Targeting the N-Terminal Domain of the Androgen Receptor: A New Approach for the Treatment of Advanced Prostate Cancer

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ABSTRACT

Despite the recent approval and widespread use of abiraterone acetate and enzalutamide for the treatment of castration-resistant prostate cancer (CRPC), this disease still poses significant management challenges because of various tumor escape mechanisms, including those that allow androgen receptor (AR) signaling to remain active. These AR-related resistance mechanisms include AR gene amplification or overexpression, constitutively active ligand-independent AR splice variants, and gain-of-function mutations involving the AR ligand-binding domain (LBD), among others. Therefore, the development of AR-targeted therapies that function independently of the LBD represents an unmet medical need and has the potential to overcome many of these resistance mechanisms. This article discusses N-terminal domain (NTD) inhibition as a novel concept in the field of AR-directed therapies for prostate cancer. AR NTD-targeting agents have the potential to overcome shortcomings of current hormonal therapies by inhibiting all forms of AR-mediated transcriptional activity, and as a result, may affect a broader AR population including mutational and splice variant ARs. Indeed, the first clinical trial of an AR NTD inhibitor is now underway. The Oncologist 2016;21:1427–1435

Implications for Practice: Because of emerging resistance mechanisms that involve the ligand-binding domain of the androgen receptor (AR), there is currently no effective treatment addressing tumor escape mechanisms related to current AR-targeted therapies. Many patients still demonstrate limited clinical response to current hormonal agents, and castration-resistant prostate cancer remains a lethal disease. Intense research efforts are under way to develop therapies to target resistance mechanisms, including those directed at other parts of the AR molecule. A novel small-molecule agent, EPI-506, represents a new pharmaceutical class, AR N-terminal domain inhibitors, and shows preclinical promise to overcome many known resistance mechanisms related to novel hormonal therapies.

INTRODUCTION

Prostate cancer is the second most prevalent cancer among men in the United States, leading to approximately 30,000 deaths annually [1]. The course of prostate cancer from diagnosis to death is usually categorized by clinical states based on extent of disease, hormonal status (i.e., castration resistance), and the presence or absence of detectable metastases on radiographic imaging [2]. Initial growth of prostate cancer depends highly on androgen signaling, which mediates its effects through the androgen receptor (AR), a transcription factor that regulates the expression of hundreds of genes including those involved in tumor cell growth and proliferation [3, 4]. Because of the dependency of the disease on androgen, androgen deprivation therapy (ADT) has been a mainstay of prostate cancer therapy for decades [5]. Although ADT can delay prostate cancer progression for several years, this treatment modality eventually becomes ineffective as patients develop castration-resistant prostate cancer (CRPC).

The management of patients with CRPC has evolved rapidly over the past 5 years with the advent of next-generation hormonal agents, such as abiraterone acetate (Zytiga) and enzalutamide (Xtandi). Despite these advances, additional treatment options are still needed to improve clinical outcomes and prolong survival of patients with CRPC, particularly those who have failed existing treatments or those who have contraindications or other limitations precluding the use of currently available drugs. Most patients with CRPC who fail current treatment options experience continued disease progression and may develop complications such as urinary
obstruction and worsening pain, leading to substantial morbidity and limited survival rates. The development of resistance to current hormonal therapies and their potential underlying biology have been increasingly described [6–12]. In light of these evolving resistance mechanisms, CRPC remains a lethal disease with a particularly high unmet need in patients for whom existing treatment options are not effective.

**CURRENT TREATMENTS FOR CRPC**

Before 2011, the mainstay of treatment for CRPC was docetaxel-based chemotherapy. Since the approval of abiraterone and enzalutamide for the treatment of CRPC, the reported efficacy has been considerable; however, treatment failures are noted frequently with both agents. The vast majority of patients with CRPC demonstrate primary resistance (patients who do not respond to therapy upfront) or acquired resistance (patients who initially respond to therapy but then relapse) to these agents, with a gain in median overall survival of less than 6 months at the end of the treatment spectrum compared with standard of care [13–16]. It is estimated that approximately one-quarter of patients treated with abiraterone or enzalutamide will show primary resistance to these agents [13, 15–17]. Moreover, the development of acquired resistance will occur in nearly all patients with CRPC, even those who initially benefit from hormonal therapy.

