
Combination Treatment Options for Castration- Resistant Prostate Cancer

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Abstract: Prostate cancer is the most commonly diagnosed solid tumor and the second leading cause of cancer-related deaths in men in the United States. While localized prostate cancer has an excellent prognosis for patients, about one-third of patients are diagnosed with high-risk disease, including metastatic cancer. The 5-year survival rate of metastatic prostate cancer is only about 30%. Due to the androgen dependence of prostate cancer cells, androgen-deprivation therapy is the standard of care for metastatic prostate cancer, which includes both surgical and medical approaches. Nevertheless, androgen-deprivation therapy in general

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is not curative; patients can develop castration-resistant prostate cancer. Despite current chemotherapies, including the utilization of novel androgen signaling inhibitors and immunotherapy, patients still succumb to the disease. Hence, castration-resistant prostate cancer is a lethal disease. Combination treatment is a strategy for treating this lethal disease and thus will be the focus of discussion in this chapter.

Keywords: androgen deprivation therapy; castration-resistant prostate cancer; chemotherapy; combination treatment; immunotherapy

INTRODUCTION

Prostate cancer is the most commonly diagnosed solid tumor, and the second leading cause of cancer-related deaths in men in the United States (1). Patients with localized prostate cancer have an excellent prognosis (2), however, up to 15% of prostate cancer patients are diagnosed with high-risk disease, i.e., disease with prostate-specific antigen (PSA) levels of over 20 ng/mL and Gleason scores of 8 or higher (3). The 5-year survival of patients with metastatic prostate cancer is about 30%.

Androgens are essential for normal prostate development and differentiation but are also involved in prostate cancer initiation and progression. Hence, androgen-deprivation therapy (ADT), which blocks androgen receptor (AR) signaling, is the standard of care for treating metastatic prostate cancer (4, 5). Nevertheless, ADT is not curative; most prostate cancer cells eventually become resistant to ADT, becoming a castration-resistant (CR) phenotype. The CR phenotype of prostate cancer cells can be achieved through a variety of mechanisms, including AR elevation to sustain AR signaling with residual levels of circulating androgens, AR mutation in the ligand-binding site causing receptor promiscuity, truncation of AR structure generating constitutively activated variants, intra-tumoral androgen biosynthesis for intracrine AR activation, and/or ligand-independent AR activation by growth factor signaling pathways, such as ErbB-2 (6–14).

Neuroendocrine (NE)-like prostate cancer cells can also support the CR phenotype. In a normal prostate, authentic NE cells are a minor population; in cancer, it makes up less than 5% of total prostate cancer cases. Nevertheless, up to 60% of CR tumors are found to contain the NE-like cells (15–17), i.e., cells that express NE biomarkers. NE-like cells undergo trans-differentiation from adenocarcinoma cells during therapies, especially prolonged ADT, and can support prostate cancer cell survival and progression under ADT through secretion of growth factors (15–17). Currently, there are no FDA-approved agents that can effectively treat patients with CR prostate cancer, authentic NE prostate cancer, or NE-like prostate cancer. The current FDA-approved drugs either alone or in combination can only extend the life of a patient by a few months. In this chapter, we discuss current treatments and summarize the recent completed combination trials as well as ongoing emerging combination trials for the management of CR prostate cancer.

CURRENT TREATMENT STRATEGIES FOR PROSTATE CANCER

Currently, treating prostate cancer patients is a well-organized roadmap according to FDA guidelines, however, none of these options are curative and the disease will often progress after a short period of time. Below, we discuss the current therapeutic strategies utilized for each stage of prostate cancer including surgery and radiotherapy, ADT, taxanes, and sipuleucel-T.

Surgery and radiotherapy

While watchful waiting and active surveillance are the preferred method of choice for men with certain low-risk prostate cancer (18), several other strategies are available for localized disease. Surgery, as well as external beam radiotherapy (EBRT) and brachytherapy are all common treatment regimens for localized prostate cancer. EBRT is often utilized in patients with high-risk disease, while brachytherapy is effective for patients with low-risk disease (19, 20). Primary surgery is a viable treatment option for prostate cancer and allows for histopathological analysis of the tumor (21). Surgery has been shown to be more beneficial than watchful waiting in terms of mortality, disease progression and metastasis (22). To date, surgery and radiotherapy remain the first line of defense against localized prostate cancer (Figure 1). However, it is important to note that there is no difference in mortality rate between active surveillance, surgery, or radiotherapy for low-risk patients (23). Nevertheless, these treatment options are not 100% effective, as relapse of metastatic disease and progression to CR prostate cancer can occur. Some completed clinical trials are shown in Table 1, while those ongoing emerging combination trials are in Table 2.

