ESSA Pharma, Inc. (EPIX)
Encode Ideas, L.P. **INITIATION REPORT**

November 11, 2019

Encode Ideas, L.P.
28 Rudnick Lane, Dover, DE 19901

ENCODE IDEAS

FINANCIAL SUMMARY TABLE

Symbol	EPIX
Price	$4.30*
Exchange	NASDAQ
52 week High	$4.90
52 week Low	$1.41
O/S	32.6mm**
Average Volume (30D)	42.7k
Debt	$3.4mm**
Cash	$55mm***

* as of 11/8/2019
** as of 6/30/2019
*** as of 6/30/2019 + financing proceeds

KEY CATALYST DATES

Q1 2020	IND Submission for EPI-7386
Q2 2019	Ph1 Initiation of EPI-7386
Q4 2020 (or Q1 2021)	Ph1data release for EPI-7386 in mCRPC

KEY DISCLOSURES

One or more of the Encode Ideas partners own stock in the covered company

HIGH CONVICTION IDEA

Valuation Summary

We are initiating coverage on ESSA Pharma as a high conviction investment idea.

ESSA is developing a new class of prostate cancer drugs, known as anitens, which target a novel binding site, the N-terminal domain, on the androgen receptor (AR). The benefits of targeting the AR in men with advanced prostate cancer are well established and have yielded blockbuster drugs. However, all approved AR drugs target the same site on the receptor, namely the ligand binding domain, and eventually resistance develops, which in turn leads to tumor progression. We believe N-terminal domain antagonism is a unique and elegant mechanism of action that could complement existing antiandrogen therapies, while also potentially addressing AR resistance.

ESSA is currently completing IND-enabling work for its lead aniten candidate, EPI-7386, and expects to file an IND in 1Q20. The company is expected to release data from their Ph1 study in late 2020 or early 2021, including prostate specific antigen (PSA) results. Although not designed for efficacy, these Ph1 PSA results will be highly suggestive for the potential benefit of EPI-7386. ESSA has previously run a Ph1 study with a first generation aniten compound, a study which demonstrated an acceptable safety profile and provided some hints of PSA-lowering. This first-generation compound was determined to lack potency, so the company returned to the lab and eventually nominated EPI-7386, an aniten with a 20-fold improvement in AR potency in comparison to the first-generation compound. The preclinical efficacy data disclosed by ESSA for EPI-7386 are encouraging. In standard prostate cancer animal models, EPI-7386 has appeared efficacious as a monotherapy and in combination with market leading AR antagonists. Furthermore, it appears EPI-7386 is active and effective in models of AR antagonist resistance, indicating a potential benefit unique to anitens. We recognize that putting too much emphasis on animal studies is foolhardy; yet, when combined with the hints of efficacy from the Ph1 study with the first generation aniten, it further emboldens our optimism regarding EPI-7386.

We view the well-established path for AR antagonist drug development, and approval, as a key attribute in our ESSA investment thesis. Highly successful AR antagonists, such as Xtandi (Pfizer and Astellas), have established a clinical development playbook and expectations, which companies such as ESSA simply ought to meet and follow. Therefore, the interpretation of Ph1 data, specifically PSA-reductions, and inferring the probability of future clinical success, should be relatively straightforward. For that reason, we believe ESSA's Ph1 data for EPI-7386 will be far more important and predictive than most early-stage oncology studies.

2020 is going to be a major year for ESSA. By entering the clinic with EPI-7386, the company will create not only clinical, but also M&A interest and intrigue. With Ph1 success, as determined by acceptable safety and meaningful PSA-reductions (>50% from the baseline), we feel ESSA should achieve a market cap of $500mm, which is approximately a 3–4x return from today's valuation. We would like to draw investors' attention to another Ph1 oncology company, Arvinas (Nasdaq: AVNX), with a focus on AR resistance and prostate cancer, which currently has a market cap of ~$750mm. We note that Arvinas does not exclusively focus on prostate cancer; nevertheless, it is a highly relevant peer, and highlights the near-term upside potential for ESSA as it transitions into a clinical stage company.