The optimal sequence of therapies to maximize the clinical benefit for patients with CRPC remains undetermined. Clinical trials investigating the efficacy of chemotherapy after novel hormonal therapy, the efficacy of sequential or parallel use of novel hormonal therapy after chemotherapy, the efficacy of sequential use of novel hormonal therapies, and the efficacy of subsequent treatment after first-line novel hormonal therapy have not revealed definitive answers [6, 9, 18–25]. Two randomized phase III trials (Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy [STAMPEDE] and ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer [CHAARTED]) support the upfront use of chemotherapy with ADT (GETUG-AFU-15), however, did not show a survival benefit [28]. In addition, a recent review suggests that the optimal sequencing of agents in CRPC is unclear because of the abundance of robust surrogate measures of survival and the lack of predictive biomarkers [29]. Until there is a greater biological understanding of which patients may benefit from upfront use of chemotherapy, the impact on the landscape of using AR-directed therapies is largely unknown and remains to be evaluated.

**CRPC PROGRESSION AND RESTORED AR SIGNALING**

The AR is structurally composed of an androgen-independent N-terminal domain (NTD), a DNA-binding domain (DBD), and an androgen-dependent ligand-binding domain (LBD). Androgens such as testosterone and dihydrotestosterone bind to the AR LBD, resulting in conformational changes and posttranslational modifications, dimerization, nuclear translocation, and ultimately, binding to the regulatory regions of the DNA of target genes, known as androgen response elements [30]. The transcriptional activity of the AR is also governed by complex epigenetic mechanisms involving coactivators and corepressors that help localize the AR to chromatin.

The AR signaling pathway remains essential for CRPC progression, and under conditions of androgen depletion, multiple mechanisms might lead to reactivation or restoration of AR signaling [31, 32]. Amplification of the AR gene is a mechanism that has been frequently observed clinically and is predominantly seen in response to treatment with ADT. AR overexpression and gene amplification have been reported to occur rarely in untreated primary prostate cancers, with observed frequency of 0%–5% [33–37], but the frequency increases significantly to 20%–52% in ADT-resistant populations [33–42].

Intracrine and paracrine androgen production has also been shown to contribute to continued AR stimulation in the castration-resistant state [43]. Studies evaluating tissue biopsies before and after initiation of abiraterone or enzalutamide have demonstrated increased levels of testosterone as a compensatory mechanism in the tumor tissue of men with CRPC [44–47]. This may result from conversion of weak androgens to potent androgens or de novo production of androgens within the tumor itself [48, 49].

AR splice variants have emerged as another potential mechanism associated with resistance, especially in the context of treatment with new hormonal agents, such as abiraterone and enzalutamide [4, 50–52]. The protein products of AR splice variants have an NTD that is required for transactivation, but have a truncated C-terminal domain in which the LBD is absent, resulting in ligand-independent constitutive activation [53–55]. Antiandrogen therapies are ineffective at inhibiting AR splice variants, because these target the LBD, which is truncated from the AR protein. The presence of AR splice variants, such as AR-V7 and AR-V667es, has been correlated with both primary and acquired resistance to antiandrogens and has been linked to more rapid disease recurrence, poor prognosis, and shorter survival [8, 54–56]. Of these, AR-V7 may be the most important, has been implicated in resistance to abiraterone and enzalutamide in men with advanced prostate cancer [8, 11, 57, 58], and may play a role in partial resistance to docetaxel as well [59].

Point mutations in the AR have been found more commonly in CRPC compared with primary or hormone-sensitive tumors [60, 61], and some have been shown to confer agonist properties and cross-resistance among antiandrogens [62, 63]. A recent prospective study conducting sequencing of bone and soft tissue tumor biopsies from a cohort of 150 patients with CRPC showed that AR mutations were enriched in CRPC and soft tissue tumor biopsies from a cohort of 150 patients with CRPC showed that AR mutations were enriched in CRPC and soft tissue tumor biopsies from a cohort of 150 patients with CRPC. The AR signaling pathway remains essential for CRPC progression, and under conditions of androgen depletion, multiple mechanisms might lead to reactivation or restoration of AR signaling [31, 32]. Amplification of the AR gene is a mechanism that has been frequently observed clinically and is predominantly seen in response to treatment with ADT. AR overexpression and gene amplification have been reported to occur rarely in untreated primary prostate cancers, with observed frequency of 0%–5% [33–37], but the frequency increases significantly to 20%–52% in ADT-resistant populations [33–42].