Androgen deprivation therapy (ADT)

ADT is the standard of care for the treatment of metastatic prostate cancer and can be carried out by various approaches, including orchiectomy, chemical castration, antiandrogen therapy and/or combinations thereof. Chemical castration employs chemicals to reduce testosterone production in the testes thus preventing androgen stimulation of prostate cancer cells. Currently, the chemicals for castration include luteinizing hormone releasing hormone (LHRH) or gonadotropin releasing hormone (GnRH) agonists or antagonists (1, 5).

Typically, androgens are primarily produced in the testes and adrenal glands. Unexpectedly, about 50% of CR prostate cancer cells exhibit intracrine regulation, i.e., they can perform *de novo* testosterone biosynthesis from cholesterol (10, 14). Hence, a novel avenue for treating CR prostate cancer is to inhibit androgen biosynthesis in those cells. To enhance the efficacy of ADT, antiandrogens can be utilized in conjunction with chemical or surgical castration, which will further reduce androgen stimulation of prostate cancer cells by mitigating the ability of cancer cells to synthesize or utilize androgen signaling. One class of antiandrogens are the androgen biosynthesis inhibitors, such as abiraterone acetate. These agents abrogate the activity of CYP17A, an enzyme involved in two crucial steps of androgen biosynthesis; therefore, these compounds are effective treatment options

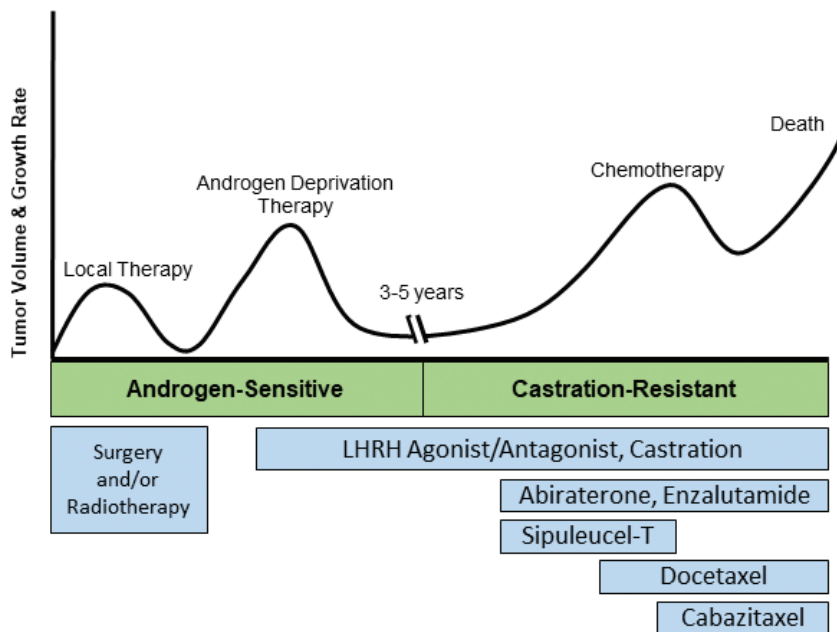


Figure 1. Prostate cancer progression and treatment options. Most prostate cancer cases are detected prior to its spread to other parts of the body. Surgery and radiotherapy can treat localized tumors. The standard-of-care treatment for metastatic prostate cancer is ADT. Nevertheless, most metastatic prostate cancer will relapse, i.e., the development of CR prostate cancer. The CR prostate cancer can be initially treated with antiandrogens such as enzalutamide, abiraterone or with immunotherapy agent such as Sipuleucel-T. Upon further progression of the disease, docetaxel and cabazitaxel can be used, in addition to abiraterone and enzalutamide, if the patient has not previously been treated with these agents. Unfortunately, these CR prostate cancer treatments will only prolong a patient's life by less than one year before they succumb to the disease (1–3).

for prostate cancer that is capable of intra-tumoral androgen biosynthesis. A phase III clinical trial (NCT00887198) in chemotherapy-naïve CR prostate cancer patients showed a 3.7 month increase in overall survival as well as increased time to initiation of chemotherapy and PSA progression upon abiraterone treatment (24). The phase III trial (NCT00638690) of abiraterone after progression on docetaxel prolonged the survival of patients by four months and increased progression-free survival (PFS) by two months (25). These two studies led to the FDA approval of abiraterone acetate in 2011 for treatment of CR prostate cancer in chemotherapy-naïve patients as well as upon docetaxel resistance.

