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Novel mechanism-based therapeutics for androgen axis blockade in castration-resistant prostate cancer

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Abstract

PURPOSE OF REVIEW—Understanding the mechanisms by which castration-resistant prostate cancer progresses provides an opportunity to identify novel therapeutic strategies to treat this disease. This understanding has led to approaches to attack prostate cancer's androgen axis in unique ways. This review will examine the classes of novel therapies for androgen axis blockade in castration-resistant prostate cancer, with a particular focus on the unique characteristics of drugs in various stages of clinical development.

RECENT FINDINGS—The success of abiraterone and enzalutamide has stimulated multiple investigations into novel approaches to attack the androgen-signaling pathway. Drugs under development include cytochrome P17 inhibitors with 17,20-lyase specificity, androgen receptor antagonists that are active against mutated and constitutively-active splice variant forms of the protein, androgen receptor degraders, and bromodomain/BET inhibitors that prevent chromatin binding of activated receptors. The clinical development of several of these experimental agents is reviewed.

SUMMARY—Given the unique mechanisms of action for drugs in development, and the possibility that the novel agents may be active in the setting of common resistance mechanisms, treatment options for patients are likely to expand greatly in the coming years. Future studies should prioritize combinations of agents with unique mechanisms of action to optimize outcomes for patients, and should rely on precision-medicine approaches to target known molecular alteration.

Keywords

metastatic prostate cancer; antiandrogens; mechanisms of action; clinical trials

1 Introduction

Novel approaches for targeting the androgen-signaling pathway have led to new and promising treatments for patients with castration-resistant prostate cancer (CRPC) in recent years. While nearly all patients have an initial response to androgen deprivation therapy

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(ADT), most tumors adapt and continue to use the androgen-signaling pathway for growth despite castrate levels of testosterone (typically defined as serum testosterone concentrations <50 ng/dl). It is in this space that drugs designed to attack the androgen-signaling pathway using unique mechanisms are leading to new treatments for patients. Multiple compounds are in clinical development, including drugs that are already FDA-approved based upon extended survival for patients with CRPC. This review will examine novel compounds and approaches for treating prostate cancer, with a focus on their mechanisms of androgen signaling blockade.

1.1 Androgen signaling in prostate cancer

Androgen signaling is critical to prostate cancer growth and progression. Much work has focused on the mechanisms by which the androgen-signaling axis adapts to castrate levels of testosterone (1), and knowledge of these adaptive resistance mechanisms informs strategies for novel targeted agents for CRPC (2, 3). The androgen receptor (AR) can be overexpressed due to gene amplification and stabilization of mRNA, allowing for AR signaling to occur despite low levels of testosterone. Mutations in AR can result in receptors that can bind to other ligands besides testosterone, and mutations convert the action of antiandrogens from antagonist into agonists. Splice variants of the AR mRNA can be produced that allow for ligand-independent signaling. Outside of changes in AR, intratumoral testosterone production to restore effective testosterone levels to non-castrate levels can occur through upregulation and overexpression of enzymes needed to produce testosterone from steroid precursors. These principles of sustained androgen axis signaling in CRPC have been recently reviewed(4).

2 Androgen synthesis inhibitors

Medical or surgical castrating therapies effectively eliminate testosterone originating from the testes. However, androgens are also synthesized to a lesser degree in adrenal tissue, as well as intratumorally (5). Historically, treatments administered to patients with CRPC that suppress adrenal synthesis of androgens have led to tumor responses. Agents that have been used previously include corticosteroids (through adrenal suppression) (6) and high-dose ketoconazole (through inhibition of adrenal enzymes involved in androgen biosynthesis) (7). While ketoconazole and corticosteroids are blunt tools given their relatively non-specific modes of action, their modest success has led to investigation of more elegant compounds to use clinically in prostate cancer.

2.1 Abiraterone

The discovery and FDA-approval of abiraterone as the first hormonal agent to increase survival for patients with CRPC serves as a proof-of-concept that targeting the androgen-signaling pathway in CRPC is fruitful. Abiraterone is an orally bioavailable small molecule steroid that is a potent inhibitor of cytochrome P17 (CYP17), an enzyme critical in biosynthesis of steroid hormones. The pharmacodynamic studies of abiraterone demonstrated that testosterone levels were suppressed to undetectable levels (<0.1 ng/dl) (8), thus achieving profound suppression of testosterone compared to traditional ADT alone.

Abiraterone functions by interference with steroid metabolism (9). Normally in the adrenal glands, ACTH stimulates metabolism of the steroid precursor pregnenolone. Pregnenolone can be further metabolized to aldosterone or to 17OH-pregnenolone, a common precursor for cortisol and testosterone. The action of 17 α -hydroxylase converts pregnenolone to 17OH-pregnenolone, and 17,20-lyase further converts this product to dehydroepiandrosteredione (DHEA). DHEA is subsequently converted to an intermediary and finally testosterone. Abiraterone is a potent inhibitor of the 17 α -hydroxylase and 17,20-lyase enzymatic functions of CYP17. Recent preclinical work has also identified 4-abiraterone, an active metabolite of abiraterone, that further inhibits 3 β -HSD, CYP17A1, and 5 α -reductase (10). In the presence of ACTH stimulation and abiraterone, pregnenolone is shunted to mineralocorticoid synthesis. Abiraterone used without replacement corticosteroids to suppress ACTH results in a syndrome of mineralocorticoid excess. Abiraterone thus was studied in conjunction with corticosteroids in its clinical development.

Abiraterone, in combination with prednisone, was approved by the FDA in 2011 after a pivotal phase III trial demonstrated improved survival compared to prednisone alone (11). In that study, 1195 patients with metastatic CRPC with disease progression after docetaxel chemotherapy were randomized to abiraterone 1000mg daily and prednisone 5mg twice daily versus placebo and prednisone (12). Patients receiving abiraterone had superior overall survival (14.8 vs. 10.9 months), superior progression-free survival (5.6 vs 3.6 months), and superior >50% PSA response rates (29% vs 6%). A similarly designed study in chemotherapy-naïve patients with metastatic CRPC showed benefit as well, with a median overall survival difference of 4.3 months for abiraterone plus prednisone compared to placebo plus prednisone (34.7 vs 30.3 months) (13, 14). Despite the co-administration of prednisone with abiraterone, adverse events were more common in the abiraterone cohorts—in particular mineralocorticoid excess-related side effects. These adverse events included hypokalemia, hypervolemia, hypertension, cardiac arrhythmias, and liver-function abnormalities. Abiraterone currently holds FDA-indications for patients with CRPC either before or after docetaxel chemotherapy.

