Recent Advances and Future Directions in the Management of Metastatic Castration-Resistant Prostate Cancer Asing Androgen Receptor Signaling Inhibitors and Poly-adipose Polymerase Inhibitors: A Literature Review

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Abstract
Prostate cancer is still the most common cancer in men and the second leading cancer-related cause of death in men worldwide. There are several types of prostate cancer. One of which is castration-resistant prostate cancer (CRPC). According to current studies, the mechanism of resistance can be categorized into classical androgen receptor (AR) pathway overexpression, abnormal AR pathway activation, and non-AR pathway. These mechanisms develop overtime to further induce treatment resistance in mCRPC. Development of novel therapeutic treatments is necessary to tackle this issue. Recent studies have been conducted on the combination therapy of androgen receptor signaling inhibitors (ARPi) and poly (ADP-ribose) polymerase inhibitors (PARPi) in treating mCRPC shows a nuanced perspective regarding its efficacy compared to monotherapy. Studies shows the combination therapy has significantly prolong radiographic progression-free survival (rPFS) compared to monotherapy in certain genetic groups. Further research is necessary to fully understand their role in the broader mCRPC treatment landscape.

Keywords: prostate cancer, castration-resistant, androgen receptor signaling inhibitors, poly (ADP-ribose) polymerase inhibitors

1. Introduction
Prostate cancer is still the most common cancer in men and the second leading cancer-related cause of death in men worldwide. There are several types of prostate cancer. One of which is castration-resistant prostate cancer (CRPC), and hormone-sensitive prostate cancer (HSPC) patients [1]. CRPC is an advanced form of prostate cancer characterized by unresponsiveness to androgen deprivation therapy, and its progressiveness despite castration levels of serum testosterone. On a biomolecular level, the molecular mechanism that underlies this resistance has been proposed due to several factors, such as androgen
receptor pathways which include AR upregulation, de novo androgen synthesis, altered splicing, AR gene mutations, and co-regulatory activity [2].

In addition to that, prostate cancer can be localized or metastasized. Metastatic prostate cancer has a very low survival rate, and there is no effective therapy for metastatic prostate cancer to date. When both are combined, the metastatic nature of CRPC, which is called metastatic castration-resistant prostate cancer (mCRPC), compared to nonmetastatic castration-resistant prostate cancer (nmCRPC), is by far the most difficult type of prostate cancer to treat, and research is still being conducted worldwide. The symptoms of mCRPC are no different than metastatic prostate cancer in general. The Urological Tumours Working Group (URONCOR) has a consensus on the diagnosis of mCRPC which can be made if there is a documented increase in PSA ≥ 2 ng/mL, PSA increase in three consecutive determinations at least one week apart, PSA values > 25% above nadir, and/or castrated patients with serum testosterone levels < 50 ng/dL (<1.7 nmol/L) with evidence of radiological progression. The prognosis of mCRPC is severely poor with a short overall survival (OS) [3].

Over the past decade, there have been remarkable advancements in the understanding of mCRPC pathophysiology and the development of novel therapeutic strategies. One of the novel strategies is through combination therapy. Several newly published studies have begun to explore the possibilities regarding the combination of androgen receptor signaling inhibitors (ARSi) with poly (ADP-ribose) polymerase inhibitors (PARPi). This literature review aims to provide a comprehensive overview of recent advances in mCRPC therapy, focusing on the emerging ARSi and PARPi combination therapies, and its comparison with the traditional monotherapy.

2. Methods

To carry out the current review, in 2024, we began to collect information and carry out a comprehensive search from 3 different databases, which are Google Scholar, PUBMED, and SCOPUS. We limit the studies published from 2014 to 2024 to focus more on comprehensively elaborating the recent and emerging therapeutic modalities. Inclusion criteria are randomized control trials, and publication within the last 10 years. Exclusion criteria are cohort studies, case studies/series, observational studies, language other than English, and articles with inadequate information. The following keywords were used for the search strategy: “prostate cancer”, “castration”, “therapy”, “therapeutic”, and “metastatic”. Duplicate papers were eliminated, the data were screened using inclusion and exclusion criteria, and then full-text documents were screened. Meta-analysis was not performed due to the lack of randomized control trials in mCRPC patients using ARPi and PARPi combination therapy.