Another class of antiandrogens is the AR blocker, an AR antagonist that prevents androgen receptors from nuclear translocation and DNA binding. AR blocker bicalutamide (Casodex) and second-generation agent enzalutamide (Xtandi) were FDA-approved in 1995 and 2012, respectively, for the treatment of prostate cancer. The phase III AFFIRM trial (NCT00974311) determined that enzalutamide prolongs the survival period by five months in CR prostate cancer patients, post-docetaxel treatment (26). In the PREVAIL phase III trial

TABLE 1
A list of completed clinical trials of combination treatments for CR prostate cancer

Clinical Trial	Primary Anticancer Agent	Secondary Anticancer Agent	Result	Reference
NCT00002874	ADT	Radiation	Reduced mortality and metastasis compared to ADT alone	Shipley et al. 2017 (39)
ISRCTN01534787	ADT	Radiation	Reduced 10-year mortality rate and PSA recurrence	Widmark et al. 2009 (36)
NCT00002633/ ISRCTN24991896	ADT	Radiation	Reduced mortality rate	Warde et al. 2011 (37)
GETUG-AFU 15 (NCT00104715)	ADT	Docetaxel	Increased Survival by 5.7 Months; Toxic to Patients	Gravis et al. 2013 (44)
CHAARTED (NCT00309985)	ADT	Docetaxel	Increased Survival by 13.6 Months Compared to ADT Alone	Sweeney et al. 2015 (45)
STAMPEDE (NCT00268476)	ADT	Docetaxel	Increased Survival by 10 Months; Toxic to Patients	James et al. 2016 (46)
STAMPEDE (NCT00268476)	ADT	Zolendronic Acid	No Survival Benefit	James et al. 2016 (46)
NCT01972217	Abiraterone	Olaparib	Increased survival by 5.6 months compared to abiraterone alone	Clarke et al. 2018 (50)
ERA 223 (NCT02043678)	Abiraterone	Radium 223	No Survival Benefit	Smith et al. 2019 (43)
	Abiraterone	Enzalutamide	No Survival Benefit	Efstathiou et al. 2020 (90)
NCT01807065	Sipuleucel-T	Radiation	Radiation does not affect delivery or effectiveness of Sipuleucel-T	Twardowski et al. 2017 (65)
	Sipuleucel-T	Docetaxel	Increases Survival by 10 Months	Petrylak 2007 (66)

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TABLE 1
A list of completed clinical trials of combination treatments for CR prostate cancer (Continued)

Clinical Trial	Primary Anticancer Agent	Secondary Anticancer Agent	Result	Reference
NCT00861614	Ipilimumab	Radiation	No Survival Benefit	Kwon et al. 2014 (70)
NCT02484404	Durvalumab	Olaparib	PSA and radiographic response	Karzai et al. 2018 (71)
NCT00091364	Docetaxel	Thalidomide and Bevacizumab	Median Survival Time of 28.2 Months, Well-tolerated	Ning et al. 2010 (72)
MAINSAIL (NCT00988208)	Docetaxel	Lenalidomide	Reduced Overall Survival	Petrylak et al. 2015 (73)
NCT00110214	Docetaxel	Bevacizumab	No Overall Survival Benefit	Kelly et al. 2012 (74)
READY (NCT00744497)	Docetaxel	Dastinib	No Survival Benefit	Araujo et al. 2013 (80)
NCT01685125	Abiraterone	Dastinib	No Survival Benefit	Dorff et al. 2019 (81)
TRAPEZE (NCT00554918)	Docetaxel	Zoledronic Acid	Reduced Bone Metastasis, No Survival Benefit	James et al. 2016 (82)
SYNERGY (NCT01188187)	Docetaxel	Custirsen	No Survival Benefit	Chi et al. 2017 (83)
AFFINITY (NCT01578655)	Cabazitaxel	Custirsen	No Survival Benefit	Beer et al. 2017 (84)