2.2 Orteronel

Orteronel (TAK-700) is a non-steroidal androgen synthesis inhibitor that was developed for the treatment of CRPC. Orteronel, like abiraterone, is a CYP17A inhibitor (See Figure 1 for chemical structures of several of the androgen synthesis inhibitors in development). It selectively inhibits 17,20-lyase activity and weakly inhibits 17 α -hydroxylase (15). This differential selectivity of orteronel has a theoretical advantage of inhibiting testosterone biosynthesis while minimizing interference with cortisol production to reduce risk of mineralocorticoid-related toxicities. In the presence of orteronel, 17OH-pregnenolone conversion to DHEA is minimized, thus resulting testosterone suppression to near-undetectable levels (< 0.2 ng/dl) (16). Promising preclinical and early-phase studies led to two phase III investigations of orteronel. In a study of 1099 patients with metastatic CRPC with progression after docetaxel chemotherapy, orteronel 400mg daily plus prednisone 5mg twice daily was compared to placebo plus prednisone (17). Although orteronel demonstrated statistically improved secondary endpoints including prolonged radiographic progression-free survival, PSA response rates, and PSA progression-free survival; overall survival was

not statistically improved (17.0 vs 15.2 months). A second study of orteronel in the chemotherapy-naïve CRPC setting similarly failed to meet an endpoint of improved overall survival (18). In that study, 1560 patients were randomized to receive orteronel plus prednisone versus placebo plus prednisone. Those patients receiving orteronel benefited in terms of radiographic progression-free survival (13.8 vs 8.6 months), but overall survival was not statistically improved (31.4 vs 29.5 months). While mineralocorticoid side effects were not noticeably increased compared to the studies of abiraterone, more increases in amylase, lipase, and clinical pancreatitis were observed with orteronel. It was speculated that tolerability of orteronel was poor, as evidenced by a high percentage of drug discontinuation. There were also regional differences in survival based upon *post-hoc* analysis, where locations with less available of other novel life-prolonging therapies demonstrated a benefit. Nonetheless, further clinical development for orteronel in CRPC is not being pursued, although orteronel continues to be investigated in other settings. Orteronel at a dose of 600mg—without prednisone—is included as part of a cooperative group trial as first-line systemic therapy in conjunction with ADT for newly-diagnosed metastatic prostate cancer (NCT01809691).

2.3 Galeterone

Galeterone (TOK-001) is a steroidal compound in clinical development for CRPC. Similarly to abiraterone and orteronel, galeterone inhibits CYP17 interfering with androgen biosynthesis, with more potent action against 17,20-lyase (19). Preclinical data of galeterone has also suggested multiple other therapeutic effects, including antagonizing AR and promoting its degradation at the protein level (20). Galeterone may have activity in decreasing AR-V7 splice variant levels by targeting them for proteosomal degradation after ubiquitination (21). Activity against AR-V7-positive prostate cancer would provide a distinct advantage over abiraterone, given the emerging data regarding AR-V7 and abiraterone resistance (22, 23). Phase I and II trials testing galeterone in CRPC have been recently published (24). These trials established a formulation and dose for galeterone that is being pursued in further clinical study, specifically 2550mg in a spray-dry dispersion tablet once daily. Galeterone was not co-administered with corticosteroids, and there were no increased adverse events related to mineralocorticoid excess. Testosterone levels were lowered to a median of 2 ng/dl in the phase II study, without significant change in cortisol levels. There was evidence of anti-tumor activity, based upon PSA responses seen with increasing doses of drug. A phase III trial of galeterone versus enzalutamide in a population of patients with CRPC and circulating tumor cell that express AR-V7 is currently underway (see Table 1 for summary of pending clinical trials) (25).

2.4 VT-464 (Seviteronel)

VT-464 is a 17,20-lyase-selective non-steroidal CYP17 inhibitor. Preclinical studies of VT-464 in prostate cancer xenograft models of prostate cancer cell lines demonstrated suppression of testosterone and AR activity (26). AR antagonism activity was also seen in prostate cell lines, including those with AR point mutations (T878A or F877L) that render them resistant to other antiandrogens. In this preclinical study, VT-464 was suggested to have more profound androgen suppression and AR antagonism than abiraterone. Multiple early-phase clinical trials have opened to test VT-464 in patients with CRPC, including those

that have progressed after other novel targeted agents including enzalutamide and abiraterone. Phase I/II results testing VT-464 in patients with CRPC have been reported in abstract form (27). No significant mineralocorticoid side effects were noted even in the absence of prednisone co-administration, and the most common side effects included dizziness, tremors, and vasovagal syncope. Objective tumor responses (3 of 23 evaluable patients) were observed in the early phase trials, including in patients who had progressed after enzalutamide and taxane chemotherapy (28). This drug has recently received FDA fast-track designation for the treatment of CRPC patients who have failed abiraterone and/or enzalutamide.

2.5 CFG920

CFG920 is a non-steroidal inhibitor of CYP17 and CYP11B2 (29). The inhibition activity on CYP11B2 interferes with aldosterone biosynthesis, which theoretically reduces the risk of mineralocorticoid side effects. A phase I/II study of CFG920, without prednisone, in patients with metastatic CRPC is currently ongoing.

2.6 EN3356

EN3356 is a non-steroidal inhibitor of CYP17 17-20-lyase. As discussed with orteronel, galeterone, and VT464, the selectivity for inhibition of the lyase activity of CYP17 has the potential to spare cortisol biosynthesis and minimize mineralocorticoid side effects (30). Early-phase trials with this agent have been announced, but no clinical data is yet available.

2.7 ASP9521

Precursors hormones DHEA and androstenedione are converted to androstenediol and testosterone, respectively, through the action of 17 β -hydroxysteroid dehydrogenase (also known as aldo-keto reductase 1C3 [AKR1C3]). ASP9521 is a first-in-class small molecule selective inhibitor of AKR1C3 that had been undergoing development for CRPC. Preclinical studies demonstrated significant reduction in intratumoral testosterone and PSA in xenograft prostate cancer models (31). Based upon these promising data, a phase I trial was conducted in 13 patients with CRPC with previous treatment with chemotherapy (32). However, the trial failed to demonstrate evidence of clinical activity (through lack of radiographic responses, PSA responses, nor reduction in circulating tumor cells). Investigators speculated that rapid resistance and biosynthesis of testosterone bypassing AKR1C3 may have accounted for the lack of activity. No further clinical development of ASP9521 has been announced, although other AKR1C3 inhibitors are in development (33).