3. Discussion

3.1. Epidemiology, and Risk Factors

mCRPC still plays a significant role in the global health challenge, especially in elderly people. Several epidemiological data explain its significant burden, such as being the second most prevalent cancer in men globally. Prostate cancer is the most frequently diagnosed cancer in more than 100 countries with an estimated 1.4 million new cases of prostate cancer diagnosed globally every year, and the leading cause of mortality in more than 40 countries [4]. Statistically, the transition from localized disease to metastatic castration-resistant prostate cancer carries a considerable mortality risk. Roughly 20% of patients diagnosed with prostate cancer will develop the metastatic disease during their lifetime. Among these, nearly 80% will eventually progress to castration-resistant status, signifying a dire prognosis [5].
Retrospective studies across various countries show the large amount of people affected by mCRPC. In the US, a veteran-based study was conducted from 2007 - 2017. The result shows that the prevalence of nmCRPC and mCRPC was estimated at around 2.1% of prostatic cancer cases (13,818), of which the proportion was 49.8% and 50.2% respectively [6]. Another study was conducted in the US from 2008 - 2018. The result shows the prevalence of mCRPC was 1.1% of total prostatic cancer cases (343,089), with the most frequent site of initial metastasis being bone (65%), and lymph nodes (15%) [7]. Two studies in the UK compare the prevalence of nmCRPC and mCRPC. Both studies combined show that the proportion was 84.3 to 91.2% (9,779 - 27,000) and 8.8% to 15.7% (1,821 to 2,600) respectively [8-9]. A study was conducted in France discovered that 7.5% categorized as metastatic, 4.9% categorized as CRPC, and 3.4% categorized as mCRPC amongst prostatic cancer population (386,127 cases). The age-standardized prevalence of mCRPC was 62 cases per 100,000 men. This study further compares the prevalence of each age group with findings that mCRPC prevalence increased with age. Less than one case per 100,000 men versus 500 cases per 100,000 men was observed in men 40-49 years of age and 70-79 years of age respectively [10].

Risk factors associated with the development of mCRPC encompass a complex interplay of genetic, age progression, environmental, and lifestyle factors (obesity, and lack of exercise). Men with one first-degree relative and two first-degree relatives with prostate cancer show two and five-fold greater risk. There is a correlation between high calcium intake and advanced prostate cancer. Also, high saturated fat or milk product consumption, and low vitamin D blood levels have been linked to increased cancer risk. Prostatitis with the etiology of chlamydia, gonorrhea, and syphilis also have been linked to an increase in the risk of prostate cancer [11]. A retrospective study shows that the Gleason grade of a patient correlates with the progression of prostate cancer to CRPC. Gleason groups 4 and 5 showed a 4.3 and 5.1 fold higher risk for progression to CRPC compared to the Gleason grade 1 patient group [12].

### 3.2. Mechanisms of Resistance to Androgen Deprivation Therapy

The AR is encoded by eight exons in the X chromosome (q11-q12), resulting in a protein consisting of four parts which are the central DNA-binding domain (DBD), and C-terminal ligand-binding domain (LBD), an N-terminal structural domain (NTD), and a hinge region linking the LBD and DBD. The mechanism of prostate cancer to become castration resistant remains poorly understood. However, according to current studies, it can be categorized into classical AR pathway overexpression, abnormal AR pathway activation, and non-AR pathway. The classic pathway is hypothesized to involve several different mechanisms including androgen receptor (AR) upregulation, de novo androgen synthesis, and AR co-regulatory proteins. The abnormal pathway is hypothesized to involve mutation of AR, and altered AR splicing. The non-AR pathway involves mechanisms such as glucocorticoid receptor induction, DNA repair pathway, hedgehog pathway, PI3K-AKT-mTOR pathway, Wnt pathway, and non-coding RNAs (miRNAs and LncRNAs) [13-15].