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**CURRENT THERAPIES TARGET THE AR C-TERMINUS**

Current inhibitors of the AR function by lowering levels of circulating or intratumoral androgen or by preventing

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androgen binding to the AR, all of which depend on an intact C-terminal LBD. Abiraterone inhibits CYP17, a critical enzyme in the synthesis of testosterone, and has been shown to block androgen biosynthesis by the adrenal glands and testes and within the tumor. Treatment with abiraterone reduces serum testosterone levels from 20–50 ng/dL with surgical castration or gonadotropin-releasing hormone analogs alone to 1–2 ng/dL, leading to a “super-castration” state. In addition to decreases seen in the serum, CYP17 inhibition also leads to decreased intratumoral testosterone synthesis within the prostate cancer cells themselves [72], ultimately leading to an inhibition of AR activity. Enzalutamide is a next-generation AR antagonist with significantly increased affinity for the AR compared with previous AR antagonists such as bicalutamide. Furthermore, enzalutamide is reported to inhibit nuclear translocation and coactivator recruitment of the ligand-receptor complex, leading to effective inhibition of AR signaling [73].

Despite their impressive efficacy outcomes, resistance to abiraterone and enzalutamide occurs frequently [13–16], with most patients demonstrating primary or acquired resistance through various AR-dependent and -independent mechanisms. As a result, a number of new-generation CYP17 inhibitor and AR antagonist agents are in clinical development (Table 1). These agents have been shown to exhibit increased affinity to the AR, greater potency, decreased agonist properties, and multiple inhibitory functions compared with their predecessors [74–79]. However, these third-generation agents may potentially face the same issue of cross-resistance conferred by mutations in the LBD (either existing or yet unknown). In addition, these newer agents have yet to demonstrate clinical effectiveness against AR splice variants. In light of the current issues facing AR inhibitors that target the LBD, development of novel class of agents that target other domains of the AR is necessary. Agents targeting the AR NTD and DBD are currently in development, in addition to agents that can induce degradation of the AR protein (Table 1).

**The AR N-Terminal Domain as a Therapeutic Target**

All current therapies that target the AR rely on the presence of its LBD. However, it is the NTD of the AR that harbors the critical region for AR transcriptional activity. Within the NTD lies the activation function-1 (AF1) region, which is essential for AR transactivation [80–82]. Deletions of this region render the AR transcriptionally inactive [80–82]. The AR NTD contains a high degree of intrinsic disorder because of few α-helices and β-sheets and, therefore, has been difficult to target using structure-based drug design [83]. However, in spite of these challenges, efforts to develop drugs that target the AR NTD are ongoing and have the potential to overcome shortcomings of current LBD-targeting therapies. A potential pharmacologic consequence of AR NTD inhibitors is the ability to affect a broader AR population. Because the NTD is required for all AR transcriptional activity and is present in all forms of the AR, targeting this critical region would be expected to inhibit the activity of resistance-related AR splice variants as well as AR species harboring gain-of-function LBD mutations. This is in contrast to current therapies, which can affect only AR populations that possess an intact LBD.

Recent efforts to develop drugs that target the AR NTD have yielded several compounds that are in preclinical or early clinical development (Table 1). The use of bispecific antibodies (bsAbs) to simultaneously bind to two different targets has shown promise, with at least two US Food and Drug Administration-approved agents to date [84]. 3E10-AR441 is a bsAb in preclinical development for CRPC that functions by penetrating prostate cancer cells via its affinity for DNA and, at the same time, binding to the AR NTD to inhibit AR signaling [85]. In vitro treatment of LNCaP prostate cancer cells with 3E10-AR441 demonstrated nuclear accumulation and target engagement of the bsAb. Immunoprecipitation assays in VCaP and 22Rv1 prostate cancer cell lines showed that 3E10-AR441 was able to bind full-length AR as well as splice-variant AR lacking the LBD (AR-V7) [85]. In addition, 3E10-AR441 was shown to block AR signaling in both reporter gene-based assays and assays that monitor endogenous levels of prostate-specific antigen (PSA). To date, no information on the impact of this agent on tumor growth has been released; however, the current data indicate the potential of 3E10-AR441 bsAb as a therapeutic agent that targets the AR in a manner that does not rely on the LBD.