TABLE 2 Ongoing clinical trials for combination therapies in prostate cancer

Clinical Trial	Primary Anticancer Agent	Secondary Anticancer Agent	Current Status	Phase
LACOG-0415 (NCT02867020)	Abiraterone	Apalutamide	Recruiting	2
LATITUDE	Abiraterone	ADT	Active, not recruiting	3
NCT03732820	Abiraterone	Olaparib	Recruiting	3
NCT00450463	ADT	PROSTVAC	Completed (No compiled results)	2
NCT01867333	ADT	PROSTVAC	Active, not recruiting	2
NCT02913196	Apalutamide	Abiraterone, Docetaxel	Recruiting	1
NCT01420250	Cabazitaxel	Radiation, ADT	Active, not recruiting	1
NCT02649855	Docetaxel	PROSTVAC-IF	Active, not recruiting	2
NCT0155242	Docetaxel	Aneustat	Completed (No compiled results)	1
NCT03834506	Docetaxel	Pembrolizumab	Recruiting	3
NCT02788773	Durvalumab	Tremelimumab (Anti-CTLA-4)	Active, not recruiting	2
NCT02207504	Enzalutamide	Crizotinib (TKI)	Active, not recruiting	1
NCT03834493	Enzalutamide	Pembrolizumab	Recruiting	3
NCT02280356	ERBT	Brachytherapy	Active, not recruiting	2
NCT01688492	Ipilimumab	Abiraterone	Active, not recruiting	1 and 2
NCT03488810	LHRH	Apalutamide, Radiation	Not yet recruiting	3
NCT03810105	Olaparib	Durvalumab	Recruiting	2

Table continued on following page

TABLE 2 Ongoing clinical trials for combination therapies in prostate cancer (Continued)

Clinical Trial	Primary Anticancer Agent	Secondary Anticancer Agent	Current Status	Phase
NCT02861573	Pembrolizumab	Various Therapeutics	Recruiting	1
NCT03910660	Pembrolizumab	BXCL701 (immune activator)	Recruiting	1 and 2
NCT03805594	Pembrolizumab	177Lu-PSMA-617 (Radioconjugated PSMA)	Recruiting	1
NCT04191096	Pembrolizumab	ADT, Enzalutamide	Recruiting	3
NCT03315871	PROSTVAC	MSB0011359C (anti-PD-L1 and TGF- β) CV301 (anti-CEA and Muc-1)	Recruiting	2
PEACE III (NCT02194842)	Radium 223	Enzalutamide	Recruiting	3
NCT03574571	Radium 223	Docetaxel	Recruiting	3
NCT03737370	Radium 223	Docetaxel	Recruiting	2
NCT02463799	Sipuleucel-T	Radium 223	Active, not recruiting	2

(NCT01212991), enzalutamide was shown to delay radiographic disease progression in chemotherapy-naïve patients with 65% of patients disease-free for 12 months compared to 14% with the placebo. This trial also showed an improved overall survival of two months with enzalutamide treatment (27). Interestingly, the STRIVE trial (NCT01664923) in CR prostate cancer patients showed that enzalutamide had a significantly higher PFS at 19.4 months compared to 5.7 months with bicalutamide, and increased time to PSA progression (28). These results have led to the popularity of enzalutamide over bicalutamide in treating prostate cancer in recent years. Recently, apalutamide (Erleada) was approved by the FDA for treatment of non-metastatic CR prostate cancer due to the success of the SPARTAN trials (NCT01946204) which demonstrated that apalutamide could prolong metastasis-free survival by over two years (29).

While ADT has been the gold standard for treating metastatic prostate cancer since 1941 (4), and is a life-long treatment, this therapy eventually fails. Therefore, ongoing studies are currently analyzing potential combination treatments to reduce the risk of recurrence after ADT or to treat CR prostate cancer.

Taxanes

Taxanes are anticancer agents that stabilize microtubules to prevent cell division and mitosis, and thus result in cell death of rapidly dividing tumor cells. Paclitaxel (Taxol) is the first and most common of these anti-microtubule agents for advanced cancer treatments (FDA approved in 1998). Docetaxel (Taxotere) is one of the few FDA-approved drugs for CR prostate cancer. In combination with prednisone, docetaxel has been shown to provide a survival benefit of 2.4 months compared with mitoxantrone. Cabazitaxel (Jevtana) is another member of the taxane family used to combat docetaxel resistance in several cancers; however, resistance to both taxanes can occur via upregulation of ABC1 transporter P-glycoprotein (30, 31). It should be noted that taxanes are highly toxic, often leading to severe side effects in patients (30). Hence, the development of more selective compounds continues.

