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*Review Article*

# Targeting treatment options for castration-resistant prostate cancer

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**Abstract:** Prostate cancer (PCa) is the most commonly diagnosed solid tumor and the second leading cause of cancer-related deaths in U.S. men in 2020. Androgen-deprivation therapy (ADT) is the standard of care for metastatic PCa. Unfortunately, PCa relapse often occurs one to two years after initiation of ADT, resulting in the development of castration-resistant PCa (CRPCa), a lethal disease. While several anticancer agents such as docetaxel, abiraterone acetate, and enzalutamide are currently utilized to extend a patient's life after development of CRPCa, patients will eventually succumb to the disease. Hence, while targeting androgen signaling and utilization of docetaxel remain the most crucial agents for many of these combinations, many studies are attempting to exploit other vulnerabilities of PCa cells, such as inhibition of key survival proteins, anti-angiogenesis agents, and immunotherapies. This review will focus on discussing recent advances on targeting therapy. Several novel small molecules will also be discussed.

**Keywords:** Prostate cancer, castration-resistant prostate cancer, androgen deprivation therapy, targeting therapy, combination treatment

## Introduction

Prostate cancer (PCa) is the most commonly diagnosed solid tumor with 1 in 7 males developing the disease. It is also the second leading cause of cancer-related deaths in men in the United States in 2020 [1]. While nonmetastatic (M0) PCa has an excellent prognosis for patients [2], patients who develop metastatic (M1) PCa have a 5-year survival rate of only 31%. Due to the dependence of PCa cells on androgens for survival and growth [3], androgen-deprivation therapy (ADT), which blocks androgen receptor (AR) signaling, has been the standard of care for treating M1 PCa. Unfortunately, many patients will often remain on ADT for the rest of their lives [1, 4].

PCa cells have many mechanisms by which they can overcome and become resistant to ADT or androgen biosynthesis inhibition, thus developing the castration-resistant (CR) phenotype. The CR phenotype results from the ability of the cells to bypass the need for normal physiological testosterone levels. For example, development of castration-resistance can arise from AR overexpression, mutation in the ligand-binding site of AR, constitutive AR activation through splice variants (e.g. AR-V7), or intra-tumoral androgen biosynthesis due to overexpression of CYP17A1. Some PCa tumors exhibit ligand-independent AR activation through activation of growth factor signaling pathways, such as ErbB-2, AKT, MAPK, etc. to promote progression and survival [5-17]. Moreover, neuroendocrine (NE)-like cells can support the CR phenotype of adenocarcinoma. While the authentic NE cell and its tumors may account for less than 5% of total PCa, NE-like PCa cells have been found in more than 40% of CRPCa tumors [18-21]. While,

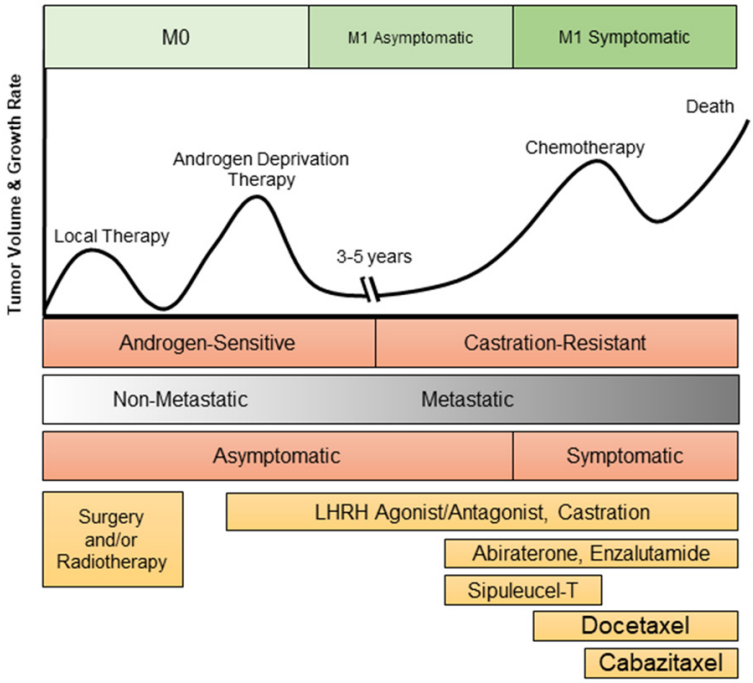


**Figure 1.** PCa Disease Progression and Current Treatment Options. PCa originates within the prostate and will often be detected before it invades into other areas of the body. Localized PCa is treated via surgery and/or radiotherapy. When the PCa is metastatic, the standard-of-care treatment is ADT. Three to five years after treatment with ADT, the PCa is likely to relapse, thus the development of CRPC. CRPC is initially treated with antiandrogens such as enzalutamide or abiraterone or immunotherapy Sipuleucel-T. Upon further progression of the disease, docetaxel and cabaitaxel may be utilized, in addition to abiraterone and enzalutamide if the patient has not previously been treatment with these agents. Unfortunately, these anti-cancer treatments utilized for CRPC will only prolong a patient's life by several months before they succumb to the disease [120].

these NE-like PCa cells express NE biomarkers, they are derived from adenocarcinoma cells via trans-differentiation pathways during ADT. NE-Like cell are vital to prostate tumor survival by altering the microenvironment for promoting CRPCa cell growth [18-21].