3 AR Antagonists – Targeting the Ligand Binding Domain (LBD)

The approach of using drugs that antagonize the AR has been employed in both castration-sensitive and castration-resistant disease. Historically, “first-generation” antiandrogens (*e.g.* bicalutamide, nilutamide, flutamide) were added to ADT to achieve a more complete androgen blockade in hormone-sensitive disease (34). Responses can also be observed when antiandrogens are used in the setting of progression despite castrate levels of testosterone (35). More recently, highly potent AR antagonists have been developed that have shown significant efficacy in CRPC.

3.1 Enzalutamide

Enzalutamide is a non-steroidal compound that potently antagonizes AR. The objective of the preclinical development of this drug was to identify a compound that would maintain anti-androgen activity in the face of AR overexpression (36). In addition, investigators sought to identify a pure antagonist of AR without agonistic activity. First-generation anti-androgens are weak partial agonists of AR, which can paradoxically cause tumor growth in certain clinical settings (35). In preclinical studies, enzalutamide was shown to bind AR with high affinity, reduce its nuclear translocation, prevent binding to androgen response elements, and prevent recruitment of coactivators. Phase I/II trials identified common side effects to be fatigue, nausea and anorexia (37).

The efficacy of enzalutamide was confirmed in two phase III trials in men with metastatic CRPC. In the first trial, 1199 patients with progressive disease after chemotherapy were randomized to 160mg of enzalutamide daily versus placebo (38). The median overall survival in patients receiving enzalutamide was significantly improved by 4.8 months (18.4 vs 13.6 months). Patients receiving the enzalutamide also had superior progression-free survival, response rates, and quality-of-life. In the second phase III trial, enzalutamide was tested in men with metastatic CRPC prior to chemotherapy (39). In that trial, 1717 patients were treated with enzalutamide or placebo, and those receiving enzalutamide had superior overall survival with a hazard ratio of 0.71. The co-primary endpoint of the study was radiographic progression-free survival, and this objective was overwhelmingly met with a hazard ratio of 0.35. The vast majority of patients (87%) entered into these studies had experienced progression after prior treatment with first-generation antiandrogens, thus confirming that enzalutamide is effective in sequence after prior antiandrogen therapy. Similar to abiraterone, enzalutamide is FDA-approved for the treatment of metastatic CRPC either before or after chemotherapy (40). Finally, two new studies have shown that enzalutamide is far superior to bicalutamide when tested head-to-head in the CRPC setting (41, 42).

3.2 Apalutamide

Apalutamide (ARN-509) is an AR antagonist in development for treatment of CRPC (see Figure 2 for chemical structures of several of the antiandrogens in development). Similar to enzalutamide, apalutamide binds AR with high affinity and minimal-to-no agonist activity (43). In prostate cancer cell lines, apalutamide prevented AR nuclear localization and binding to androgen response elements. In xenograft prostate cancer models, a low dose of apalutamide was necessary to achieve maximal response, leading investigators to speculate that the therapeutic index for apalutamide may be superior to other next-generation antiandrogens. One specific concern in the clinical development of enzalutamide was the induction of seizures in patients with a predisposition, which is thought to be secondary to binding of GABA-A receptors in the central nervous system (CNS). With a lower efficacious dose—and subsequently lower levels of drug present in the CNS—a potential advantage of apalutamide is reduced risk of seizures.

The first-in-human phase I study of apalutamide was published in 2013, and multiple phase II and III investigations are pending. In the phase I study, no maximum tolerated dose was

identified, and grade 1–2 fatigue was commonly reported across dose ranges (44). An optimal biologic dose of 240mg was chosen for phase II investigations based upon data including drug efficacy and correlative studies of testosterone update. The correlative study utilized 16β-[18F] fluoro-α-dihydrotestosterone (F-DHT)–positron emission tomography (PET)/CT scans as an investigational study to provide a measurement the suppression of tumoral AR uptake in response to apalutamide. A dose of at least 120mg produced maximum suppression of PET uptake, and the dose of 240mg produced steady-state plasma levels that were predicted to have anti-tumor efficacy based upon preclinical models.

The phase II portion of this study has been presented in abstract form (45). In that study, patients with CRPC received 240mg of apalutamide daily, with divisions into cohorts based upon whether they had non-metastatic disease, treatment-naïve metastatic disease, or metastatic disease with prior abiraterone treatment. When used as a first-line therapy for metastatic CRPC, apalutamide produced >50% PSA responses in the vast majority of patients (88%, n=25). For patients with prior abiraterone treatment, PSA responses were observed at a much more modest rate (24%, n=21). Of note, inclusion in the abiraterone cohort required that patients had been treated with abiraterone for at least 6 months before progression. The pivotal phase III study of apalutamide, called SPARTAN, is currently randomizing men with non-metastatic CRPC (2:1) to apalutamide versus placebo (46); the primary endpoint of this trial is radiographic metastasis-free survival.

In addition, apalutamide is being investigated in combination with other AR-directed therapies for CRPC. A phase Ib study of apalutamide plus abiraterone has been presented (47). This study combined standard doses of abiraterone (1000mg daily), prednisone (5mg twice daily), and apalutamide (240mg daily), and this combination was well tolerated. PSA responses were observed in patients with the combination, including in patients with progression after treatment with abiraterone and/or enzalutamide.

3.3 ODM-201

ODM-201 is another AR antagonist in development for CRPC. It functions in a similar manner to enzalutamide and apalutamide—specifically by binding to AR, preventing nuclear translocation, and preventing DNA binding (48). ODM-201 has features that set it apart from other next-generation anti-androgens. First, ODM-201 does not significantly cross the blood-brain barrier, which may reduce risk of seizures by minimizing binding to GABA-A receptors in the CNS. In addition, by not crossing the blood-brain barrier, ODM-201 does not induce production of endogenous testosterone. ODM-201 also has *in vitro* activity against mutated androgen receptors, including F877L, W742L, and T878A. The activity against F877L-mutated androgen receptors is particularly notable as this mutation renders resistance to enzalutamide and apalutamide.

In phase I investigations, ODM-201 was well-tolerated with no maximum tolerated dose identified (49). Common grade I/II adverse events included fatigue, arthralgias, and constipation. In the phase II portion of the study, patients without prior abiraterone exposure (including those with prior chemotherapy) showed promising preliminary efficacy based upon PSA and objective responses notes. However, no significant signal of activity was seen in patients with prior treatment with abiraterone (1 of 17 patients with >50% PSA response).

The dose of 1200mg daily (in two divided doses) is being pursued in a phase III trial (ARAMIS) for patients with non-metastatic CRPC (50); the primary endpoint here is also radiographic metastasis-free survival.