Sintokamides have also been shown to display inhibitory activity against the AR NTD. These chlorinated peptides, isolated from the marine sponge Dysidea sp., were identified through a screening of marine natural extracts and show inhibition of AR activity as measured by reporter gene-based assays [86]. In addition, sintokamides effectively blocked proliferation of LNCaP prostate cancer cells but not PC3 prostate cancer cells, which do not express AR, indicating that the inhibitory effect of sintokamides on cell proliferation was likely caused by its effect on the AR and not via cell cytotoxicity. Further characterization of sintokamides will be useful in assessing these agents as a potential AR-targeted therapy.

Agents directed at preventing the AR NTD from properly initiating transcription are also currently being explored. At least four compounds (GSK525762, GS-5829, OTX015, and JQ1) are in development for CRPC that target bromodomain-containing protein 4 (BRD4), a member of the bromodomain extraterminal (BET) family of proteins. BRD4 is a coregulator of the AR and interacts with the AR NTD to facilitate transcriptional activity [87]. BRD4 inhibitors have been shown to block BRD4-AR interactions and prevent binding of both full-length and splice variant AR to chromatin, thereby impairing transcription of downstream genes [87, 88]. BRD4 inhibition also induced apoptosis and cell-cycle arrest in AR-driven prostate cancer cell lines (VCaP, LNCaP, and 22Rv1), but not in cell lines that are negative for AR signaling (PC3, DU145) [87]. In vivo, BRD4 blockade was shown to significantly reduce tumor volume and weight in VCaP xenograft mice compared with enzalutamide. In addition, BRD4 inhibitors can suppress the transcription of c-Myc, a key mediator of ligand-independent prostate cancer growth and a ligand-independent AR target gene [89, 90]. Together, these data show the potential for BET protein inhibitors as novel treatments for CRPC that function by blocking BRD4 contact with the AR NTD and do not depend on AR-ligand interactions.

**EPI Compounds: Direct AR NTD Inhibitors**

The EPI family of compounds was originally discovered from a marine sponge extract. They bind specifically to Tau-5 within the AF1 region of the AR NTD and have been shown to block protein-protein interactions of the AF1 region with CREB-binding protein and the large subunit of the transcription factor 3 (CREBF). This interaction leads to a significant reduction in transactivation function of the AF1 region of the AR NTD. However, EPI compounds are not selective for the AR and may also inhibit the transcription of other genes, leading to potential side effects. Therefore, further research is needed to develop EPI compounds that are specific for the AR NTD and have minimal impact on other genes.

EPI compounds have shown promising results in preclinical studies. They have been shown to inhibit the growth of prostate cancer cell lines and xenografts in mice. In addition, EPI compounds have been shown to reduce the levels of PSA in serum and to increase the sensitivity of prostate cancer cells to androgen deprivation therapy. However, further research is needed to determine the optimal dose and dosing schedule for EPI compounds and to evaluate their safety and efficacy in clinical trials.

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factor TFIIH (RAP74) [91, 92]. In vitro experiments using LNCaP prostate cancer cells that endogenously express AR show that treatment with EPI blocked AR-driven transcriptional activity both in the presence and absence of androgen [91, 93]. In addition to inhibition of full-length AR, EPI was shown to inhibit transcriptional activity of AR splice variants [93, 94]. In LNCaP cells transfected with a plasmid to overexpress AR-V567es, EPI treatment resulted in inhibition of constitutive AR-V567es-driven transcriptional activity [93]. By contrast, bicalutamide and enzalutamide were unable to inhibit transcriptional activity driven by AR-V567es [93]; bicalutamide and enzalutamide target the LBD, which is absent from AR splice variants.