AR overexpression is thought to be related to CRPC with 20.3% of CRPC patients exhibiting upregulation of AR expression compared to just 2% in HSPC. AR mRNA expression has been documented to increase twofold in CRPC patients. The constant production of dihydrotestosterone (DHT) in CRPC tumors can lead to more AR expression and progression of the CRPC. An alternative pathway to DHT production is that steroids produced by the adrenal glands and catalyzed by HSD3B2, AKR1C3, CYP17A1, and CYP11A1 can later be converted to DHT via the 5a-diketone-pathway. Even in post-castration therapy patients with low levels of DHT, it is still sufficient to promote the progression of prostate cancer to be
castration-resistant, thus DHT produced via alternative pathways remains a constant challenge. AR co-regulatory proteins also play a role in both activating and repressing AR transcription. It is believed that these proteins can maintain the transcription of AR even under low levels of DHT. There are more than 180 proteins identified to date, and specific proteins such as JMJD2C, LSD1, 37CBP/P300, p160/SRC, and SUV39H2 are known to function as co-activator proteins that drive AR overexpression and upregulation resulting in tumor growth. Another finding is that protein βArr1 was observed to be correlated with the progression of CRPC. This protein is encoded in the AEEB1 gene, and the deletion of βArr1 was observed to be correlated with impaired growth, invasion, and metastatic progression of the tumor. Another co-activator that has been observed to play a role in the progression is CKβBP2/CRIF1 and STAT3, with the decrease of CKβBP2/CRIF1 expression, and the increase in the expression of the co-activator STAT3 in CRPC [14-17].

Point mutations in the AR encoding genes are often discovered in CRPC patients. These mutations (T878A, L702H, H875Y, F876L, T877A, etc.) are believed to cause several anti-androgenic agents into agonists, thus favoring CRPC progression. The most frequent site of mutation is the LBD region, and it is rare to be found in other sites such as NTD and DBD. Another mechanism in the abnormal AR pathway is with AR splice variants (AR-V) which have been identified in over 20 variants to date. AR-V is thought to form in response to ADT or low DHT levels. It lacks AR LBD, which is the target of many drugs, in its structure, thus favoring the progression of CRPC. The most clinically relevant AR-V to date is AR-V7, which is highly expressed in 75% of CRPC patients, followed by AR-V3 and AR-V9. AR-V567es is also discovered to promote oncogenic factors such as K-RAS, FLI1, STK33, NF-κB, and β-linked protein signaling, and only has been detected in advanced prostatic cancer, including CRPC [14-15, 18-19].

Glucocorticoid receptors (GR) are thought to be able to bypass the AR pathway and promote the progression of CRPC. This is because the GR and AR have similar structures, particularly in the DBD region. The defect in the DNA repair genes, and altered DNA repair pathway is one of the mechanisms that is related to the progression of CRPC, with 25% of CRPC patients have been documented alterations in the DNA repair pathway. BER, NER, and MMR are among the SNPs that have been documented to be associated with the development of CRPC. BRCA2 is among the homologous recombination repair (HHR) genes in which mutations most frequently occur. The deletion of BRCA2 and RB1 has been documented to increase castration resistance. Another mechanism that contributes to the progression of CRPC is via the hedgehog pathway (Hh), with high levels of Hh pathway ligands such as Shh, Ihh, and Dhh leading to transcription factor GLI activation. Study shows that GLI2 and GLI3 expression have been linked to androgen-independent growth of prostate cancer, and repression of these transcription factors resulted in the prevention of CRPC development. CRPC also has been documented to activate the PI3K-AKT-mTOR pathway which regulates pro and anti-apoptotic signaling (inactivation of Bad and activation of Bcl-2 and Bcl-Xl). Mitogen-activated protein kinases (MAPK), and Wnt pathways have also been shown to enhance the proliferation of CRPC. The altered Wnt pathways have been documented in 18% of CRPC tumors, with the classical Wnt/β-linked protein pathway to have been found interacting with AR. The non-classical Wnt pathway, especially Wnt5a has been observed to be capable of enhancing CRPC development through ERK pathway activity [15, 20-25].

### 3.3. Novel Therapeutic Strategies

Understanding the underlying mechanism that drive prostate cancer into castration resistant is key to developing the treatment. As discussed in the previous section, several mechanisms have been proposed...
that led to numerous pharmaceutical advancements. Treatments that have been developed for prostate cancer are ARSi, PARPi, bromodomain and extra-terminal (BET) inhibitors, dual PI3K/mTOR inhibitors, radiopharmaceuticals, CAR-T Cell therapy, AKT inhibitors, and Immunotherapy. This section will primarily discuss the latest findings regarding these treatments and on-going clinical trials regarding ARSi and PARPi in mCRPC patients.