3.4 ODM-204

ODM-204 is non-steroidal antiandrogen that also inhibits CYP17. In preclinical studies presented in abstract form, ODM-204 antagonized AR as well as androgen receptors with common mutations in CRPC including F877L, W742L, and T878A (51). In addition, ODM-204 has *in vitro* and *in vivo* inhibitory activity against CYP17A1, demonstrating the ability to suppress testosterone to undetectable levels when used in conjunction with LHRH agonists. A clinical trials of this compound in patients with metastatic CRPC is underway (NCT02344017). Of note, the announced trial is co-administering ODM-204 with prednisone, analogous to abiraterone.

3.5 AZD-3514

AZD-3514 is a novel antiandrogen with a potentially unique mechanisms of action. In preclinical studies, AZD-3514 was demonstrated to bind AR and inhibit its translocation to the nucleus (52). In addition, the compound reduced the rate of synthesis of AR in cell lines resulting in AR downregulation (53). Given this mechanism of AR downregulation, AZD-3514 has been designated as both an anti-androgen and selective AR down-regulator. Phase I studies on AZD-3514 have been published (54). Dose escalation of the compound demonstrated that nausea and vomiting were common (79% of patients with grade I or II). In addition, PK properties of the drug prevented achievement of plasma steady-state levels that were predictive of anti-tumor efficacy. PSA and soft tissue responses were seen in some patients; however, activity in patients with prior progression after abiraterone was minimal. Therefore, further clinical development of this agent is not being pursued.

3.6 TAS3681

TAS3681 is another agent in development that potentially possessed both anti-androgen and AR downregulation properties. TAS3681 exhibits *in vitro* and *in vivo* activity in prostate cancer cell lines, including those expressing wild-type and mutated AR (F877L) (55). Preclinical studies demonstrated that TAS3681 prevents nuclear translocation of the AR after binding, and the drug reduces AR levels for both full-length and AR-variant receptors. The potential activity against AR-V7–positive lines, due to AR downregulation, has led to announcement of a phase I study in patients with mCRPC (NCT02566772).

4 AR Antagonists – Targeting the N-Terminal Domain (NTD)

4.1 EPI-001 and EPI-506

The AR antagonists that have been previously discussed all bind the ligand-binding domain at the C-terminal of the AR protein. However, the N-terminal domain is essential for the transcriptional activity of AR (56). By targeting the N-terminal domain—instead of the ligand-binding domain of the C-terminus—a drug may be able to interfere with androgen signaling, even after the development of resistance that typically allows for ligand-independent AR signaling including signaling mediated by AR splice variants. EPI-001 is

small molecule that specifically binds and inhibits the N-terminus of AR. Preclinical work demonstrated that EPI-001 prevented transactivation of AR (57). EPI-001 was also effective in interfering with signaling in prostate cancer cells with constitutively active splice variants (58). Its efficacy against AR splice variants, which is emerging as an important clinical resistance mechanism to anti-androgen therapy, may set N-terminal domain-targeted agents apart from other antiandrogens. Clinical trials are underway testing the lead agents EPI-506, a related compound to EPI-001, in patients with CRPC who have progression after enzalutamide and/or abiraterone (59).

5 AR agonists

5.1 High-dose testosterone therapy

While the basis for hormonal therapy for prostate cancer has been aimed at lowering testosterone to interfere with the androgen-signaling pathway, a recent approach being trialed uses supraphysiologic androgen therapy in CRPC. Laboratory studies have demonstrated that prostate cancer cells that grow in the presence of physiologic androgen concentrations can paradoxically experience growth inhibition in the setting of supraphysiologic androgens. As the cells progress through the cell cycle, AR functions as a DNA licensing factor and must be degraded (60). In the setting of overexpressed androgen receptors—commonly seen with CRPC—testosterone binding to the overexpressed receptors can result in stabilization, inhibition of DNA relicensing, double-strand DNA breaks through recruitment of topoisomerase II β , and eventually growth arrest and apoptosis (61).

A pilot trial of supraphysiologic androgen therapy, administered at the FDA-approved dose of 400mg intramuscular monthly, was recently reported with promising initial results (62). PSA responses were seen in 7 of 14 patients with CRPC, and radiographic responses were seen in 5 of 10 evaluable patients. The initial trial co-administered etoposide; however, toxicity was excessive and further studies will omit chemotherapy. Larger trials of supraphysiologic androgen therapy in sequence with abiraterone and/or enzalutamide are underway. The first, called RESTORE (NCT02090114), will employ high-dose testosterone therapy to attempt to re-sensitize CRPC patients who have progressed on abiraterone and/or enzalutamide. The second, TRANSFORMER (NCT02286921), will randomize men with abiraterone-pretreated CRPC to either enzalutamide or high-dose testosterone therapy.

6 AR expression inhibitors

6.1 ENZ-4176

Another strategy to interfere with androgen signaling in CRPC is to attack the production of androgen receptors in the cell. In this approach, prostate cancer cells are treated with an antisense oligonucleotide to interfere with AR mRNA, so that AR protein is not translated. ENZ-4176 is a locked nucleic acid-based antisense oligonucleotide designed to bind and down-modulate AR mRNA. The agent was shown to be effective in cell-based experiments in reducing AR expression (63). Based upon that data, a phase I trial was performed in patients with CRPC (64). 22 patients were treated; however, no PSA or radiographic

responses were seen, and the highest dosing level was associated with liver toxicity. Further trials with ENZ-4176 are not being pursued at this time.

7 BET/Bromodomain-targeted agents

The androgen-signaling pathway in CRPC may also be attacked by interfering with epigenetic chromatin binding of the activated AR to prevent transcription of its target gene products. BRD4, a protein that is a member of the bromodomain and extraterminal (BET) family, regulates expression of genes through histone binding. Recent work has shown that AR interacts with BRD4 in CRPC cell lines (65). In the presence of a BRD4 inhibitor, AR (both full-length and variants) was unable to bind androgen response elements (66). In addition, inhibition of BRD4 prevents transcription of other oncogenes, including c-Myc (67). Multiple BET bromodomain inhibitors have begun clinical trials in a variety of cancers, including two that include CRPC patients as discussed below.

7.1 GSK525762

GSK525762 (I-BET762) is the first BRD4 inhibitor to be tested in a trial that includes patients with CRPC. The BRD4–AR interaction in CRPC cell lines was disrupted by GSK525762 in preclinical models (65). In addition, CRPC cell lines treated with the drug also had growth inhibition through interference with Myc transcription (67). A phase I/II study that includes a cohort of patients with CRPC is currently underway (NCT01587703).