### Table 1. Investigational agents with potential activity against mechanisms of resistance in CRPC

| Resistance mechanism                                      | Compound                  | Description                      | Development phase in CRPC |
|-----------------------------------------------------------|---------------------------|----------------------------------|---------------------------|
| **Androgen/AR-dependent mechanisms**                      |                           |                                  |                           |
| Intracrine/paracrine androgen synthesis                   | Seviterone                | CYP17 inhibitor                  | Phase II (NCT02130700, NCT02445976) |
|                                                           | CFG920                    | CYP17 inhibitor                  | Phase I/II (NCT01647789)  |
|                                                           | EN3356                    | CYP17 inhibitor                  | Preclinical               |
| AR gain-of-function point mutations                       | Apalutamide               | AR antagonist (LBD)              | Phase III (NCT01946204, NCT02257736) |
|                                                           | Darolutamide              | AR antagonist (LBD)              | Phase III (NCT02200614)  |
|                                                           | ODM-204                   | AR antagonist (LBD)              | Phase I (NCT02344017)   |
|                                                           | TAS3681                   | AR antagonist (LBD)              | Phase I (NCT02566772)   |
|                                                           | EPI-506                   | AR NTD inhibitor                 | Phase I/II (NCT02606123) |
|                                                           | 3E10-AR441 bsAb           | AR NTD inhibitor                 | Preclinical               |
|                                                           | Sintokamides              | AR NTD inhibitor                 | Preclinical               |
|                                                           | VPC-14449                 | AR DBD                           | Preclinical               |
|                                                           | Galeterone                | CYP17 inhibitor; AR degrader     | Phase III (NCT02438007)  |
|                                                           | Niclosamide               | AR degrader                      | Phase I (NCT02532114)   |
|                                                           | ARV-330                   | AR degrader                      | Preclinical               |
|                                                           | GSK525762                 | BET/bromodomain inhibitor       | Phase I (NCT01587703)   |
|                                                           | GS-5829                   | BET/bromodomain inhibitor       | Phase I/II (NCT02607228) |
|                                                           | OTX015                    | BET/bromodomain inhibitor       | Phase Ib (NCT02259114)  |
|                                                           | JQ1                       | BET/bromodomain inhibitor       | Preclinical               |
| **AR splice variants (e.g., AR-V7)**                     | EPI-506                   | AR NTD inhibitor                 | Phase I/II (NCT02606123) |
|                                                           | 3E10-AR441 bsAb           | AR NTD inhibitor                 | Preclinical               |
|                                                           | Sintokamides              | AR NTD inhibitor                 | Preclinical               |
|                                                           | VPC-14449                 | AR DBD                           | Preclinical               |
|                                                           | Galeterone                | CYP17 inhibitor; AR degrader     | Phase III (NCT02438007)  |
|                                                           | Niclosamide               | AR degrader                      | Phase I (NCT02532114)   |
|                                                           | ARV-330                   | AR degrader                      | Preclinical               |
|                                                           | GSK525762                 | BET/bromodomain inhibitor       | Phase I (NCT01587703)   |
|                                                           | GS-5829                   | BET/bromodomain inhibitor       | Phase I/II (NCT02607228) |
|                                                           | OTX015                    | BET/bromodomain inhibitor       | Phase Ib (NCT02259114)  |
|                                                           | JQ1                       | BET/bromodomain inhibitor       | Preclinical               |
| **AR bypass mechanisms**                                  |                           |                                  |                           |
| Glucocorticoid receptor activation                        | Dexamethasone             | GR agonist                       | Phase II (NCT02491411)  |
|                                                           | Mifepristone              | GR antagonist                    | Phase I/II (NCT02012296) |
| Progesterone receptor activation                          | Onapristone               | PR antagonist                    | Phasel/II (NCT02049190) |
| **Androgen/AR-independent mechanisms**                    |                           |                                  |                           |
| RB loss/mutation                                          | Ribociclib                | CDK4/6 inhibitor                 | Phase I/II (NCT02555189, NCT02494921) |
|                                                           | Palbociclib                | CDK4/6 inhibitor                 | Phase II (NCT02059213)  |
| PTEN loss                                                 | LY3023414                 | PI3K/mTOR inhibitor              | Phase II (NCT02407054)  |
|                                                           | Buparlisib                | PI3K inhibitor                   | Phase II (NCT01385293)  |
| Neuroendocrine differentiation                           | Alisertib                 | Aurora Kinase A Inhibitor        | Phase I/II (NCT01848067) |
| DNA repair pathways                                       | Olaparib                  | PARP inhibitor                    | Phase II (NCT01682772)  |
|                                                           | Niraparib                  | PARP inhibitor                    | Phase I (NCT02500901)   |