Sipuleucel-T

Sipuleucel-T is an immunology product of peripheral blood mononuclear cells harvested by leukaphoresis. The dendritic cells are co-cultured with PA2024, a recombinant fusion protein of prostatic acid phosphatase (PACP) and granulocyte-macrophage colony-stimulating factor (GM-CSF) before being infused into the patient. PACP is a prostate epithelia-specific differentiation antigen (11–13) expressed in about 95% of prostate cancers, while GM-CSF stimulates dendritic cell maturity and activation. The infusion of these autologous dendritic cells stimulates the patient's immune system, particularly antitumor T-cells, to target the cancer cells. This immunotherapy has been shown to provide a survival benefit of 4.5 months in patients with CR prostate cancer and is well tolerated by patients (32, 33). The IMPACT trial demonstrated that patients received the greatest effects from Sipuleucel-T when they had low PSA levels (34). Sipuleucel-T was approved by the FDA in 2010 as a first- or second-line therapy for the treatment of asymptomatic or minimally symptomatic metastatic CR prostate cancer before or after

docetaxel therapy (35). Currently, studies continue to expand the potential pool of immunological products that can be utilized for treating prostate cancer, including T cell activator ipilimumab, and anti-ErbB-2 antibodies trastuzumab and pertuzumab among others.

COMBINATION TREATMENTS FOR CASTRATION-RESISTANT PROSTATE CANCER

Prostate cancer often develops resistance to, and progress on, the various therapies discussed above. Combination therapies with current treatment strategies could effectively suppress the tumor and increase lifespan of patients. Most combinations utilize ADT or androgen deprived conditions, and combination therapies with radiation, chemotherapy, and immunotherapy show promise.

Combination of radiation with ADT

As the standard-of-care treatment of metastatic prostate cancer, ADT has more potential treatment combinations compared to other FDA-approved drugs for CR prostate cancer. An increasing number of patients with high-risk disease are treated with ADT and radiation therapy to prevent or delay the development of CR prostate cancer. The use of ADT before, during, and after radiation therapy is now highly encouraged for patients with intermediate- or high-risk disease. Overall survival, disease-free survival, distant metastasis-free survival, and biochemical-free survival rates all increase upon combination of ADT with radiotherapy compared to radiotherapy alone (36–39). The detailed synergistic mechanism of androgen suppression with local radiotherapy remains under investigation. One proposed mechanism is that AR suppression may lead to a downregulation of non-homologous end-joining (NHEJ) and further sensitization of prostate cancer cells to radiation (40). Nevertheless, it should be noted that the combination treatment of ADT and radiotherapy may cause the adverse increase of NE-like prostate cancer cell populations, therefore increasing the potential for resistance of CR prostate cancer to treatments (41). Patients can also be overtreated by the combination of ADT and radiotherapy. Hence, the optimal timing and duration of this combination should be further studied to reduce adverse effects (36–39). There is an emerging role of prostate radiotherapy in advanced and metastatic disease based upon the STAMPEDE trial (NCT00268476), wherein patients were randomized to receive radiation therapy to the prostate despite a diagnosis of metastatic disease (36–39). In that study, while it showed no overall survival benefits, patients with low volume metastatic disease were shown to have an overall survival advantage.

Radium-223 dichloride (radium-223, Xofigo) deserves attention. Radium-223 emits low levels of alpha particle radiation resulting in DNA double-strand breaks and cell death. It is also a “calcium mimetic”. The ALSYMPCA trial (the Alpharadin in Symptomatic Prostate Cancer Patients, NCT00699751) with Radium-223 alone in treating metastatic, CR prostate cancer showed a significant efficacy in overall survival (14.9 months vs. 11.3 months) in all patient subgroups with significantly fewer adverse events than placebo patients (42). Nevertheless, the ERA

223 trial, which combined abiraterone with Radium-223 found no improvement in skeletal event-free survival; instead, there was an increased occurrence of bone fractures with this combination (43). Hence, osteoprotective agents have been suggested and studies continue with combinations of Radium-223 with enzalutamide (PEACE III trial). The benefits of combination treatment of Radium-223 with additional therapies beyond ADT remain under further investigation for CR prostate cancer.

