therapies and hormonal deprivation. This increases the importance of advancing new approaches for this disease category, which comprises up to 25% of patients with CRPC if germline and somatic alterations are both included. PARP inhibitors have shown significant activity in a variety of cancer types associated with HR deficits including ovarian, breast, and pancreatic carcinomas, prompting enthusiasm for exploring this approach in this subtype of prostate carcinoma. This was demonstrated in prostate carcinoma patients in the TOPARP-A trial where 14 of 16 patients demonstrating deleterious *BRCA1*, *BRCA2*, and *ATM* mutations were noted to have significant responses with olaparib monotherapy.[43] Specifically in the 7 patients shown to exhibit *BRCA2* mutations, all demonstrated a >50% drop in PSA.[43] A second basket trial which included 8 patients with prostate carcinoma who had undergone at least two prior systemic treatments confirmed the activity of PARP inhibitors in this population with a 50% response rate and an additional 25% with stable disease greater than 8 weeks.[71] These data suggest the importance of incorporating PARP

inhibition into the current treatment paradigm in HR-deficient prostatic carcinomas with an eye on ongoing trials to determine if their role beyond this indication can be established.

13. Expert Opinion:

PARP inhibitors have demonstrated promising activity in HR-deficient prostate adenocarcinomas in the context of heavily pre-treated CRPC patients. Much of the increased utilization of PARP inhibition in prostate carcinoma over the next few years will likely result not from the development of broader indications, but rather from more widespread identification of HR-deficient cancers that would benefit from this approach as next-generation sequencing becomes more available and clinicians become increasingly aware of this option. Success with olaparib monotherapy in a heavily pre-treated CRPC population with HR deficiencies has also raised the question as to whether this agent may prove effective in earlier lines of treatment, which are actively being investigated in the PROFOUND and TRITON3 pivotal trials. As these studies are completed and data are reported, the field will gain a better understanding of the true promise and role of PARP inhibition in the HR-deficient population. Of the PARP inhibitors currently being assessed for use in the treatment of prostate carcinoma, olaparib appears to have experienced the most documented success, suggesting that it may prove the most valuable of these agents in this population. Olaparib is also the only agent which has garnered a breakthrough designation by the FDA for the treatment of *BRCA1/2* or *ATM-mutated* advanced prostate cancer. A summary of the various PARP inhibitors in clinical practice as well as some other late-phase trials is outlined in Table 3.

Future investigations will also focus on techniques to expand the use of PARP inhibitors to the broader population of prostate carcinoma patients through the use of combination approaches, identification of other molecular subtypes exhibiting increased sensitivity, and ways to improve the degree/duration of response in patients with HR deficiencies. In addition, we would advocate that PARP inhibition should also be examined in patients with non-metastatic or metastatic hormone-sensitive prostate cancer. To this end, it is not clear whether castration is necessary to mediate optimal responses to PARP inhibition in prostate cancer. Therefore, it is conceivable that certain patients with germline and/or somatic HR-deficiency mutations may achieve durable biochemical or radiographic responses to PARP inhibitor monotherapy in the absence of androgen ablation. This hypothesis is currently being examined in the post-prostatectomy biochemically-recurrent population (NCT03047135), and additional trials are now being designed to test PARP inhibitors as a non-castrating strategy for metastatic hormone-sensitive disease as well (e.g. TRIUMPH trial; NCT03413995).

However, despite the current excitement surrounding PARP inhibitors in prostate cancer, there are still many unanswered questions.[77] For example, it is not currently known whether particular HR defects may demonstrate different sensitivities to PARP inhibitors, since some HR genes may be more redundant than others. It is possible, for instance, that only patients with *BRCA2* and *ATM* mutations will respond most favorably to PARP inhibitors while other HR gene mutations might not be associated with the same degree of synthetic lethality. Second, current clinical-grade DNA sequencing technologies do not

detect all HR lesions even in common HR genes, because these platforms mainly focus on sequencing exonic variants. This means, for example, that deletions of the entire *BRCA2* gene will not be detected and a genetic report from such a patient might state (correctly) that there are no sequence variants in the *BRCA2* gene in that patient's tumor. Third, although the concept of PARP-induced synthetic lethality theoretically requires biallelic inactivation, in practice biallelic loss is rarely investigated or reported. Therefore, treatment decisions (and selection for enrolment in clinical trials) usually only require a single-copy pathogenic mutation in an HR gene. It is likely, however, that the best responses to PARP inhibitors would be seen in patients with true biallelic inactivation (from a second-hit mutation, loss-of-heterozygosity, or methylation). Finally, the importance of germline vs somatic HR mutations has not been fully elucidated. One would hypothesize that men who harbor inherited HR deficiency mutations would have the best response to PARP inhibition, because all of their tumor cells (rather than a smaller sub-clonal fraction) would have the same mutation; there might also be a higher chance of somatic loss-of-heterozygosity in this situation leading to biallelic inactivation. While the current ongoing trials may try to address some of these questions, future dedicated studies (perhaps in the post-approval setting) will be required to answer some of these questions in more depth. Our quest for understanding PARP inhibitor sensitivity (and primary/acquired resistance) should not stop with the FDA approval, but rather this should provide the motivation to dig deeper into our understanding of PARP inhibitor therapy for recurrent and advanced prostate cancer. We have only begun to scratch the surface.