Abbreviations: AR, androgen receptor; BET, bromodomain extraterminal; bsAb, bispecific antibody; CDK, cyclin-dependent kinase; CRPC, castration-resistant prostate cancer; DBD, DNA binding domain; GR, glucocorticoid receptor; LBD, ligand binding domain; mTOR, mechanistic target of rapamycin; NTD, N-terminal domain; PARP, poly(ADP)ribose polymerase; PI3K, phosphatidylinositol 3-kinase; PR, progesterone receptor; PTEN, phosphatase and tensin homolog; RB, retinoblastoma.
In response to androgen, full-length AR regulates the transcription of well-characterized target genes including PSA, FKBP5, TMPRSS2, and NKX3.1 [4]. The transcriptome of AR splice variants may have some overlap with that of full-length AR, but splice variants also regulate expression of a distinct set of genes [4]. AR splice variants, such as AR-V7, preferentially increase the expression levels of genes such as UBE2C, CDC20, CYCLIN A2, and AKT1 [4]. Consistent with upstream blockade of both full-length and splice variant AR transcriptional activities, EPI treatment inhibits gene expression that is regulated by both full-length and AR-V7 in LNCaP95 and VCaP cells, whereas enzalutamide and bicalutamide had no effect, respectively [93, 94]. Notably, both LNCaP95 cells and VCaP cells endogenously express the full-length AR and AR-V7 protein [4]. An adaptive shift to AR-V7 signaling is suggested to occur in androgen-depleted environments and with antiandrogen treatment [4]. Thus, LNCaP95 and VCaP cells represent an important population of mixed full-length and splice variant ARs that may be reflective of human CRPC.

Consistent with targeting the AR NTD without reliance on the LBD for AR inhibition, EPI did not compete with androgen in a competitive ligand-binding assay [91]. Increasing concentrations of unlabeled synthetic androgen, bicalutamide, and EPI were used to compete with fluorescent-labeled androgen for binding to the AR LBD. Increasing concentrations of both synthetic androgen and bicalutamide displaced the fluorescent-labeled androgen and competed for the ligand-binding pocket. By contrast, EPI did not affect binding of the fluorescent-labeled androgen, regardless of androgen concentration [91]. In another study, elevated androgen levels were shown to compete for, and reverse, the inhibitory effect of enzalutamide [73]. Thus, the reversible binding of antiandrogens to the AR may indicate the reason for their possible failure when intratumoral androgen becomes elevated in CRPC. In contrast, EPI neither targets the AR LBD nor does it compete for binding to the LBD. Thus, EPI compounds possess a unique mechanism of action and do not depend on the presence of the LBD.

The potential therapeutic benefits of EPI have been demonstrated using a variety of human prostate cancer cell lines and xenograft models in castrated male mice. The EPI compounds have been shown to block AR-dependent proliferation of human prostate cancer cells, but have no effect on the viability of cells that do not rely on AR signaling for growth and survival [91, 93]. EPI was shown to block growth of tumor xenografts that express full-length AR as well as xenografts that express both full-length and splice variant AR in castrated male mice [91, 93, 94]. In contrast, EPI had no effect on PC3 prostate cancer xenografts [91] that are insensitive to androgen and do not express functional AR. Importantly, EPI blocked tumor growth of enzalutamide-resistant LNCaP95 xenograft tumors [94], demonstrating an efficacy potential that may be superior to that of antiandrogens. In addition, EPI was shown to inhibit other clinically relevant resistance mechanisms, such as gain-of-function point mutations in the AR and overexpressed transcriptional coactivators [94], further supporting its capability to target a broad range of AR-dependent drivers of tumor growth. Furthermore, in an exploratory toxicity assessment in mice, no toxicity was observed in animals treated systemically with EPI: no loss of body weight, no changes in behavior, and no pathologic changes in the histology of internal organs [91, 93]. Based on specificity of this agent to its target, apparent lack of toxicity, and antitumor activity in preclinical models, these data suggest that EPI is a promising anticancer agent in CRPC.