ADT is a long-term treatment for metastatic PCa; unfortunately, PCa cells eventually develop resistance to this treatment. Currently, FDA-approved drugs such as docetaxel, abiraterone acetate, and enzalutamide that can treat CRPCa have a modest impact on extending survival in patients by only a few months (**Figure 1**). Finding alternative therapies or combinations of therapies that can directly target these mechanisms of resistance are necessary to improve patients' clinical outcomes and potentially achieve longer term survival. Because targeting androgen signaling is the primary mechanism of CR PCa therapy, this review will briefly overview ADT and then focus on discussing recent advances on targeting other vulnerabilities of PCa cells, for example, inhibition of key survival proteins and anti-angiogenesis agents. We will also discuss several novel small molecules that are currently under investigation in preclinical models that could be utilized for the management of CRPCa.

## Single agent therapy with lifelong ADT

Due to the reliance of PCa cells on androgens for survival and proliferation, inhibition of the AR signaling pathway is the standard-of-care for the treatment of metastatic PCa. ADT can be carried out by one or more of the following methods: orchiectomy, chemical castration, and/or antiandrogen therapy. Chemical castration employs luteinizing hormone releasing hormone (LHRH) or gonadatropin releasing hormone (GnRH) agonists or antagonists to prevent androgen stimulation of PCa cells via the reduction of testosterone production in the testes [1, 4].

Androgen targeted therapies (ATTs) can also be utilized in conjunction with chemical or surgical castration to further reduce the ability of cancer cells to produce or utilize androgen signaling. One class of ATT is the androgen biosynthesis inhibitor, such as abiraterone acetate, which is an effective treatment option for tumors that have obtained the ability for extragonadal and/or intratumoral androgen biosynthesis [23, 24]. Another class of ATT is the AR antagonist that prevents AR nuclear translocation and DNA binding. First generation AR antagonists including bicalutamide, nilutamide, and flutamide are FDA-approved for the treatment of PCa. The second generation agent enzalutamide was FDA-approved for CRPCa treatments in 2012 [22, 25-27]. Demonstrating the significantly

superior activity of the second generation antiandrogens compared to first, the STRIVE trial (NCT01664923), in both M0 and M1 CRPCa patients, showed that enzalutamide had a significantly higher PFS at 19.4 months compared to 5.7 months with bicalutamide, and also increased time to PSA progression [28]. These results have led to the adoption of first-line enzalutamide (or abiraterone) over bicalutamide in treating PCa in recent years. More recently, nonsteroidal AR antagonist darolutamide has more recently become FDA-approved for the treatment of M0 CRPCa due to the ARAMIS trial (NCT02200614).

Although ADT is the gold standard treatment for metastatic PCa, hormone therapy usually fails as the cancers can overcome androgen signaling inhibition and continue to progress. The relapse can occur as early as <12 months after initiation of ADT [1, 29]. Therefore, many completed and ongoing studies are looking to combination treatments with ATTs to reduce the risk of recurrence after ADT or to treat CRPCa. In the following sections, this review will focus on analyzing recent advances on targeting the vulnerabilities of PCa cells that could be the potential regiments for managing CRPCa.

## Precision medicine combinations in prostate cancer

In the past fifteen years, precision medicine for treatment of multiple different types of cancers, including PCa, has begun to become a topic of interest for many clinicians and researchers. Some approaches of targeting therapies for CRPCa during ADT are discussed below.

### *Genetic polymorphisms in PCa*

Genetic factors are shown to play a critical role in about 40% PCa risk. Many single nucleotide polymorphisms (SNPs) have been identified to be associated with increased disease risk in PCa, which have become strong predictors of PCa aggressiveness compared to PSA alone [30, 31]. Importantly, the risk of aggressive PCa is predictably enhanced with compounding SNPs, particularly SNPs at 8q24 (*MYC*), 17q12, and 17q24.3. The potential utility of these specific SNPs in regards to targeted treatments for PCa are currently under investigation.

### *AR-V7 expression in PCa*

As mentioned previously, AR amplification, mutation, and expression of alternative splice variants often occurs in PCa in attempt to evade ADT-mediated suppression of tumor growth. Although there are no current strategies that directly target AR amplification or mutation, AR-V7 has become an important biomarker for finding new treatments for CRPCa. Several treatment combinations have been proposed to tackle this common problem, including ATT, bromodomain extraterminal enhancer protein inhibitors (BETi), immune checkpoint inhibitors, and small molecule inhibitors.

AR-V7 expression in PCa confers resistance to various ATTs [32, 33] as well as taxanes [34] and is strongly correlated with poor survival [35]. Many preclinical studies have found success in inhibiting PCa growth through the combination of ATT with small molecule inhibitors. For example, due to the ability of BETi to block AR binding to chromatin [36], the utilization of these molecules in combination with enzalutamide has shown to enhance anticancer effects [37]. As such, several clinical trials are underway to examine the combination of ATT with BETi in AR-V7 positive metastatic CRPCa patients (**Table 1**). Surprisingly, niclosamide, a treatment used for tapeworms, can effectively inhibit AR-V7 [38]. The combination of this drug with bicalutamide or abiraterone can re-sensitize PCa cells to cell death that were previously resistant to abiraterone, bicalutamide, or enzalutamide treatments [39, 40]. Similarly, bardoxolone-methyl (CDDO-Me) also inhibits both full length AR and AR-V7 and had additive efficacy in CRPCa cells when combined with enzalutamide [41]. Targeting AR and AR-V7 cofactor phosphatidylinositol-4-phosphate 5-kinase type 1 alpha (PIP5K1a) via its inhibitor ISA-2011B can also sensitize PCa cells to enzalutamide *in vitro* and *in vivo* [42]. On the other hand, the unique combination of imipridone ONC201 and mammalian target of rapamycin (mTOR) inhibitor everolimus shows synergy in AS and AI preclinical PCa models due to the ability of ONC201 to inhibit AR and AR-V7 activity [43]. It has also been noted that AR-V7 positive PCa tumors have a higher mutational burden [44], of which has been suggested to be sensitive to immune checkpoint inhibition in various tumors [45]. As such, AR-V7