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*=of importance, **= of considerable importance

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Table 1:**Summary of Treatment Options for Castration-Resistant Prostate Carcinoma**

Drug	Mechanism of Action	Overall Survival Benefit	Selected side effects	Approved Indications
Abiraterone	Androgen synthesis inhibitor	34.7 mo vs 30.3 mo with Pred in chemo naïve. 15.8 mo vs 11.2 mo with Pred in pts with prior docetaxel	Hypertension, Hypokalemia, Edema	Treatment of docetaxel-naïve and docetaxel-pretreated metastatic CRPC
Enzalutamide	Androgen receptor blocker	35.3 mo vs 31.3 mo in PBC arm in chemo naïve and 18.4 mo vs 13.6 mo in pts with prior docetaxel	Seizures, Back pain	Treatment of docetaxel-naïve and docetaxel-pretreated metastatic CRPC
Docetaxel	Microtubule inhibitor	18.9 mo vs 16.5 months with mitoxantrone	Neutropenia, neuropathy, stomatitis, tear duct sclerosis	First-line chemotherapy treatment of metastatic CRPC
Cabazitaxel	Microtubule inhibitor	15.1 mo versus 12.7 mo with mitoxantrone	Neutropenia, Diarrhea	Second-line chemotherapy for mCRPC after progression on docetaxel
Radium-223	Bone-seeking radioactive isotope	14.9 months versus 11.2 months with placebo	Myelosuppression, Diarrhea	Symptomatic bony disease with no visceral metastases
Sipuleucel-T	Patient-derived antigen-presenting cell vaccine	25.8 mo vs 21.7 mo versus placebo	Mild acute-phase reactions (fevers, chills)	Minimally or asymptomatic metastatic CRPC

Abbreviations: CRPC: Castration-Resistant Prostate Cancer, Mo: Months, PFS: Progression-Free Survival, OS: Overall Survival, Chemo: Chemotherapy, Pred: Prednisone, PBO: Placebo, pts: patients

Table 2:

Resistance mechanisms of PARP inhibitors

Summary of potential mechanisms of PARP inhibitor resistance
1. Somatic reversion mutations that restore the open reading frame (ORF) of the gene and hence protein function within the homologous recombination pathway.
2. Loss/Decreased activity within non-homologous end joining repair (NHEJ) pathway leading to partial dsDNA repair.
3. Under-expression or loss of expression of PARP1 protein
4. PARP1 mutations (e.g. point mutations in the zing-finger domain) that prevent PARP1/DNA interactions
5. Overexpression of mutant HR (e.g. BRCA1/2) proteins, or demethylation of methylated HR genes
6. Inactivation or loss of expression of REV7, which counteracts double-strand DNA break resection
7. Upregulation of alternative homologous recombination proteins in DNA repair-proficient carcinomas.

Table 3:

PARP inhibitors in clinical practice or in late-phase clinical trials

<i>Drug Name</i>	<i>Manufacturer</i>	<i>FDA Approved Indications</i>
Niraparib	Tesaro	Maintenance in recurrent ovarian carcinoma, biomarker-unselected
Rucaparib	Clovis Oncology	3 rd line treatment of BRCA-deficient ovarian carcinoma
Olaparib	Astra Zeneca	4th line treatment of BRCA-deficient ovarian carcinoma, Priority Review for maintenance therapy in ovarian carcinoma Priority review for 3 rd line treatment of BRCA+ metastatic breast cancer
<i>Drug Name</i>	<i>Manufacturer</i>	<i>Late-Phase Clinical Trials</i>
Niraparib	Tesaro/Janssen Biotech	Phase 3 prostate cancer trials being planned
Rucaparib	Clovis Oncology	In phase 3 trials (TRITON3) for HR-deficient metastatic CRPC
Olaparib	Astra Zeneca	In phase 3 trials (PROFOUND) for HR-deficient metastatic CRPC
Veliparib	AbbVie	In phase 3 trials for ovarian, triple negative breast, and lung cancer
Talazoparib	Pfizer	In phase 3 trials for BRCA-positive breast carcinoma