Combination of chemotherapy with ADT

ADT with chemotherapy is another potential combination treatment option to target both androgen-sensitive (AS) and androgen-independent (AI) prostate cancer cells. The GETUG-AFU 15 trial (NCT00104715) revealed that ADT with docetaxel increased survival by 5.7 months, however, this combination increases severe side effects as well as deaths due to the toxicity of docetaxel (44). The CHAARTED trial (NCT00309985) found a statistically significant increase in overall survival with this combination, extending a patient's life by 13.6 months longer than ADT alone as well as providing an 8.5 month increase in time to biochemical, symptomatic, and radiographic progression (45). The STAMPEDE trial (NCT00268476) confirmed that the combination of ADT and docetaxel provides a survival benefit of about 10 months compared to ADT alone as well as an increase in PFS seen in the CHAARTED trial, and confirmed the high toxicity found in the GETUG-AFU 15 trial. Additionally, the STAMPEDE trial showed that zoledronic acid (Zometa), an agent that slows osteoclast activity, had little effect on the survival of prostate cancer patients in combination with ADT (46). Short and long-term toxicities for docetaxel are real, and efforts are needed to find alternative agents or mitigate toxicity.

Extracellular signal-regulated kinase (ERK) inhibitors are a possible alternative to reduce taxane toxicity. ERK inhibitors can increase the potency of docetaxel on CR prostate cancer cells (47). Hence, ERK inhibitors can be employed with docetaxel under ADT, which will reduce the docetaxel dosage as well as its toxicity while achieving a similar therapeutic index (47). Future clinical trials of this new combination may shed more light on this subject.

Other chemotherapeutics for combination treatment of CR prostate cancer are Poly (ADP-ribose) polymerase (PARP) inhibitors. Two pre-clinical models showed synergistic anticancer effects of Olaparib and enzalutamide in androgen-sensitive and -independent cell lines and in xenograft models (48, 49). The combination of abiraterone and Olaparib initially in a phase II trial (NCT01972217) found a 5.6 month increase in PFS in metastatic CR prostate cancer patients compared to abiraterone alone (50). A Phase III trial (NCT03732820) for this combination has had significant outcomes, including extending survival in a biomarker selected population. Hence, both inhibitors Rucaparib and Olaparib have received FDA approval for treating metastatic CR prostate cancer with specific genetic alterations.

Combination of immunotherapy with ADT

Immunotherapy, namely cancer vaccines, represent another promising treatment to combine with ADT. One such option is a PSA-targeted poxviral vaccine,

PROSTVAC-IF, which was initially reported to reduce death rates by 44% and provide prostate cancer patients with an 8.5 month increase in survival alone (51). Nevertheless, further studies showed that PROSTVAC-IF alone did not effectively increase overall survival (52). Prostate cancer-specific immunotherapy is thus being explored as part of combination treatments. Currently, two phase III clinical trials are ongoing which analyze the survival effects of the combination of PROSTVAC-IF with ADT (NCT00450463, NCT01867333).

Other preclinical studies include the analysis of CAR-T cells targeted to Muc1, a glycoprotein that is often expressed on the surface of prostate cancer cells but not in non-cancerous tissues. Studies found that Muc1 CAR-T cells effectively reduce prostate cancer tumor growth in combination with the antiandrogen flutamide. The study further ensured that flutamide does not negatively affect CAR-T-Muc1 activity (53). Combination therapy can also be utilized through targeting prostate-specific membrane antigen (PSMA); Murga *et al.* (54) showed that an anti-PSMA antibody conjugated to anti-microtubule agent monomethyl auristatin E is effective against prostate cancer cells that express PSMA. The combination of this antibody-drug conjugate with enzalutamide or abiraterone resulted in the synergistic inhibition of prostate cancer growth, as the antiandrogens increased the expression of PSMA. Recent advances determined that insulin-like growth factor (IGF) also contributes to castration-resistance. Hence, targeting PSMA with the IGF-1/IGF-2 neutralizing antibody xenuzumab in combination with enzalutamide has been successful in inhibiting prostate cancer growth in preclinical models (55).