**Table 1.** Ongoing clinical trials for ATT combination therapies in PCa

| Clinical Trial | Primary Anticancer Agent | Secondary Anticancer Agent | Phase | Current Status | Estimated Completion Date |
|---|---|---|---|---|---|
| LACOG-0415 (NCT02867020) | Abiraterone | Apalutamide | II | Recruiting | December 2020 |
| NCT03419234 | Abiraterone | Cabazitaxel | II | Recruiting | April 1, 2025 |
| NCT02703623 | Abiraterone, Apalutamide | Ipilimumab, Cabazitaxel, Carboplatin | II | Active, not recruiting | May 1, 2020 |
| NCT03072238 | Abiraterone | Ipatasertib | III | Active, not recruiting | November 17, 2023 |
| NCT01485861 | Abiraterone | Ipatasertib or Apitolisib | I/II | Recruiting | April 30, 2021 |
| LATITUDE (NCT01715285) | Abiraterone | LHRH agonists or castration | III | Active, not recruiting | December 31, 2022 |
| NCT03732820 | Abiraterone | Olaparib | III | Recruiting | August 17, 2022 |
| NCT01576172 | Abiraterone | Veliparib | II | Active, not recruiting | March 30, 2020 |
| HERO (NCT03085095) | ADT | Relugolix (Reluminia) | III | Active | November 1, 2021 |
| NCT02913196 | Apalutamide | Abiraterone, Docetaxel | I | Recruiting | June 2022 |
| NCT02106507 | Apalutamide | Everolimus | I | Active, not recruiting | April 2021 |
| NCT01251861 | Bicalutamide | MK2206 (AKT Inhibitor) | II | Active, not recruiting | June 19, 2020 |
| ARNEO (NCT03080116) | Degarelix (GnRH antiagonist) | Apalutamide | II | Recruiting | December 30, 2021 |
| IMbassador250 (NCT03016312) | Enzalutamide | Atezolizumab (Anti-PD-L1) | III | Active, not recruiting | Sept 30, 2020 |
| NCT02833883 | Enzalutamide | CC-115 (Dual DNA-dependent protein kinase and mTOR Inhibitor) | I | Active, not recruiting | July 2021 |
| NCT02207504 | Enzalutamide | Crizotinib (TKI) | I | Active, not recruiting | March 2021 |
| NCT02125084 | Enzalutamide | Everolimus (mTOR Inhibitor) | I | Active, not recruiting | January 2021 |
| NCT03834493 | Enzalutamide | Pembrolizumab | III | Recruiting | April 30, 2024 |
| NCT01867333 | Enzalutamide | PROSTVAC | II | Active, not recruiting | January 1, 2021 |
| NCT00450463 | Flutamide | PROSTVAC | II | Completed (No compiled results) | June 8, 2017 |
| NCT03488810 | LHRH, Radiation | Apalutamide | III | Not yet recruiting | June 15, 2026 |

To date, there are many active clinical trials analyzing the efficacy of combination trials in advanced PCa and CRPCa, many based on the preclinical studies mentioned above. Here we have listed some studies of interest that focus on combinations with ATTs will have results shortly.

positive tumors have been treated with multiple immunotherapies, such as anti-PD-1 nivolumab and anti-CTLA-4 ipilimumab with quite some success [44].

*DNA damage repair deficient PCa*

Mutations and deletions in DNA damage repair proteins are seen in up to 20% of primary PCa. Commonly lost DNA damage repair genes include *BRCA1*, *BRCA2*, *CDK12*, *ATM*, *FANCD2*, among many others. Tumors with any of these genetic abnormalities will often receive radiation, and occasionally radiation plus ADT for patients with local disease, which appears to be effective [46, 47]. Poly (ADP-ribose) polymerase (PARP) inhibition in post-abiraterone metastatic CRPCa patients was found to have some success, mainly in patients with mutations in DNA repair genes who experiences an increased survival of 6.3 months [48]. Two PARP inhibitors, Rucaparib and Olaparib, have since received FDA approval for treating metastatic CRPCa. Two pre-clinical models showed synergistic anticancer effects of Olaparib and enzalutamide in AR-sensitive and AR-independent cell lines and in xenograft models [49, 50]. The combination of abiraterone and Olaparib in a phase II trial (NCT01972217) initially found a 5.6 month increase in PFS in metastatic CRPCa patients compared to abiraterone alone [51] (**Table 2**). Another phase III trial (NCT03732820) for this combination is currently ongoing. Several studies are also ongoing to determine the anti-cancer efficacy of Olaparib and Veliparib in PCa in combination with abiraterone or enzalutamide (**Table 1**). However, initial results suggest that PCa tumors with homologous recombination deficiency (HRD) are already more susceptible to androgen deprivation than those tumors who have intact DNA damage repair response and do not require PARP inhibitors [52]. HRD was shown to give metastatic CRPCa patients increased sensitivity to radionucleotide Radium-223 [53], therefore the combination of Olaparib and Radium-223 will be studied in phase II trials in attempt to further increase anti-tumor effects of this molecule. Chemotherapeutics, such as combinations of docetaxel and carboplatin, have also been utilized for these particular tumors with some efficacy in metastatic CRPCa patients with HRD [54, 55]. Preclinical studies have suggested that there is synergistic anti-tumor effects in combining DNA repair protein inhibitors, specifically Olaparib and ATR-inhibitor AZD6738 (Ceralasertib) [56], which have spurred clinical trials in metastatic CRPCa, among several other cancers (**Table 3**).