Big Pharma dominate the commercial antiandrogen market; most notably, Pfizer / Astellas, and J&J each own franchises with >$3b global annual sales. However, Bayer, Sanofi-Aventis, and Abbvie, among others, also traffic in the category. There is a well-established history of M&A in the antiandrogen market, most notably with J&J's acquisition of Cougar Biotech and Aragon Pharmaceuticals, and Pfizer's acquisition of Medivation. As we have hinted above, we believe Big Pharma's familiarity with AR antagonism make M&A a legitimate possibility for ESSA.

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HIGH CONVICTION IDEA

Financial Considerations

Over the past three months, ESSA has been recapitalized through two transactions, and has in the process attracted some of the best known deep-science investors as shareholders. In July, the company completed the acquisition of Realm Therapeutics, adding ~$20mm to their balance sheet, and then in August they completed a $36mm financing. Through one or both of these transactions, existing deep-science shareholders, Biotech Value Fund, Eventide and Omega Funds, added to their ESSA ownership, while RA Capital and Soleus Capital became notable new shareholders. ESSA has disclosed its cash balance should last into 2023, thus fully funding it through Ph1 and into Ph2 development. We are encouraged by the quality of institutional support and validation ESSA has earned over the past few months, and we feel assured that the company's cash runway can see itself through key Ph1 clinical catalysts and beyond.

Key Risks

The most notable near-term risk for ESSA would be a Ph1 clinical setback with EPI-7386, with either a negative safety signal and / or muted PSA response. Financially ESSA could weather a clinical setback, but the damage to the optimism around N-terminal domain antagonism may be difficult to recover from.

Executive Summary

Prostate cancer has long been the most commonly diagnosed non-cutaneous cancer in men in the United States and currently has the second highest cancer-associated deaths after lung cancer. The American Cancer Society estimates that 1 in 7 men will be diagnosed with prostate cancer in their lifetime.

The prognosis and treatment options for prostate cancer depend on the stage of the cancer, the patient's age, and whether the cancer has just been diagnosed or has recurred. Prostate cancer may be cured when localized and it frequently responds to treatment when widespread. Radical prostatectomy and/or radiation are the standard primary treatments for patients with localized prostate cancer. For recurrent disease and/or advanced stage prostate cancer, the main therapy is androgen deprivation therapy. Androgen deprivation therapy includes surgical castration, medical castration, antiandrogens and androgen biosynthesis inhibitors.

These therapies relieve symptoms, reduce tumor burden, and prolong patient survival, while having relatively modest side effects. Unfortunately, hormone deprivation therapy rarely cures the cancer itself. Prostate cancer almost always recurs, resulting in deadly castration-resistant prostate cancer.

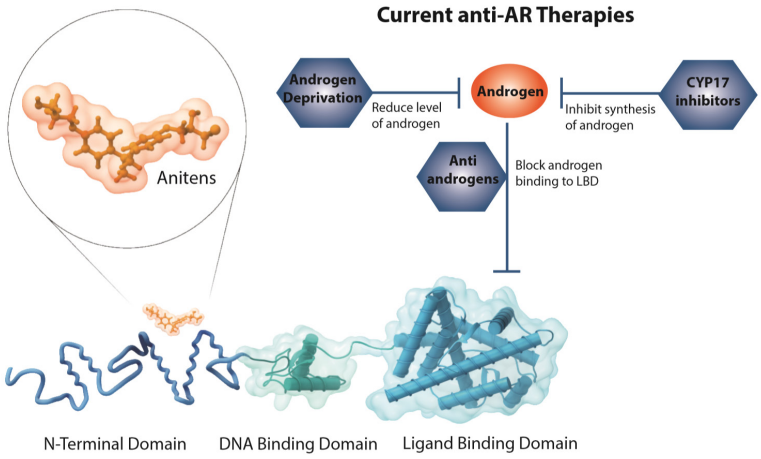
Androgen signaling plays a pivotal role in the development and function of a normal prostate gland. The androgen receptor is a ligand-activated transcription factor that plays a central role in male sexual development and in the etiology of prostate cancer. Like other nuclear hormone receptors, the androgen receptor protein contains three main functional domains:

- NH2-terminal unstructured transcriptional activation domain,
- Central DNA binding domain,
- Carboxyl-terminal ligand binding domain.