7.2 GS-5829

Gilead has announced clinical trials testing the BET/bromodomain small molecule inhibitor GS-5829. In the planned open-label trial (NCT02607228) that will be performed in patients with metastatic CRPC, GS-5829 will be tested as a single agent in the phase I portion of the trial. In the phase II portion, GS-5829 will be tested in combination with enzalutamide. The trial will prospectively evaluate cell-free DNA and CTCs for AR mutations and AR-variant expression to determine if GS-5829 retains clinical activity in AR-mutated and AR-V expressing phenotypes.

7.3 OTX015

Preclinical data for OTX015 (MK-8628), which is a drug targeting BRD4, has focused on models of hematologic malignancies (68, 69). Its clinical development is continuing in hematologic malignancies and CNS tumors. In addition, a phase IB study is open wherein patients with CRPC are specifically eligible. No clinical data for patients with CRPC is yet available.

8 AR degraders

8.1 AR PROTACs

One novel strategy for interfering with AR signaling is to use drugs that direct proteins for intracellular degradation (70). Several bi-functional molecules that combine a motif with affinity for a target of interest (such as AR) with an E3 ligase-recruiting element are under preclinical development for CRPC. These agents have been termed PROTACs (protein-

targeting chimeras). ARV-330 is an example of an AR-directed PROTAC that has been shown to degrade AR in prostate cancer cell lines, resulting in growth inhibition (71). ARV-825 is a PROTAC directed at BRD4, which was effective against AR-V7-expressing tumors in prostate cancer models (72). Clinical trials using these agents are currently being planned.

9 Conclusion

The future is hopeful for patients with CRPC, as more options for treatment will become available as this research matures. These novel approaches to attack androgen axis signaling in CRPC have already led to FDA approval of two agents, and many other drugs are in late-stage clinical trials. One important area for future research is whether combinations of drugs with different mechanisms of action will provide the optimal therapy. Another area for future research will involve ongoing characterization of a patient's tumor, in order to understand the evolving changes in AR, and to match those changes with the therapy with the appropriate mode of action. Such a precision medicine-based approach is increasingly being facilitated by evolving technologies allowing molecular characterization of 'liquid biopsies' in real time and tracked serially across the therapeutic continuum of CRPC (73–75).

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References

1. Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. *Nat Med.* 2004; 10(1):33–9. [PubMed: 14702632]
2. Ferraldeschi R, Welti J, Luo J, et al. Targeting the androgen receptor pathway in castration-resistant prostate cancer: progresses and prospects. *Oncogene.* 2015; 34(14):1745–57. [PubMed: 24837363]
3. Karantanos T, Corn PG, Thompson TC. Prostate cancer progression after androgen deprivation therapy: mechanisms of castrate resistance and novel therapeutic approaches. *Oncogene.* 2013; 32(49):5501–11. [PubMed: 23752182]
4. Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nature reviews Cancer.* 2015; 15(12):701–11. [PubMed: 26563462]
5. Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: A mechanism for castration-resistant tumor growth. *Cancer Res.* 2008; 68(11):4447–54. [PubMed: 18519708]
6. Kassi E, Moutsatsou P. Glucocorticoid receptor signaling and prostate cancer. *Cancer Lett.* 2011; 302(1):1–10. [PubMed: 21078539]
7. Mahler C, Verhelst J, Denis L. Ketoconazole and liarozole in the treatment of advanced prostatic cancer. *Cancer.* 1993; 71(3 Suppl):1068–73. [PubMed: 8428329]
8. O'Donnell A, Judson I, Dowsett M, et al. Hormonal impact of the 17 alpha-hydroxylase/C-17,C-20-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. *Brit J Cancer.* 2004; 90(12):2317–25. [PubMed: 15150570]
9. Attard G, Reid AHM, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol.* 2008; 26(28):4563–71. [PubMed: 18645193]
- 10*. Li ZF, Bishop AC, Alyamani M, et al. Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. *Nature.* 2015; 523(7560):347–51. The activity of the active metabolite

of abiraterone may explain efficacy of the drug and provide advantages of other more narrowly targeted CYP17 inhibitors. [PubMed: 26030522]

11. Kluetz PG, Ning YM, Maher VE, et al. Abiraterone Acetate in Combination with Prednisone for the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer: US Food and Drug Administration Drug Approval Summary. *Clin Cancer Res*. 2013; 19(24):6650–6. [PubMed: 24150234]
12. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *The New England journal of medicine*. 2011; 364(21):1995–2005. [PubMed: 21612468]
13. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy. *New Engl J Med*. 2013; 368(2):138–48. [PubMed: 23228172]
- 14**. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015; 16(2):152–60. Abiraterone's ability to extend survival in its phase III investigations, both before and after chemotherapy, have provided a proof of concept for the strategy of further attack of the androgen receptor pathway. Furthermore, an endpoint of overall survival has become the standard that novel drugs must meet when testing in a similar fashion. [PubMed: 25601341]
15. Kaku T, Hitaka T, Ojida A, et al. Discovery of orteronel (TAK-700), a naphthylmethylimidazole derivative, as a highly selective 17,20-lyase inhibitor with potential utility in the treatment of prostate cancer. *Bioorgan Med Chem*. 2011; 19(21):6383–99.
16. Dreicer R, MacLean D, Suri A, et al. Phase I/II Trial of Orteronel (TAK-700)-an Investigational 17,20-Lyase Inhibitor-in Patients with Metastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res*. 2014; 20(5):1335–44. [PubMed: 24418642]
- 17*. Fizazi K, Jones R, Oudard S, et al. Phase III, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or After Docetaxel-Based Therapy: ELM-PC 5. *J Clin Oncol*. 2015; 33(7) Promising preclinical data and early stage clinical trials do not guarantee that these novel agents will reach the clinic. Despite meeting objectives of response rates and extending progression-free survival, ultimately an overall survival benefit must be reach for these drugs.
18. Saad F, Fizazi K, Jingo V, et al. Orteronel plus prednisone in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. *Lancet Oncol*. 2015; 16(3):338–48. [PubMed: 25701170]
19. Njar VCO, Brodie AMH. Discovery and Development of Galeterone (TOK-001 or VN/124-1) for the Treatment of All Stages of Prostate Cancer. *J Med Chem*. 2015; 58(5):2077–87. [PubMed: 25591066]
20. Yu ZY, Cai CM, Gao S, et al. Galeterone Prevents Androgen Receptor Binding to Chromatin and Enhances Degradation of Mutant Androgen Receptor. *Clin Cancer Res*. 2014; 20(15):4075–85. [PubMed: 24874833]
21. Kwegyir-Afful AK, Ramalingam S, Purushot-Tamachar P, et al. Galeterone and VNPT55 induce proteasomal degradation of AR/AR-V7, induce significant apoptosis via cytochrome c release and suppress growth of castration resistant prostate cancer xenografts in vivo. *Oncotarget*. 2015; 6(29): 27440–60. [PubMed: 26196320]
- 22**. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *The New England journal of medicine*. 2014; 371(11):1028–38. AR-V7 positivity in circulating tumor cells was associated with clinical resistance to antiandrogen therapies, highlighting the need for development of therapies effective against AR-V7 positive cancers. The ability to detect clinically important changes in the androgen receptor and make decisions based upon those changes is rapidly becoming the standard of care. [PubMed: 25184630]
23. Antonarakis ES, Lu C, Luber B, et al. Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer. *JAMA oncology*. 2015; 1(5):582–91. [PubMed: 26181238]