*ERG-positive PCa*

Gene fusion events are also common in PCa and often include ETS transcription factors ERG or ETV. The fusion of *TMPRSS2* and *ERG* oncogenes occurs in up to 50% of PCa [57, 58]. Although a frequent mutation, several studies have shown mixed associations between TMPRSS2-ERG, Gleason grade, and patient outcome [59-61]. While other ETS fusion proteins can occur in PCa, most have a frequency of less than 1%, thus they are rarely studied [62]. One method to treat PCa with TMPRSS2-ERG fusions is through inhibition of ETS co-factors, such as PARP or histone deacetylase 1 (HDAC1), often in combination with ADT. Unfortunately, these phase I and II trials for patients with metastatic CRPCa have not achieved much success compared to ADT alone [52, 63, 64]. As such, novel inhibitors of ERG are under development and show some promise. For example, selective ERG inhibitor ERGi-USU effectively inhibited ERG-positive VCaP xenograft tumor growth alone, but had additive effects when cells were treated in combination with enzalutamide [65]. This same group found that dual inhibition of NOTCH (GSI-1) and AR (bicalutamide, enzalutamide, or abiraterone) signaling also synergistically suppressed ERG-positive PCa cells [66]. Additionally, silencing *TMPRSS2-ERG* mRNA through Arg-Gly-Asp (RGD)-peptide-coated liposomal siRNA nanovectors has shown to enhance PCa sensitivity to docetaxel *in vivo* [67].

*PTEN-Null PCa*

Phosphatase and tensin homolog (*PTEN)* deletion is another common genetic alteration in PCa that positively correlates with *TMPRSS2-ERG* fusions. The loss of *PTEN* has a strong relationship with aggressive PCa and increased mortality rates, especially when the tumor exhibits no ERG overexpression [68, 69]. Because the loss of *PTEN* leads to increased activation of the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway, this pathway is the most common target for *PTEN*-null PCa [70], however there has been little success in these mono-

**Table 2.** Completed clinical trials of abiraterone combination treatments for CRPCa

| Clinical Trial | Secondary Anticancer Agent | Phase | N | Primary Outcome | Result | Reference |
|---|---|---|---|---|---|---|
| NCT01685125 | Dastinib (Src Inhibitor) | II | 26 | PFS | No Benefit | Dorff et al. 2019 [100] |
| NCT01485861 | Ipatasertib (AKT inhibitor) | II | 253 | Radiographic PFS | Increased PFS, time to PSA progression, and survival | De Bono et al. 2019 [77] |
| NCT01972217 | Olaparib | II | 142 | Radiographic PFS | Increased PFS by 5.6 months, more dramatic response in HHR mutant tumors | Clarke et al. 2018 [51] |

Many clinical trials have analyzed the toxicity and effectiveness of combination treatments with abiraterone for the potential of PCa and CRPCa therapy.

**Table 3.** Current clinical trials analyzing the safety and efficacy of combinations treatments with small molecule inhibitors or radium 223

| Clinical Trial | Primary Anticancer Agent | Secondary Anticancer Agent | Phase | Current Status | Estimated Completion Date |
|---|---|---|---|---|---|
| NCT03840200 | Ipatasertib (AKT inhibitor) | Rucaparib (PARP inhibitor) | I/II | Recruiting | November 5, 2021 |
| NCT03874884 | Olaparib | $^{177}$Lu-PSMA-617 | II | Recruiting | October 2022 |
| TRAP (NCT03787680) | Olaparib | AZD6738 (ATM Inhibitor) | II | Recruiting | November 2025 |
| NCT02893917 | Olaparib | Cediranib (Anti-angiogenesis) | II | Active, not recruiting | December 2020 |
| NCT03810105 | Olaparib | Durvalumab | II | Recruiting | February 2021 |
| NCT03574571 | Radium 223 | Docetaxel | III | Recruiting | June 2023 |
| NCT03737370 | Radium 223 | Docetaxel | II | Recruiting | October 31, 2021 |
| PEACE III (NCT02194842) | Radium 223 | Enzalutamide | III | Recruiting | December 2025 |
| NCT02225704 | Radium 223 | Enzalutamide | II | Active, not recruiting | December 2022 |
| NCT04019327 | Talazoparib (PARP Inhibitor) | Temozolomide | I/II | Recruiting | July 2022 |
| NCT02711956 | ZEN003696 (BETi) | Enzalutamide | I/II | Active, not recruiting | October 2019 |
| NCT04471974 | ZEN003696 | Enzalutamide, Pembrolizuman | II | Not yet recruiting | August 31, 2025 |

Other various small molecule or Radium 223 combinations have emerged due to the fact that not many anti-cancer agents can effectively suppress CRPC for less than a year. PARP inhibitors have becoming an area of major interest as they have been shown to be quite effective in patients with mutations in DNA repair pathways.

therapies due to crosstalk activation of AR [71]. Preclinical models demonstrated that inhibition of PI3K or AKT with small molecules AZD8186 or AZD5363, respectively, in combination with ADT resulted in enhanced growth suppression of cells and xenograft PCa tumors [72-74]. While the combinations of dual PI3K/mTOR inhibitor BEZ235 and abiraterone or pan-class I PI3K inhibitor buparlisib and enzalutamide caused many adverse side effects in phase I and II trials [75, 76], other clinical trials were more successful. For example, phase II clinical studies of abiraterone acetate in combination with AKT inhibitor ipatasertib have shown efficacy against metastatic CRPC, particularly in patients with PTEN loss [77] (**Table 2**). Similarly, inhibition of mTOR can sensitize *PTEN*-null PCa cells to radiation *in vitro* [78]. The combination of olaparib and PI3K inhibitor BKM120 [79] or radiation [80] can also be utilized to effectively suppress the growth of *PTEN/TP53*-deficient PCa cells *in vivo*. Further studies on the combination of PI3K pathway inhibitors are warranted. Nevertheless, while AKT inhibitors may inhibit PCa tumorigenicity, treatments of those compounds can cause an adverse elevation of PSA levels [81]. Therefore, alternative biomarkers to determine the success of this treatment should be developed.