Many aspects of androgen receptor signaling allows for therapeutic exploitation, such as sequestration of dihydrotestosterone ligands that activate androgen receptor, blockade of androgen receptor N-C terminal interaction, disruption of androgen receptor coactivator interaction and prevention of androgen receptor nuclear translocation. Conventional antiandrogen therapies have concentrated on androgen-dependent activation of the androgen receptor through its C-terminal ligand binding domain.

ESSA Pharma Inc. is a pharmaceutical company focused on developing novel therapies for the treatment of prostate cancer. ESSA has developed a new class of drugs called anitens that block a novel target on the androgen receptor, the N-terminal domain. The N-terminal domain controls the transcriptional activity of the androgen receptor. This domain is critical for androgen receptor function and is not currently targeted by any other therapy.

The first aniten compound (EPI-001) was identified by screening a library of marine sponge extracts for inhibition of both ligand-dependent and ligand-independent activation of the androgen receptor by blocking transactivation of the androgen receptor N-terminal domain. It was found that EPI-001 selectively interacted with a partially folded region of the transactivation domain of the androgen receptor, known as transactivation unit 5 (Tau-5). This region is key for the ability of prostate cells to proliferate in the absence of androgens which is a distinctive feature of castration-resistant prostate cancer.



EPI-001 is able to block transactivation of the N-terminal domain and is specific for inhibition of androgen receptor without attenuating the transcriptional activities of related steroid receptors. EPI-001 interacts with the AF-1 region, inhibits protein-protein interactions with androgen receptor, and reduces androgen receptor interaction with androgen-response elements on target genes. Importantly, EPI-001 blocks androgen-induced proliferation and caused cytoreduction of castration-resistant prostate cancer in xenografts dependent on androgen receptor for growth and survival without causing toxicity.

EPI-001 has two stereogenic centers and can therefore be found as four stereoisomers. The four compounds all interact with the N-terminal domain of androgen receptor and thus the interaction appears to occur with little or no stereoselectivity. EP-002 is the most potent of EPI-001's four stereoisomers and has improved properties compared with the others.

To be able to move EPI-002 into clinical development, ESSA developed a triacetate prodrug of EP-002 called EPI-506. EPI-506 was tested in a two-part, 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. The trial was the first to evaluate a compound targeting the androgen receptor N-terminal domain. The results indicated that EPI-506 was well-tolerated with an acceptable safety profile. However, the study was terminated at the end of part 1 because of an excessively high pill burden on patients (18 capsules/day). Therefore, the overall conclusion of this study was that more stable and potent compounds were needed to address EPI-506/EPI-002's limitations.

Subsequently, ESSA has identified and developed several anitens with improved cellular potency compared to EPI-506, which are also metabolically stable. EPI-7386 demonstrates a 20-fold improvement in androgen receptor-driven cellular potency, while being highly stable in human and animal hepatocytes. In vitro proliferation assays demonstrated on-target activity across a panel of prostate cancer cell lines, with activity in AR-V7-driven cellular models. EPI-7386 was able to control tumor growth and induce tumor regressions in several castration-resistant prostate cancer xenografts, including antiandrogen resistant models. In addition, the combination of antiandrogen with EPI-7386 demonstrated a more robust and more homogeneous antitumor response.

EPI-7386 represents a new generation of anitens and has been selected as ESSA's next clinical candidate. The IND filing for EPI-7386 is expected in 1Q of 2020 and a Phase 1 study is scheduled to start shortly thereafter. If successful in clinical trials, EPI-7386 offers a unique opportunity to expand and/or improve upon conventional castration-resistant prostate cancer therapies.