24. Montgomery B, Eisenberger MA, Rettig MB, et al. Androgen Receptor Modulation Optimized for Response (ARMOR) Phase I and II Studies: Galeterone for the Treatment of Castration-Resistant Prostate Cancer. *Clin Cancer Res*. 2015
25. Taplin ME, Antonarakis ES, Dransfield DT, et al. Androgen receptor modulation optimized for response: Splice variant (ARMOR3-SV)-Randomized, open-label, multicenter, controlled study of galeterone vs enzalutamide in men with metastatic castration-resistant prostate cancer (mCRPC) expressing AR-V7 splice variant. *J Clin Oncol*. 2015; 33(15)
26. Toren PJ, Kim S, Pham S, et al. Anticancer Activity of a Novel Selective CYP17A1 Inhibitor in Preclinical Models of Castrate-Resistant Prostate Cancer. *Mol Cancer Ther*. 2015; 14(1):59–69. [PubMed: 25351916]
27. De Bono JS, Pezaro CJ, Gillessen S, et al. The oral CYP17-Lyase (L) inhibitor VT-464 in patients with CRPC. *ASCO Meeting Abstracts*. 2015; 33(7_suppl):187.
28. Nordquist LT, Shore ND, De Bono JS, et al. Objective response of the dual CYP17-Lyase (L) inhibitor / androgen receptor (AR) antagonist, VT-464, in patients with CRPC. *ASCO Meeting Abstracts*. 2016; 34(2S_suppl) abstr 273.
29. Gaul, C.; Mistry, P.; Moebitz, H., et al. Discovery of CFG920, a dual CYP17/CYP11B2 inhibitor, for the treatment of castration resistant prostate cancer. Division of Medicinal Chemistry Scientific Abstracts for the 250th National Meeting and Exposition; 2015; MEDI 341
30. Laping NJ, Sivanandhan D, Kethiri RR, et al. Abstract C134: EN3356, a novel CYP17A inhibitor for the treatment of castration resistant prostate cancer. *Mol Cancer Ther*. 2013; 12(11 Supplement):C134.
31. Kikuchi A, Furutani T, Azami H, et al. In vitro and in vivo characterisation of ASP9521: a novel, selective, orally bioavailable inhibitor of 17beta-hydroxysteroid dehydrogenase type 5 (17betaHSD5; AKR1C3). *Investigational new drugs*. 2014; 32(5):860–70. [PubMed: 24981575]
32. Lorient Y, Fizazi K, Jones RJ, et al. Safety, tolerability and anti-tumour activity of the androgen biosynthesis inhibitor ASP9521 in patients with metastatic castration-resistant prostate cancer: multi-centre phase I/II study. *Investigational new drugs*. 2014; 32(5):995–1004. [PubMed: 24771350]
33. Yin YD, Fu M, Brooke DG, et al. The Activity of SN33638, an Inhibitor of AKR1C3, on Testosterone and 17beta-Estradiol Production and Function in Castration-Resistant Prostate Cancer and ER-Positive Breast Cancer. *Frontiers in oncology*. 2014; 4:159. [PubMed: 24995161]
34. Akaza H. Combined androgen blockade for prostate cancer: Review of efficacy, safety and cost-effectiveness. *Cancer Sci*. 2011; 102(1):51–6. [PubMed: 21091846]
35. Lorente D, Mateo J, Zafeiriou Z, et al. Switching and withdrawing hormonal agents for castration-resistant prostate cancer. *Nat Rev Urol*. 2015; 12(1):37–47. [PubMed: 25563847]
36. Tran C, Ouk S, Clegg NJ, et al. Development of a Second-Generation Antiandrogen for Treatment of Advanced Prostate Cancer. *Science*. 2009; 324(5928):787–90. [PubMed: 19359544]
37. Scher HI, Beer TM, Higano CS, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study. *Lancet*. 2010; 375(9724):1437–46. [PubMed: 20398925]
38. Scher HI, Fizazi K, Saad F, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. *New Engl J Med*. 2012; 367(13):1187–97. [PubMed: 22894553]
- 39*. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *The New England journal of medicine*. 2014; 371(5):424–33. Enzalutamide increases survival when used both before or after chemotherapy for CRPC. Similar to the endpoints in abiraterone studies, a bar of increasing survival has been set for the development of further antiandrogens. [PubMed: 24881730]
40. Ning YM, Brave M, Maher VE, et al. US Food and Drug Administration Approval Summary: Enzalutamide for the Treatment of Patients With Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer. *Oncologist*. 2015; 20(8):960–6. [PubMed: 26070917]
41. Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. *The Lancet Oncology*. 17(2):153–63. [PubMed: 26774508]
42. Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. *J Clin Oncol*. 2016