*MYC amplified or dysregulated PCa*

*MYC* encodes a transcription factor oncogene that drives many cancers by increasing expression of pro-proliferative genes. *MYC* is amplified in about 8% of primary PCa tumors and can predict biochemical recurrence [82, 83]. MYC dysregulation can also occur upon loss of prostate-specific transcription factor NKX.3.1, which competes for MYC binding spots [84]. Importantly, amplification or dysregulation of MYC results in the CR phenotype [85, 86]. Targeting MYC transcription through BETi has shown some efficacy in preclinical models through interrupting AR-mediated transcription of *MYC* [87, 88]. Importantly, combination treatment of PI3K and BET inhibitors showed strong anti-cancer effects against a murine model of PCa with PTEN deletion and forced MYC expression [89]. New evidence has also demonstrated that SPOP mutants, which are commonly seen in PCa, are resistant to BETi [90]. This has been attributed to increased AR and PI3K signaling [91], therefore this type of therapy would be beneficial for a limited patient population.

Targeting MYC interacting proteins PIM or Pol I has become an interesting strategy to prevent MYC function in PCa. Inhibition of PIM (AZD1208) or Pol I (CX-5461) alone have shown to effectively suppress MYC-driven cancers in preclinical studies [92, 93], therefore the combination of these two inhibitors was attempted in PCa. *In vivo* studies from a MYC overexpression and PTEN-deficient mouse model and patient derived xenografts (PDX) showed effective suppression of tumor growth as well as induced cell death with their combination [94]. Additionally, attempts have been made to target *MYC* mRNA and expression. In a study by Leonetti et al., it was demonstrated that utilization of of bcl-2 (G3139) and c-myc (INX-6295) antisense olidodeoxynucleotides in combination with docetaxel effectively promoted tumor regression PC3 PCa xenograft growth, in addition to increasing survival [95]. Another preclinical study by Ciccarelli et al. showed that *in vitro* and *in vivo* PCa cells with overexpression of MYC could be sensitized to radiation by MEK/ERK inhibitors, which down regulated MYC protein levels [96].

*Combinations of standard treatments with novel small molecule inhibitors*

Expanding the toolbox of anticancer agents for CRPCa is currently ongoing with some novel small molecules showing to be quite effective against this disease. While most of these molecules can be effective alone, they are often analyzed for their anti-tumor effects in combination with other standard-of-care therapies for PCa.

Although many small molecule inhibitors have been combined with docetaxel, mixed results have been obtained. Due to the frequent alterations in kinase signaling pathways upon progression to the CR phenotype [7, 8, 97], inhibition of tyrosine kinases and their corresponding downstream molecules was attempted for a treatment for CRPCa. Phase I/II trials (NCT00439270) showed that dasatinib (Sprycel), a Src and BCR-ABL tyrosine kinase inhibitor (TKI), in combination with docetaxel was well tolerated by patients [98]; however the phase III READY trial (NCT00744497) demonstrated that there was no improvement in patient survival [99] (**Table 4**). Similarly, the combination of dasatinib and abiraterone also did not show any benefit to patients [100] (**Table 4**). Phase III

**Table 4.** Clinical trials of combination therapies for CRPCa with taxanes

| Clinical Trial | Primary Anti-Cancer Agent | Secondary Anticancer Agent | Phase | N | Primary Outcome | Result | Reference |
|---|---|---|---|---|---|---|---|
| SYNERGY (NCT01188187) | Docetaxel | Custirsen | III | 1022 | Overall Survival | No Survival Benefit | Chi et al. 2017 [102] |
| READY (NCT00744497) | Docetaxel | Dastinib (Src Inhibitor) | III | 1522 | Overall Survival | No Survival Benefit | Araujo et al. 2013 [99] |
| TRAPEZE (NCT00554918) | Docetaxel | Strontium-89 or Zolendronic Acid (Osteoclast Inhibitor) | II | 757 | PFS and Cost-Efficacy | St-89 improved PFS, ZA Reduced Bone Metastasis, No Survival Benefit | James et al. 2016 [101] |

Several other combinations with docetaxel have been analyzed for their efficacy against CRPC. However, docetaxel continues to have associated toxicities that result in reduced survival or lower the quality of life.

**Table 5.** Current clinical trials for CRPCa of combination therapies with taxanes

| Clinical Trial | Primary Anticancer Agent | Secondary Anticancer Agent | Phase | Current Status | Estimated Completion Date |
|---|---|---|---|---|---|
| upFrontPSMA (NCT04343885) | Docetaxel | $^{177}$Lu-PSMA-617 | II | Recruiting | April 2024 |
| TheraP (NCT03392428) | Post-Docetaxel | $^{177}$Lu-PSMA-617 | II | Active, not recruiting | January 2021 |
| NCT02218606 | Cabazitaxel | Abiraterone | II | Active, not recruiting | August 2020 |
| NCT03110588 | Cabazitaxel | Abiraterone and Enzalutamide | I | Recruiting | August 1, 2023 |
| NCT01555242 | Docetaxel | Aneustat | I | Completed (No compiled results) | January 2014 |
| ProCAID (NCT02121639) | Docetaxel | AZD5363 (AKT Inhibitor) | I/II | Active, not recruiting | February 2020 |
| NCT03218826 | Docetaxel | AZD8186 (PI3K Inhibitor) | I | Recruiting | April 1, 2021 |
| NCT01505868 | Cabazitaxel | Carboplatin | I/II | Active, not recruiting | July11, 2030 |
| NCT02522715 | Cabazitaxel | Enzalutamide | I/II | Active, not recruiting | August 31, 2025 |
| PROSTRATEGY (NCT03879122) | Docetaxel/ADT | Nivolummab, Ipilimumab | II/III | Active, not recruiting | December 31, 2023 |
| NCT03834506 | Docetaxel | Pembrolizumab | III | Recruiting | February 28, 2023 |
| NCT02649855 | Docetaxel | PROSTVAC | II | Active, not recruiting | January 1, 2021 |
| NCT01420250 | Cabazitaxel | Radiation (IMRT), Bicalutamide | I | Active, not recruiting | January 1, 2021 |
| NCT02494921 | Docetaxel | Ribociclib (CDK4/6 Inhibitor) | I/II | Active, not recruiting | June 30, 2021 |

Similar to combination therapies with ATTs, many trials are looking to combinations with docetaxel to effectively suppress CRPCa. The intent is to find other therapies that can reduce the amount of taxane necessary for cancer treatment to prevent the toxicities commonly associated with these types of agents.