**Clinical Development of EPI-506**

EPI-506 is a novel small-molecule potent inhibitor of the AR NTD that is currently under investigation for the treatment of metastatic CRPC (mCRPC). EPI-506 is related to the EPI compound family originally discovered by functional assay screening of marine sponge extracts [91] and is the first AR NTD inhibitor to enter human clinical development. The discovery compound was EPI-001, which is a mixture of four stereoisomers, each of which has the same chemical constitution, but different spatial orientation of its constituent atoms. The most potent stereoisomer is EPI-002. EPI-506, the clinical candidate with desired pharmaceutical properties, is a prodrug of EPI-002.

The EPI compounds have important mechanistic differences from current AR-targeted therapies in that EPI directly inhibits the essential function of the AR, which is its transcriptional activity. By targeting the NTD, EPI has the ability to inhibit AR splice variants and LBD-mutant ARs that have been implicated in resistance to current therapies (Fig. 1). The unique mechanism of action for EPI-506 suggests that EPI-506 and other potential NTD inhibitors may have a different pharmacological action. Although there are several investigational agents under development for patients with CRPC who are failing abiraterone and/or enzalutamide, many of these agents are LBD-targeting drugs that have similar mechanisms of action to abiraterone and enzalutamide and will potentially face the same issues of cross-resistance conferred by AR splice variants and AR LBD mutations. By comparison, EPI-506 is anticipated to overcome these resistance mechanisms and may be effective in CRPC driven by both canonical and aberrant AR signaling by targeting the NTD common to full-length, splice variant, and LBD-mutated AR isoforms.

A phase I/II study of EPI-506 is currently ongoing in men with mCRPC with progression after enzalutamide and/or abiraterone (NCT02606123). This open-label, single-arm study will evaluate the benefit of 12-week once-a-day oral dosing with EPI-506, after establishing the safety, pharmacokinetics, and optimal dose of EPI-506 in single- and multiple-dose escalations. The phase I portion of the study will follow an adaptive 3 + 3 dose escalation design. The phase II portion of the study will evaluate activity in 3 patient populations: postenzalutamide but abiraterone-naïve patients with mCRPC, postabiraterone but enzalutamide-naiïve patients with mCRPC, and postenzalutamide and -abiraterone patients with mCRPC (Fig. 2). The planned total enrollment is approximately 166 patients. Inclusion criteria include mCRPC with progression of disease after one or more lines of hormonal therapy or taxane chemotherapy, and progression of disease while under treatment with enzalutamide or abiraterone. Exclusion criteria include hematologic, hepatic, or renal insufficiency. Primary endpoints include PSA response rate at week 12, defined as a 50% PSA decrease from baseline. Secondary endpoints include pharmacokinetics, objective Response Evaluation Criteria in Solid Tumors (RECIST) response rate, time to PSA progression, radiographic progression-free survival, and safety/tolerability. Exploratory endpoints include evaluation of biomarkers of AR-driven treatment resistance, including AR splice variants and AR LBD mutations, with circulating tumor cell-based and plasma-derived cell-free DNA-based methodologies [62, 95]. Information gathered will be used to evaluate the clinical
activity of EPI-506 in the context of known AR resistance mechanisms. This clinical study will be the first to evaluate the novel AR NTD inhibitor EPI-506 in men with mCRPC who have failed enzalutamide and/or abiraterone. EPI-506 is the first agent with the potential to inhibit both canonical and variant-mediated AR signaling.

**CONCLUSION AND FUTURE PERSPECTIVES**

Despite significant recent advances in the treatment of CRPC, many patients demonstrate limited clinical response or develop secondary progression despite treatment with currently available next-generation drugs. Given the heterogeneity of mechanisms that may contribute to progression of CRPC, ongoing and future trials should consider approaches to optimize delivery of care to CRPC patients who are most likely to benefit. One such approach is to incorporate the longitudinal tracking of disease (both genotypic and phenotypic) so that a change in therapy may be triggered at the time actionable biomarkers are detected. Several trials evaluating the clinical utility of AR-V7 as a putative biomarker for informing treatment decisions in CRPC are ongoing and are summarized in a recent review [96]. Most recently, Scher et al. reported on the clinical validation of AR-V7 protein as a treatment-specific