Combination of targeting androgen biosynthesis and ADT

Several studies have investigated combinations with androgen biosynthesis inhibitors beyond those traditionally utilized in ADT for CR prostate cancer treatment. Shutting down androgen signaling with concurrent abiraterone and enzalutamide treatment was found to be of no benefit (54). Alternately, while combining abiraterone and LHRH agonists could reduce tumor burden, it produced no change to patient outcomes. Unexpectedly, the study discovered the upregulation of glucocorticoid receptor (GR) in response to androgen blockage, suggesting a potential mechanism of resistance (56). Hamid *et al.* showed that the combination of dutasteride, a 5 α -reductase inhibitor, and enzalutamide resulted in a synergistic inhibition of prostate cancer cell growth in culture (57).

Analyses of cohort studies revealed that the usage of statins (cholesterol-lowering drugs) correlated with reduced risk of several cancers, including prostate cancer and its advanced stage progression, as well as increases in survival rates. This could be due to the fact that cholesterol is the unique source of steroid biosynthesis, including testosterone, which prostate cancer cells rely on. Several studies have shown that the combination of ADT and statins reduces the risk of advanced prostate cancer and increases the survival rates of prostate cancer patients (58–60). The combination of statins and abiraterone exhibits an added effect of cell growth inhibition (61). Interestingly, a novel statin derivative simvastatin hydroxyl acid (SVA) appears to be more potent than its parent compound simvastatin toward CR prostate cancer cells, with minimal

toxicity (62). Further, SVA exhibits an added inhibitory effect on CR prostate cancer cells in cultures in combination with abiraterone acetate or docetaxel (personal observation). Due to promising *in vitro* studies, the potential clinical usage of SVA in combination with ADT for treating CR prostate cancer warrants further investigation.

Combination of radiation therapy with immunotherapy under ADT

Radiation was initially thought to be immunosuppressive, thus combining immunotherapy treatments with radiation was considered implausible. Nevertheless, radiation is not as detrimental to the immune system as initially thought and can even stimulate an immune response to a variety of cancers (63). Kwilas *et al.* first showed that there was evidence of synergy in the combination of immunotherapy and radiation (64). Subsequently, many studies have tailored this combination to their specific cancer of interest.

In the context of prostate cancer, a phase II trial (NCT01807065) analyzed the combination of sipuleucel-T and radiation in men with CR prostate cancer. It was shown that radiation therapy did not affect product parameters or delivery of sipuleucel-T therapy (65). Clinical trials of this combination are ongoing to determine if sipuleucel-T and radiation therapy provide a survival benefit to patients with CR prostate cancer.

Combination of chemotherapy with immunotherapy under ADT

A phase III trial of Sipuleucel-T combined with docetaxel has been conducted, in which it was found there was about a 10 month increase in overall survival when patients were treated with docetaxel several months after Sipuleucel-T treatment (66). In parallel, efforts are still ongoing to get FDA approval of PROSTVAC-IF for treatment of prostate cancer or CR prostate cancer. A phase III clinical trial that combines PROSTVAC-IF with docetaxel (NCT02649855) is underway.

Clinical trials with immune checkpoint inhibitors as a single agent have been unsuccessful (67). Therefore, studies have looked to combinations with these molecules. A phase I/II study in CR prostate cancer analyzed the effects of ipilimumab, a monoclonal antibody that blocks the binding of immunoregulatory molecule Cytotoxic T-lymphocyte Associated Protein 4 (CTLA-4) to its ligand to enhance T cell activation and proliferation (68). Trials showed the combination of ipilimumab and radiation therapy were well tolerated by patients, and had effective antitumor properties, including a 50% reduction in PSA levels and stable disease (69). Unfortunately, a phase III trial showed that this combination provided no survival advantage in patients with docetaxel-resistant prostate cancer (70). Interestingly, the anti-PD-L1 antibody durvalumab has had some success in the clinical setting. A small study by Karzai *et al.* determined that durvalumab with Olaparib was effective against CR prostate cancer with a high mutational burden in DNA damage response proteins (71). Many other studies with immunotherapies, including pembrolizumab and durvalumab, are currently in progress with combination therapies, including Olaparib, AKT inhibitors and others, for CR prostate cancer treatment.