TRAPEZE trial (NCT00554918) combining docetaxel with strontium-89, zoledronic acid, or both showed significantly reduced bone metastasis, while no effect on overall patient survival upon treatment with zoledronic acid and docetaxel [101]. The SYNERGY trial (NCT01188187) demonstrated that the combination of docetaxel and custirsen, an antisense oligonucleotide that inhibits production of resistance-associated chaperone protein Clusterin, also does not improve overall patient survival [102] (**Table 4**).

As for pre-clinical models, one promising small molecule is Aneustat (OMN54), a multivalent botanical drug currently undergoing a phase I clinical trial (NCT01555242) for advanced cancers, primarily lymphomas. Interestingly, pre-clinical studies revealed that treatment of PCa mouse xenografts with docetaxel and Aneustat dramatically reduced PCa tumor growth with potential synergistic effects [103]. Additionally, fatty acid binding protein 5 (FABP5) inhibitors with docetaxel or cabazitaxel show synergistic cytotoxic effects *in vitro* and *in vivo* [104]. Inclusion of ERK inhibitors can be an alternate approach to reduce taxane toxicity. Because ERK inhibitors are shown to increase the potency of docetaxel inhibition of CRPCa cells [97], ERK inhibitors may be included with docetaxel under ADT, which will allow to reduce the docetaxel dosage, as well as its cytotoxicity, while accomplish a similar therapeutic index [97]. Another study aimed at targeting the PI3K/mTOR survival pathway in combination with docetaxel through N-(2-hydroxypropyl) methacrylamide (HPMA) drug conjugates. They found increased solubility and anti-tumor effects with the HPMA conjugate combinations against PC-3 xenograft tumors, in addition to a reduction in the cancer stem cell population [105]. Because focal adhesion kinase (FAK) expression positively correlates with advanced disease, inhibition of this protein via defactinib in combination with docetaxel enhanced cancer cell death in CRPCa and docetaxel-resistant CRPCa preclinical models [106]. Another combination of docetaxel with additional anti-microtubule agent mebendazole was found to be effective against PCa through a drug screen. Interestingly, further analysis showed enhanced anti-tumor activity; unfortunately, potential toxicities due to excessive disruption of the microtubule network were not reported in this study [107].

Other successes with docetaxel have been found through inhibition of specific receptors. Docetaxel nanoparticles in combination with a receptor activator of nuclear factor κB ligand (RANKL) monoclonal antibody, denosumab, led to an increase in survival and reduction in tumor burden and bone metastasis in PCa xenograft animal models [108]. Other preclinical studies have found success by inhibition of endothelin-1 (ET-1) binding to its receptor Endothelin A ($ET_A$) through $ET_A$ antagonist ABT-627 to reduce *in vitro* and *in vivo* LNCaP and C4-2b PCa cell growth [109]. Meanwhile, early *ex vivo* studies showed that the combination of docetaxel and dopamine D2 receptor agonist bromocriptine did effectively reduce tumor growth and bone metastasis in PCa xenograft models [110], suggesting another novel treatment combination for utilization in PCa. Future clinical trials of these new combinations may provide an answer. As of late, many clinical trials have aimed to tackle late stage disease through combination therapies with docetaxel. Examples include docetaxel plus radioligand therapy, immunotherapies, or small molecule inhibitors (**Table 5**).

Other combinations with two non-standard PCa treatments have also been analyzed in preclinical and clinical studies. While *in vitro* results of DNA damaging agent temozolomide in combination with olaparib have shown to have enhanced anti-tumor efficacy [111], a phase 1 trial (NCT01085422) of veliparib and temozolomide showed little synergy in M1 CRPCa patients [112]. It is important to note that although these particular results showed no survival benefit, clinical studies continue to analyze the efficacy of PARP inhibitors with temozolomide combinations in CRPCa (**Table 3**). Similarly, anti-angiogenesis agent cediranib showed modest activity alone in M1 CRPC patients [113], therefore, this drug is now being explored in combination therapy with olaparib in PCa (**Table 3**), as ovarian cancer patients have benefited from this combination [114].

It is noteworthy that statin derivative SVA is of particular interest. In addition to functioning as a single agent with minimal toxicity, SVA exhibits an added effect when combined with docetaxel (**Figure 2A** and **2B**) and novel anti-microtubule CIL-102 derivatives (**Figure 2C** and **2D**). Those novel CIL-102 derivatives are shown to have increased selectivity over CRPC cells