3.3.1. Androgen Receptor Signaling Inhibitors Monotherapy
Enzalutamide acts as a competitive inhibitor of the AR signaling pathway. It binds to the ligand-binding domain of the AR, preventing androgens from binding and activating the receptor. This inhibition blocks AR translocation to the nucleus, DNA binding, and subsequent transcriptional activation of genes involved in prostate cancer cell proliferation and survival. The efficacy of enzalutamide has been studied from a total of 4317 patients were enrolled in AFFIRM, PREVAIL, and PROSPER randomized control trials comparing it to placebo in mCRPC patients. The result demonstrated a 37% [hazard ratio (HR) for death, 0.63; 95% confidence interval (CI), 0.53 to 0.75; P<0.001], 29% [HR = 0.71; 95% CI, 0.60 to 0.84; P<0.001], and 71% [HR = 0.29; 95% CI, 0.24 to 0.35; p<0.001] reduction in the risk of radiographic progression or death than the placebo respectively. Enzalutamide was also shown to be superior for all secondary points, which are PSA response rate [54% vs 2%, 47% vs 1%, 76% vs 2%; p<0.001], soft tissue response rate [29% vs 4%, 59% vs 5%, not reported; p<0.001], progression free survival [8.3 vs 3.0 month, 11.2 vs 2.8 month, 37.2 vs 3.9 month; p<0.001], FACT-P quality of life response [43% vs 18%, 11.3 vs 5.6 month, 11.1 vs 11.1 month; p<0.001], and the time to the first skeletal-related event [16.7 vs 13.3 month, 32% vs 37%; p<0.001] [26-28].

There are no reported phase III randomized clinical trials that compares the efficacy darolutamide alone with placebo in mCRPC patients. A study documented that darolutamide shows a statistically significant result as a maintenance treatment after taxane or ARSi therapy with improved median rPFS compared to placebo (5.5 vs 4.5 months) [hazard ratio [HR] = 0.54 [95% CI, 0.32 to 0.91]; p = 0.017], and PSA 50% response rate was improved [22% v 4%; p = 0.014] [29].ARADES trial was conducted as a phase 1-2 trial to assess safety profile and PSA response of darolutamide in mCRPC patients. Patients divided into 3 groups were given either 200mg, 400mg, or 1400mg resulted in 29%, 33%, and 33% PSA response at 12th week [30]. Saad, et al. conducted a double blind RCT comparing apalutamide plus abiraterone-prednisone versus abiraterone-predisone with a total of 982 men with mCRPC. The result shows that the addition of apalutamide increase the median radiographic progression-free survival (rPFS) compared to abiraterone-prednisone alone (24.0 vs 16.6 month) [13-9–19·3; HR = 0·70, 95% CI 0·60–0·83; p<0·0001] [31]. TITAN trial also documented that apalutamide plus ADT improved overall survival (OS), delayed castration resistance, and reduced the risk of death by 35% [hazard ratio, 0.65; 95% CI, 0.53 to 0.79; p<0.0001] compared to placebo plus ADT in mCRPC patients [32]. The only phase III trial on gilterrone, was ARMOR3-SV trial which combines androgen receptor blockade with CYP17 enzyme inhibition. Although the trial did not meet its primary endpoint compared to enzalutamide (p=0.12) because too many patients dropped off the trial before having required radiographs, it offered valuable insights into patientspecific responses based on AR-V7 splice positive variant [33]. Abiraterone Acetate (Zytiga) is a well-established therapy in mCRPC. The COU-AA-301 trial showed that abiraterone significantly improved OS, PSA response, and radiographic progression-free survival compared to placebo. Patients treated with abiraterone showed a 35% reduction in the risk of death [HR = 0.65; 95% CI, 0.54-0.77; p<0.001]. This study firmly established abiraterone as a key component in the treatment arsenal for mCRPC, particularly post-chemotherapy [34].
3.3.2. PARP Inhibitors Monotherapy

Olaparib inhibits PARP enzymes, particularly PARP-1 and PARP-2. PARP enzymes are involved in DNA repair mechanisms, particularly in base excision repair. Inhibition of PARP leads to accumulation of DNA damage, specifically single-strand breaks, ultimately resulting in cell death, particularly in cells with defects in homologous recombination repair (HRR) pathways, such as BRCA1/2 mutations. Several studies have been conducted on the efficacy of olaparib in mCRPC showed significantly positive effect than the control group of either abiraterone or enzalutamide. Bono J, et al., documented the imaging based progression free survival, and overall survival in mCRPC patients with at least one alteration in BRCA1/2 or ATM to be significantly longer, 7.4 vs 3.6 month [HR for progression or death, 0.34; 95% CI, 0.25 to 0.47; P<0.001], and 18.5 vs 15.1 month [HR for death, 0.64; 95% CI, 0.43 to 0.97; P=0.02] respectively, when treated using olaparib compared to control group [35]. The PROfound trial also conducted similar study with 387 patients enrolled to either olaparib or control group. Olaparib was documented with longer rPFS [HR = 0.22, 95% CI, 0.15 to 0.32] and OS [HR = .63, 95% CI, 0.42 to 0.95] than control [36]. Rucaparib were evaluated in the multicenter TRITON3 study with a total of 302 mCRPC patients with BRCA and 103 patients with ATM alterations randomized. The median rPFS with rucaparib (600 mg twice daily) was 10.2 months, compared with 8.3 months with docetaxel [HR = 0.80; 95% CI, 0.58 to 1.11; p = 0.2013] and 4.5 months with abiraterone/enzalutamide [HR = 1.01; 95% CI, 0.70 to 1.46; p = 0.9045] [37].