Combinations with docetaxel under ADT

Treatment combinations with docetaxel have had mixed results on patient survival. For example, thalidomide in combination with anti-VEGF-A antibody bevacizumab and docetaxel effectively reduced PSA levels in a phase II clinical trial (NCT00091364) (72). A phase III trial found that the combination of lenalidomide with docetaxel reduced patient survival compared to docetaxel alone due to toxicity (73). While adding anti-angiogenic agent bevacizumab to this particular combination resulted in significant reduction in PSA and disease, a phase III trial (NCT00110214) of docetaxel with prednisone and bevacizumab showed that there was no difference in overall survival in treatments with or without bevacizumab (74).

Efforts have continued on developing new compounds and combinations. As for pre-clinical models, the combination of fatty acid binding protein 5 (FABP5) inhibitors and docetaxel or cabazitaxel shows synergistic cytotoxic effects *in vitro* and *in vivo* (75). Similarly, docetaxel nanoparticles in combination with the receptor activator of nuclear factor κ B ligand (RANKL) monoclonal antibody, denosumab, led to an increase in survival and reduction in tumor burden and bone metastasis in prostate cancer xenograft animal model (76). Combination of docetaxel with anti-microtubule agent mebendazole was found to be effective against prostate cancer; further analysis showed enhanced anti-tumor activity without toxicity (77).

Novel small molecule inhibitors as single agents and their combinations

Small molecule inhibitors are potentially useful agents against prostate cancer, either as single agents or in combination with ADT. Phosphatase and tensin homolog (PTEN) loss is common in advanced prostate cancer, thus targeting the AKT/mammalian target of rapamycin (mTOR) pathway—a PTEN-regulating pathway—could represent a viable therapeutic option (78). Preclinical models showed that inhibition of phosphoinositide 3-kinase (PI3K) or AKT with small molecules AZD8186 or AZD5363, respectively, in combination with ADT resulted in enhanced growth suppression of xenograft prostate cancer tumors (79). Nevertheless, AKT inhibitors can cause an elevation of PSA level (62). Hence, alternate biomarker(s) for this treatment should be developed.

Small molecule inhibitors have also been combined with docetaxel with mixed results. Due to the frequent alterations in kinase signaling pathways upon progression to the CR phenotype (8, 47), inhibition of tyrosine kinases and corresponding downstream molecules was attempted as a treatment for CR prostate cancer. While 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, the phase III READY trial (NCT00744497) revealed no improvement in patient survival (80). The combination of dasatinib and abiraterone also did not show any benefit to patients (81). Phase III TRAPEZE trial (NCT00554918) combining docetaxel with strontium-89, zoledronic acid, or both showed significantly reduced bone metastasis while having no effect on overall patient survival upon treatment with

zoledronic acid and docetaxel (82). 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 (83). The AFFINITY trial (NCT01578655) also resulted in no improvement for patient survival with a combination of custirsen and cabazitaxel (84).

An interesting small molecule is Aneustat (OMN54), a multivalent botanical drug undergoing a phase I clinical trial (NCT01555242) for advanced cancers, primarily lymphomas. Pre-clinical studies revealed that docetaxel and Aneustat treatment reduced the growth of prostate cancer LNCaP C4–2 cell line and LTL-313H prostate cancer tissue mouse xenografts with potential synergistic effects via inhibition of AR, AKT phosphorylation and Bcl-2 expression (85). Hence, it is proposed that combination of docetaxel with Aneustat could further extend the life of prostate cancer patients. Meanwhile, early *ex vivo* studies showed that the combination of docetaxel and dopamine D2 receptor agonist bromocriptine effectively reduced tumor growth and bone metastasis in prostate cancer xenograft models (86), a potential novel combination for prostate cancer treatment.

Development of more novel compounds for CR prostate cancer treatment is equally important. For example, statin derivative SVA, imidazopyridine derivatives, and pregnene analogs (87–89) have been shown to be effective against CR prostate cancer cells under androgen-reduced conditions. It is imperative to continue the efforts on investigating their utilities in CR prostate cancer therapy.

CONCLUSION

In summary, while no single agent or agent combinations are shown to cure CR prostate cancer patients, significant progress continues to be made and patients are living longer with advanced prostate cancer. We propose that the next immediate step in the management of metastatic prostate cancer is to make CR prostate cancer a chronic disease, while improving the patient's quality of life. Together, these will accomplish our immediate goal of reducing the lethality of prostate cancer. While the advancement of current combinations is important, it is also imperative to develop novel compounds that can target both the adenocarcinoma and the neuroendocrine prostate cancer cell populations, while sparing normal cells from cytotoxicity.

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