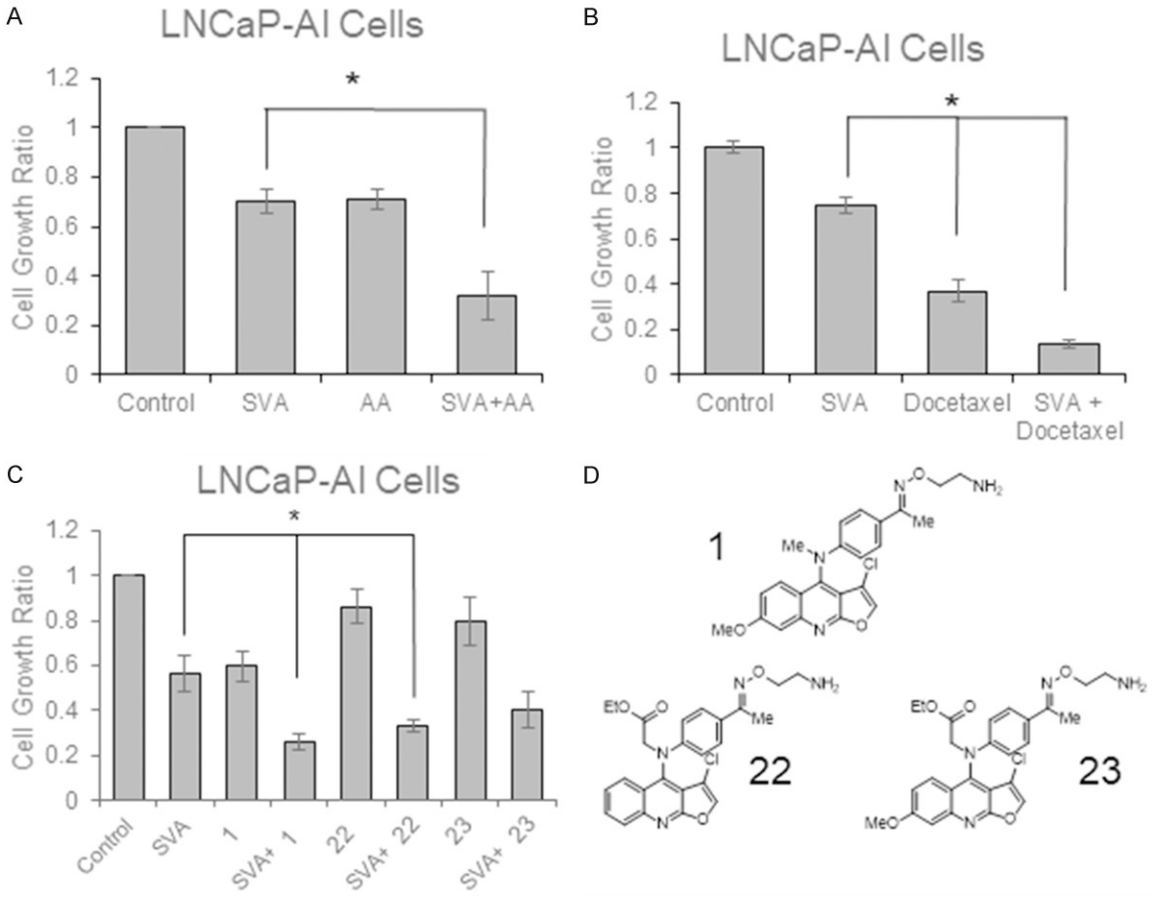


**Figure 2.** Combination treatments with Simvastatin Derivative SVA. A. LNCaP-AI cells were plated for 3 days in regular medium before being adjusted to steroid-reduced conditions for 2 days. Cells were then treated with 2.5 μM SVA and/or 5 μM abiraterone acetate for 3 days in steroid-reduced conditions. Cell number was determined with trypan blue exclusion dye assay. Results presented are mean ± SE. n=3. *P<0.05 (Unpublished data). B. LNCaP-AI cells were plated for 3 days in regular medium before being adjusted to steroid-reduced conditions for 2 days. Cells were then treated with 2.5 μM SVA and/or 1 nM docetaxel for 3 days in steroid-reduced conditions. Cell number was determined with trypan blue exclusion dye assay. Results presented are mean ± SE. n=3. *P<0.05 (Unpublished data) C. LNCaP-AI cells were plated for 3 days in regular medium before being adjusted to steroid-reduced conditions for 2 days. Cells were then treated with 5 μM SVA and/or 500 nM of the CIL-102 derivatives 1, 22, or 23 for 3 days in steroid-reduced conditions. Cell number was determined with trypan blue exclusion dye assay. Results presented are mean ± SE. n=3. *P<0.05 (Unpublished data). D. Chemical structures of CIL-102 derivatives 1, 22, and 23.

with low toxicity toward non-cancerous cells, and also effectively inhibit the tumorigenicity of both CRPCa and docetaxel-resistant CRPC [115]. Thus, these compounds have great potential for utilization in treating docetaxel-resistant CRPCa as a single agent as well as in combination with other types of therapies.

Development of more novel compounds for CRPCa treatment is equally important in this aspect. Additional novel compounds, for example, imidazopyridine derivatives [116] and pregnene analogs [117], have been shown to possess anti-tumor effect on various CRPCa cells under ADT conditions. More recently phase II and III clinical studies have begun to show the efficacy of novel compounds to treat advanced PCa including radioactive compound $^{177}$Lu-PSMA617 [118] in post-docetaxel CRPCa patients and GnRH antagonist Relugolix (Relumina) [119]. Importantly, imidazopyridine compounds exhibit activities toward CRPCa cells as well as NE-like PCa cells at a clinically achievable concentrations (**Figure 3**). The potential of these novel small compound inhibitors deserve further investigation for their utilities in advanced PCa therapy.