43. Clegg NJ, Wongvipat J, Joseph JD, et al. ARN-509: A Novel Antiandrogen for Prostate Cancer Treatment. *Cancer Res.* 2012; 72(6):1494–503. [PubMed: 22266222]
44. Rathkopf DE, Morris MJ, Fox JJ, et al. Phase I Study of ARN-509, a Novel Antiandrogen, in the Treatment of Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2013; 31(28):3525–30. [PubMed: 24002508]
45. Rathkopf DE, Antonarakis ES, Shore ND, et al. ARN-509 in men with metastatic castration-resistant prostate cancer (mCRPC). *ASCO Meeting Abstracts.* 2013; 31(6_suppl):48.
46. Smith MR, Liu G, Shreeve SM, et al. A randomized double-blind, comparative study of ARN-509 plus androgen deprivation therapy (ADT) versus ADT alone in nonmetastatic castration-resistant prostate cancer (M0-CRPC): The SPARTAN trial. *ASCO Meeting Abstracts.* 2014; 32(15_suppl):TPS5100.
47. Posadas EM, Chi KN, De Wit R, et al. Phase 1b study of ARN-509 with abiraterone acetate (AA) and prednisone (P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *ASCO Meeting Abstracts.* 2015; 33(15_suppl):5028.
48. Moilanen AM, Riikonen R, Oksala R, et al. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. *Sci Rep-Uk.* 2015:5.
49. Fizazi K, Massard C, Bono P, et al. Activity and safety of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (ARADES): an open-label phase 1 dose-escalation and randomised phase 2 dose expansion trial. *Lancet Oncol.* 2014; 15(9):975–85. [PubMed: 24974051]
50. Fizazi K, Shore ND, Tammela TLJ, et al. ARAMIS trial: Efficacy and safety phase 3 trial of ODM-201 in men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC). *ASCO Meeting Abstracts.* 2015; 33(15_suppl):TPS5080.
51. Oksala R, Moilanen A, Riikonen R, et al. ODM-204: A novel dual inhibitor of CYP17A1 and androgen receptor for the treatment of castration-resistant prostate cancer--Preclinical data. *ASCO Meeting Abstracts.* 33(7_suppl):221.
52. Loddick SA, Ross SJ, Thomason AG, et al. AZD3514: A Small Molecule That Modulates Androgen Receptor Signaling and Function In Vitro and In Vivo. *Mol Cancer Ther.* 2013; 12(9):1715–27. [PubMed: 23861347]
53. Bradbury RH, Acton DG, Broadbent NL, et al. Discovery of AZD3514, a small-molecule androgen receptor downregulator for treatment of advanced prostate cancer. *Bioorg Med Chem Lett.* 2013; 23(7):1945–8. [PubMed: 23466225]
54. Omlin A, Jones RJ, van der Noll R, et al. AZD3514, an oral selective androgen receptor down-regulator in patients with castration-resistant prostate cancer - results of two parallel first-in-human phase I studies. *Investigational new drugs.* 2015; 33(3):679–90. [PubMed: 25920479]
55. Minamiguchi K, Seki M, Aoyagi H, et al. TAS3681: New class of androgen receptor antagonist with androgen receptor downregulating activity. *ASCO Meeting Abstracts.* 33(7_suppl):266.
56. Sadar MD. Small Molecule Inhibitors Targeting the “Achilles’ Heel” of Androgen Receptor Activity. *Cancer Res.* 2011; 71(4):1208–13. [PubMed: 21285252]
57. Andersen RJ, Mawji NR, Wang J, et al. Regression of Castrate-Recurrent Prostate Cancer by a Small-Molecule Inhibitor of the Amino-Terminus Domain of the Androgen Receptor. *Cancer Cell.* 2010; 17(6):535–46. [PubMed: 20541699]
58. Myung JK, Banuelos CA, Fernandez JG, et al. An androgen receptor N-terminal domain antagonist for treating prostate cancer. *J Clin Invest.* 2013; 123(7):2948–60. [PubMed: 23722902]
59. Montgomery RB, Antonarakis ES, Hussain M, et al. A phase 1/2 open-label study of safety and antitumor activity of EPI-506, a novel AR N-terminal domain inhibitor, in men with metastatic castration-resistant prostate cancer (mCRPC) with progression after enzalutamide or abiraterone. *ASCO Meeting Abstracts.* 2015; 33(15_suppl):TPS5072.
60. Litvinov IV, Vander Griend DJ, Antony L, et al. Androgen receptor as a licensing factor for DNA replication in androgen-sensitive prostate cancer cells. *P Natl Acad Sci USA.* 2006; 103(41):15085–90.

61. Isaacs JT, D'Antonio JM, Chen SL, et al. Adaptive auto-regulation of androgen receptor provides a paradigm shifting rationale for bipolar androgen therapy (BAT) for castrate resistant human prostate cancer. *Prostate*. 2012; 72(14):1491–505. [PubMed: 22396319]
- 62**. Schweizer MT, Antonarakis ES, Wang H, et al. Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: Results from a pilot clinical study. *Sci Transl Med*. 2015; 7(269) Unique ways to attack the androgen signaling pathway in CRPC does not necessarily require the discovery of new agents. By exploiting androgen receptor overexpression and understanding the role of AR in the cell cycle, supraphysiologic testosterone administration praphysiologic testosterone had promising efficacy in this pilot trial.
63. Zhang YX, Castaneda S, Dumble M, et al. Reduced Expression of the Androgen Receptor by Third Generation of Antisense Shows Antitumor Activity in Models of Prostate Cancer. *Mol Cancer Ther*. 2011; 10(12):2309–19. [PubMed: 22027692]
64. Bianchini D, Omlin A, Pezaro C, et al. First-in-human Phase I study of EZN-4176, a locked nucleic acid antisense oligonucleotide to exon 4 of the androgen receptor mRNA in patients with castration-resistant prostate cancer. *Brit J Cancer*. 2013; 109(10):2579–86. [PubMed: 24169353]
- 65*. Asangani IA, Dommeti VL, Wang XJ, et al. Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. *Nature*. 2014; 510(7504):278–82. BRD4 plays a role in multiple malignancies including prostate cancer, and inhibition of BRD4 provides a unique way to interfere with androgen receptor signaling. [PubMed: 24759320]
66. Chan SC, Selth LA, Li YM, et al. Targeting chromatin binding regulation of constitutively active AR variants to overcome prostate cancer resistance to endocrine-based therapies. *Nucleic Acids Res*. 2015; 43(12):5880–97. [PubMed: 25908785]
67. Wyce A, Degenhardt Y, Bai YC, et al. Inhibition of BET bromodomain proteins as a therapeutic approach in prostate cancer. *Oncotarget*. 2013; 4(12):2419–29. [PubMed: 24293458]
68. Coude MM, Braun T, Berrou J, et al. BET inhibitor OTX015 targets BRD2 and BRD4 and decreases c-MYC in acute leukemia cells. *Oncotarget*. 2015; 6(19):17698–712. [PubMed: 25989842]
69. Boi M, Gaudio E, Bonetti P, et al. The BET Bromodomain Inhibitor OTX015 Affects Pathogenetic Pathways in Preclinical B-cell Tumor Models and Synergizes with Targeted Drugs. *Clin Cancer Res*. 2015; 21(7):1628–38. [PubMed: 25623213]
70. Lu J, Qian Y, Altieri M, et al. Hijacking the E3 Ubiquitin Ligase Cereblon to Efficiently Target BRD4. *Chemistry & biology*. 2015; 22(6):755–63. [PubMed: 26051217]
71. Winkler, JD.; Jin, M.; Crew, AP., et al. ARV-330: An androgen receptor PROTAC degrader for prostate cancer. Proceedings from the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; 2015; Abstract #C95
72. Coleman K, Lu J, Qian Y, et al. BRD4 degraders produce long-lasting loss of BRD4 Pprotein and robust efficacy in Burkitt's lymphoma cells. *ASCO Meeting Abstracts*. 2015; 33(15_suppl):8557.
73. Schweizer MT, Antonarakis ES. Liquid biopsy: Clues on prostate cancer drug resistance. *Sci Transl Med*. 2015; 7(312):312fs45.
74. Romanel A, Tandefelt DG, Conteduca V, et al. Plasma AR and abiraterone-resistant prostate cancer. *Sci Transl Med*. 2015; 7(312):312re10.
75. Nakazawa M, Lu C, Chen Y, et al. Serial blood-based analysis of AR-V7 in men with advanced prostate cancer. *Ann Oncol*. 2015; 26(9):1859–65. [PubMed: 26117829]