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**Figure 1.** Targeting the androgen receptor: N-terminal domain versus ligand-binding domain. EPI’s unique mechanism of action confers its ability to affect a broader AR population, including mutational and splice variant ARs implicated in resistant metastatic castration-resistant prostate cancer. (A) EPI targets the AR N-terminal domain, a region critical for AR transactivation, whereas current AR-directed therapies target the LBD and prevent androgens from binding. (B) EPI inhibits activity of constitutively active, truncated AR splice variants that lack the LBD. In contrast, current AR-directed therapies can only affect AR populations that have an intact LBD. (C) Mutations in the LBD have been shown to confer agonist activity to antiandrogens. EPI inhibition occurs despite the presence of these gain-of-function mutations in the AR.

Abbreviations: AR, androgen receptor; LBD, ligand-binding domain.
biomarker that may be associated with superior survival on taxane therapy over AR-directed therapy in men with AR-V7+ mCRPC [97]. Such biomarker-driven studies not only will help direct caregivers to using the right treatment at the right time, but also will reduce the time, burden, cost, and unnecessary toxicities experienced by patients undergoing ineffective therapies [98]. Among the multiple pathways that drive CRPC, the heterogeneity within AR-driven CRPC alone is extensive. To this end, intense research efforts are underway to target other parts of the AR molecule, namely the AR NTD and AR DBD, and to degrade the AR protein itself. As the focus of this article is on the AR NTD as a novel molecule, namely the AR NTD and AR DBD, and to degrade the AR protein itself, the following discussion will focus on NTD-driven therapies.

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Emmanuel S. Antonarakis: Janssen, Astellas, Sanofi, Dendreon, ESSA, Medivation (C/A), Janssen, Johnson & Johnson, Sanofi, Dendreon, Genentech, Novartis, Tokai (RF), Tokai (IP); Chandtip Chandhasin: ESSA Pharmaceuticals Corp. (E); Erica Osbourne: ESSA Pharmaceuticals Corp. (E); Jun Luo: Tokai, Sun Pharma (C/A), Mirati, Gilead, Sanofi, Orion, Astellas (RF), A&G, Tokai (IP); Marianne D. Sadar: ESSA Pharma Inc. (C/A, RF, E, OI, IP); Frank Parebo: Essa Pharmaceuticals Corp. (E, OI). (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

**Figure 2.** Phase I/II study of EPI-506: clinical trial design. This open-label, single-arm phase I/II study will evaluate the benefit of 12-week once-daily dosing with EPI-506. The phase I portion of the study will establish the safety, pharmacokinetics, and optimal dosing of EPI-506. The phase II portion of the study will evaluate activity in three patient populations: postabiraterone but enzalutamide-naïve patients with metastatic CRPC, postenzalutamide but abiraterone-naïve patients with metastatic CRPC, and postabiraterone and -enzalutamide patients with metastatic CRPC. This study will be the first to evaluate the novel AR N-terminal domain inhibitor EPI-506 in men with metastatic CRPC who have failed enzalutamide and/or abiraterone.

Abbreviations: AR, androgen receptor; cfDNA, cell-free DNA; CRPC, castration-resistant prostate cancer; CTC, circulating tumor cell; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; PFS, progression-free survival; PK, pharmacokinetics; PSA, prostate-specific antigen; RP2D, recommended phase II dose.

**Phase I Dose Escalation**

- **(n = 46 patients)**
- EPI-506 oral once daily

**Phase II Dose Expansion**

- **(n = 120 patients)**
- 3 cohorts:
  1. Postabiraterone, enzalutamide naïve
  2. Postenzalutamide, abiraterone naïve
  3. Postabiraterone and -enzalutamide

**Day 28 DLTs**

**Week 12**

**First Endpoint:**
- Safety, tolerability

**Second Endpoint:**
- MTD, RP2D
- PK profile

**Exploratory:**
- CTCs (AR-V7 status)

**Phase I Dose Escalation**

- **(n = 106 patients)**

**Week 12**

**First Endpoint:**
- PSA response at week 12

**Second Endpoint:**
- PK profile
- Objective response
- Time to PSA progression
- Radiographic PFS
- Safety, tolerability

**Exploratory:**
- CTCs (AR-V7 status)
- cfDNA (AR amplification & mutations)
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