*Conclusion and prospective*

In summary, many attempts have been made to reduce the lethality of CRPCa. The search for

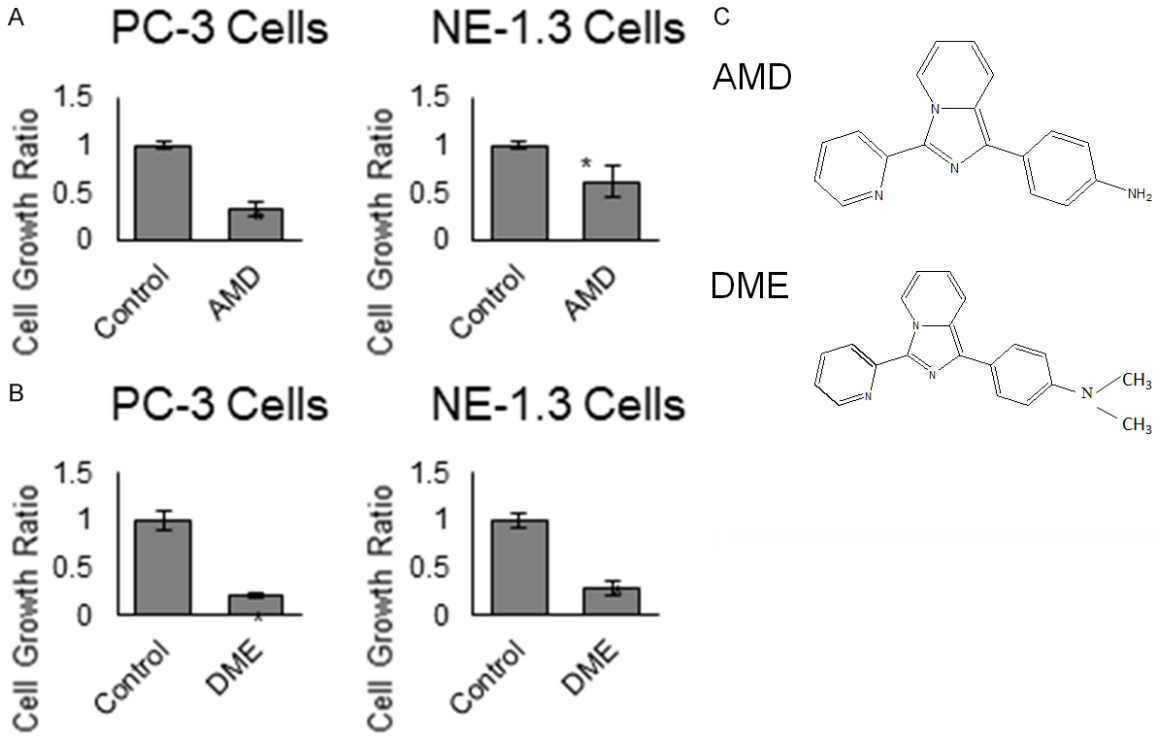


**Figure 3.** Novel Imidazopyridine derivatives on neuroendocrine-like prostate cancer cells. PC-3 and NE-1.3 cells were cultured in steroid-reduced conditions and treated with 10 μM of each compound (A) AMD and (B) DME for 3 days. Both treated and control cells were harvested and cell numbers were determined by trypan blue dye exclusion assay. Results presented are mean ± SE. n=3, *P<0.05. (C) Chemical structures of AMD and DME. (Unpublished data).

improved treatment strategies continues as current therapies are combined together or with new therapeutic agents, as well as precision medicine for specific genetic abnormalities, such as expression of AR-V7. Currently, there has been some progress made in extending a CR PCa patients lifespan, but combinations thus far have not been shown to be safe and effective options to further improve outcomes in CRPCa.

We propose that the next immediate step in the management and treatment of PCa is to make CRPCa as a chronic disease, thus reducing the lethality of this specific type of cancer. Importantly, further studies of combination treatments utilizing ADT, immunotherapy, and docetaxel, as well as studies directed towards precision medicine, are warranted in preclinical and clinical settings. Additionally, the discovery and development of novel compounds, for example, SVA, CIL-102, and imidazopyridine derivatives, as single agents and/or combination usages with efficacy toward CRPCa as well as NE-like PCa cells is imperative. An important treatment combination to be developed is one which targets both the adenocarcinoma and the neuroendocrine PCa cell populations while spare the normal cells from cytotoxicity. Nevertheless, advancements in immunotherapy and the synthesis of novel anticancer agents provide new methods and combinations for the treatment of CRPCa.

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## Disclosure of conflict of interest

None.

## Abbreviations

ADT, Androgen-deprivation therapy; AI, Androgen-independent; AR, Androgen receptor; AS, Androgen-sensitive; ATT, Androgen targeted therapies; CDDO-Me, Bardoxolone-methyl; BETi, Bromodomain extraterminal inhibitors; CRPC, Castration-resistant prostate cancer; CTLA-4, Cytotoxic T-lymphocyte Associated Protein 4; $ET_A$, Endothelin Receptor A; ET-1, Endothelin-1; FABP5, fatty acid binding protein 5; FAK, Focal adhesion kinase; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GnRH, Gonadatropin releasing hormone; GR, Glucocorticoid receptor; HDAC1, Histone deacetylase 1; HRD, Homologous recombination deficiency; IGF, Insulin-like growth factor; LHRH, Luteinizing hormone releasing hormone; mTOR, Mammalian target of rapamycin; mHSPC, Metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; NE, Neuroendocrine; NHEJ, Nonhomologous end-joining; PAcP, Prostatic acid phosphatase; PARP, Poly (ADP-ribose) polymerase; PCa, Prostate cancer; PDX, Patient-derived xenografts; PFS, Progression-free survival; PI3K, Phosphoinositide 3-kinase; PIP5K1a, Phosphatidylinositol-4-phosphate 5-kinase type 1 alpha; PMSA, Prostate-specific membrane antigen; PSA, Prostate-specific antigen; PTEN, Phosphatase and tensin homolog; RANKL, Receptor activator of nuclear factor κB ligand; SNPs, Single nucleotide polymorphisms; SVA, Simvastatin hydroxyl acid; TKI, Tyrosine kinase inhibitor.

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