Key Points

- The success of abiraterone and enzalutamide serve as a proof-of-concept that further targeting of the androgen signaling pathway can benefit patients despite development of castration-resistant prostate cancer.
- Unique mechanisms of action of agents under investigation include: androgen synthesis inhibition with specificity for enzymes to avoid mineralocorticoid excess; antiandrogens active against activating AR mutations and AR splice variants; antiandrogens targeting the N-terminal domain of AR, compounds that degrade or downregulate AR; and bromodomain/BET inhibitors epigenetically silencing AR signaling.
- Future work should focus on selecting drugs based upon the specific AR resistance characteristics for an individual patient (precision oncology), as well as pairing of drugs with unique mechanisms of action to achieve optimal outcomes.

Figure 1.
Structures of selected androgen synthesis inhibitors in development.

Figure 2.
Structures of selected androgen receptor antagonists in development.

Selected ongoing clinical trials of investigational agents with novel mechanisms of action in CRPC.

Table 1

Androgen Synthesis Inhibitors	Galeterone	NCT02438007:	ARMOR3-SV: A Phase 3, Randomized, Open Label, Multi-Center, Controlled Study of Galeterone Compared to Enzalutamide in Men Expressing Androgen Receptor-Splice Variant-7 mRNA (AR-V7) Metastatic (M1) Castrate Resistant Prostate Cancer (CRPC)
		NCT01709734:	ARMOR2: A 2 Part, Phase 2 Trial of Galeterone in the Treatment of Castration Resistant Prostate Cancer
	VT-464 (Seviteronel)	NCT02012920:	A Phase 1/2 Open-Label, Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of VT-464 in Patients With Castration-Resistant Prostate Cancer
AR antagonists targeting the LBD		NCT02361086:	A Phase 1/2 Open-Label, Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Once-Daily VT-464 in Patients With Castration-Resistant Prostate Cancer
		NCT02130700:	A Phase 2 Open-Label Study to Evaluate the Efficacy and Safety of VT-464 in Patients With Metastatic Castration Resistant Prostate Cancer Who Have Previously Been Treated With Enzalutamide
		NCT02445976:	A Single-arm, Phase 2 Study to Evaluate the Safety and Efficacy of VT-464 in Patients With Castration-Resistant Prostate Cancer Progressing on Enzalutamide or Abiraterone.
AR antagonists targeting the NTD	CFG920	NCT01647789:	A Phase I/II Multicenter, Open-label Dose Finding Study of Oral CFG920 in Patients With Metastatic Castration-resistant Prostate Cancer
	Apalutamide	NCT01946204:	SPARTAN: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men With Non-Metastatic (M0) Castration-Resistant Prostate Cancer
		NCT02106507:	Phase 1b Study of ARN-509 Plus Everolimus in Men With Progressive Metastatic Castration-Resistant Prostate Cancer After Treatment With Abiraterone Acetate
AR antagonists targeting the LBD		NCT01792687:	Phase 1b, Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumor Activity of Ascending Doses of ARN-509 in Combination With Abiraterone Acetate in Patients With Metastatic Castrate Resistant Prostate Cancer (CRPC)
		NCT02123758:	A Drug-Drug Interaction, Safety and Efficacy Study With ARN-509 and Abiraterone Acetate in Subjects With Metastatic Castration-Resistant Prostate Cancer
		NCT02257736:	A Phase 3 Randomized, Placebo-controlled Double-blind Study of ARN-509 in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer (mCRPC)
AR antagonists targeting the NTD	ODM-201	NCT02200614:	ARAMIS: A Multinational, Randomized, Double-Blind, Placebo-Controlled, Phase III Efficacy and Safety Study of ODM-201 in Men with High-Risk Non-Metastatic Castration-Resistant Prostate Cancer
	ODM-204	NCT02344017:	Safety and Pharmacokinetics of ODM-204 in Patients With Metastatic Castration-Resistant Prostate Cancer (CRPC): Open, Non-Randomised, Uncontrolled, Multicentre, Dose Escalation, First-in-man Study With a Dose Expansion
	TAS3681	NCT02566772:	A Phase 1, Open-Label, Non-Randomized, Safety, Tolerability and Pharmacokinetic Study of TAS3681 in Patients With Metastatic Castration Resistant Prostate Cancer
AR antagonists targeting the NTD	EPI-506	NCT02606123:	A Phase 1/2 Open-Label Study to Assess the Safety, Pharmacokinetics, and Anti-Tumor Activity of Oral EPI-506 in Patients With Metastatic Castration-Resistant Prostate Cancer

AR agonists	High-dose testosterone	NCT02286921:	TRANSFORMER: A Randomized Phase II Study Comparing Bipolar Androgen Therapy vs. Enzalutamide in Asymptomatic Men With Castration Resistant Metastatic Prostate Cancer
		NCT02090114:	RESTORE: A Phase II Study to Determine Sequential Response to Bipolar Androgen Therapy (BAT) Followed by Enzalutamide or Abiraterone Post-BAT in Men With Prostate Cancer Progressing on Combined Androgen Ablative Therapies
BET/Bromodomain inhibitors	GSK525762	NCT01587703:	A Phase I/II Open-Label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525762 in Subjects With NUT Midline Carcinoma (NMC) and Other Cancers
	OTX015	NCT02259114:	A Phase IB Trial With OTX015, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Patients With Selected Advanced Solid Tumors
	GS-5829	NCT02607228:	A Phase Ib/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GS-5829 as a Single Agent and In Combination With Enzalutamide in Subjects With Metastatic Castrate-Resistant Prostate Cancer