Niraparib, was evaluated in the phase II GALAHAD study (300 mg once daily) with 223 mCRPC patients enrolled with gene defects (BRCA1/2 or non-BRCA mutations) divided into BRCA cohort and non-BRCA cohort groups where it demonstrated a notable ORR of 34.2% in BRCA cohort patients. Median rPFS, and and OS in the BRCA versus non-BRCA cohort was 8.08 month (95% CI 5.55–8.38) versus 3.71 month (95% CI 1.97–5.49), and 13.01 month (95% CI 11.04–14.29) versus 9.63 month (95% CI 8.05–13.44) [38.] TALAPRO-1 is a phase 2 trial evaluating the efficacy of talazoparib in mCRPC patients. Median duration of talazoparib treatment was 6.2 months (3.6–9.9) in the antitumour activity population with a 29.8% objective response rate [95% CI 21.2–39.6] [39].

3.3.3. Combination therapy in ARSi and PARPi

Several studies have started evaluating the combination treatment of ARSi and PARPi compared to monotherapy. Hussain M, et al. conducted an RCT comparing the efficacy of abiraterone acetate-prednisone (AAP) (arm A) versus veliparib plus AAP (arm B) in a total of 148 mCRPC patients. The result was shown to be statistically insignificant in terms of PSA response rate (Arm A 63.9% vs Arm B 72.4% [p = 0.27]), ORR (Arm A 45% vs Arm B 52.2% [p = 0.51]), and median PFS (Arm A 10.1 months (m), Arm B 11.3 m [p = 0.95]) [40]. A phase 3 clinical trial, TALAPRO-2, evaluated the combination of talazoparib plus enzalutamide (0.5 mg plus 160 mg once daily) versus placebo plus enzalutamide (160 mg once daily) in with asymptomatic / mildly symptomatic mCRPC on ADT. The median follow-up of rPFS for talazoparib versus placebo group was 24.9 months (IQR 21.9-30.2) versus 24.6 months (14.4-30.2) respectively [41]. The MAGNITUDE trial was conducted in order to observe the efficacy of niraparib (200 mg) plus AAP (1000 mg / 10 mg) versus AAP alone in a total of 212 HRR+ patients. The result was niraparib plus AAP significantly prolonged the rPFS in the BRCA1/2 subgroup [median rPFS 19.5 vs 10.9 months; HR = 0.55; 95% CI 0.39-0.78; p = 0.0007], and also prolonged the rPFS in the total HRR+ population [HR = 0.76; 95% CI 0.60-0.97; p = 0.0280; median follow-up 26.8 months] [42]. Combination of alopaurib and AAP versus placebo and AAP was also conducted in the PROpel trial with 796 mCRPC patients randomly assigned to either group. Insignificant result was reported with the median OS in
olaparib versus placebo group plus AAP was 42.1 (95% CI 38.4–not reached) versus 34.7 months (31.0–39.3) [HR = 0.81, 95% CI 0.67–1.00; p=0.054] [43].

4. Conclusion
Recent studies on the combination therapy of ARPi and PARPi in treating mCRPC shows a nuanced perspective regarding its efficacy compared to monotherapy. Studies shows the combination therapy has significantly prolong rPFS compared to monotherapy in certain genetic groups such as BRCA 1/2. However, not all PARPi shows similar result. Results from some of the trials showed mixed outcomes, indicating that while some patients may experience benefits, the OS might not be as significant. These findings underscore the importance of genetic profiling in making treatment decisions. Also, the potential of combination therapy should be considered as a mean to improve outcomes in specific patient populations, though further research is necessary to fully understand their role in the broader mCRPC treatment landscape.

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