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1 Introduction

1.1 Prostate Cancer

The prostate is a small walnut-shaped gland in men that produces the seminal fluid that nourishes and transports sperm. Prostate cancer has long been the most commonly diagnosed non-cutaneous cancer in men in the United States of America (USA) and currently has the second highest cancer-associated deaths after lung cancer (Siegel et al, 2018). The American Cancer Society estimates 1 in 7 men will be diagnosed with prostate cancer in their lifetime. In the world, prostate cancer is the second most common cancer in men and the fifth most common cause of cancer-associated death (Table 1).

Table 1 Prostate Cancer Statistics for United States and World

	United States Prostate Cancer Statistics	World Prostate Cancer Statistics
Estimated New Cases in 2018	164,690 Siegel et al, 2018	1,276,106 Rawla, 2019
Estimated Deaths in 2018	29,430 Siegel et al, 2018	358,989 Rawla, 2019
Estimated New Cases 2040	281,667 Ferlay et al, 2019	2,293,818 Ferlay et al, 2019

Usually prostate cancer grows slowly and is initially confined to the prostate gland, where it may not cause serious harm. Autopsy studies have shown that many older men (and even some younger men) who died of other causes also had prostate cancer that never affected them during their lives (Bell et al, 2015). However, while some types of prostate cancer grow slowly and may need minimal or no treatment, other types are aggressive and can spread quickly.

More than 95% of primary prostate cancers are adenocarcinomas. Prostate adenocarcinomas are frequently multifocal and heterogeneous in patterns of differentiation. Prostatic intraepithelial neoplasia (PIN) is often present in association with prostatic adenocarcinoma. Other rare types of tumors include small-cell tumors, intralobular acinar carcinomas, ductal carcinomas, clear cell carcinomas and mucinous carcinomas (Zelefsky et al, 2011).

The prognosis and treatment options for prostate cancer depend on the stage of the cancer, the patient's age, and whether the cancer has just been diagnosed or has recurred. Prostate cancer may be cured when localized and it frequently responds to treatment when widespread. The 5-year relative survival rate for men diagnosed in the USA from 2001 to 2007 with local or regional disease was 100%, and the rate for distant disease was 28.7% (American Cancer Society, 2012).

Radical prostatectomy and/or radiation are the standard primary treatments for patients with localized prostate cancer. For recurrent disease and/or advanced stage prostate cancer, the main therapy is androgen deprivation therapy (ADT).

Androgen deprivation therapy includes:

- Surgical castration,
- Medical castration,
- Antiandrogens, and
- Androgen biosynthesis inhibitors.

These therapies relieve symptoms, reduce tumor burden, and prolong patient survival, while having relatively modest side effects. Unfortunately, hormone deprivation therapy rarely cures the cancer itself. Prostate cancer almost always recurs, resulting in deadly castration-resistant prostate cancer (CRPC).

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 definite answers (Cheng et al, 2015; Azad et al, 2015; Maughan et al, 2015; Nadal et al, 2016; Nadal et al 2014; Schweizer et al, 2014; Suzman et al, 2014; Loriot et al, 2013; Noonan et al, 2013; Schrader et al, 2014).

1.2 Androgen and Androgen Receptors

Identification of key drivers of cancer proliferation and spread has facilitated significant advances in the treatment of an increasing number of malignancies. For prostate cancer, the androgen receptor (AR) is the principal therapeutic target. A series of trials have demonstrated that potent suppression of androgen signaling via receptor blockade (Scher et al, 2012; Beer et al, 2014) or inhibition of ligand production (Ryan et al, 2013) extends the survival of men with metastatic castration resistant prostate cancer (mCRPC).

Androgen signaling plays a pivotal role in the development and function of a normal prostate gland. There are two native androgens in humans, testosterone (Figure 1) and dihydrotestosterone (Figure 2). In men, testosterone is produced mainly in the testes, with a small amount being produced in the adrenal glands. Testosterone is converted to the more potent androgen dihydrotestosterone by the enzyme 5 α-reductase located in the prostate, skin, scalp, etc. Testosterone and dihydrotestosterone both bind to a single nuclear receptor protein called the androgen receptor.

Figure 1 Chemical Structure of Testosterone

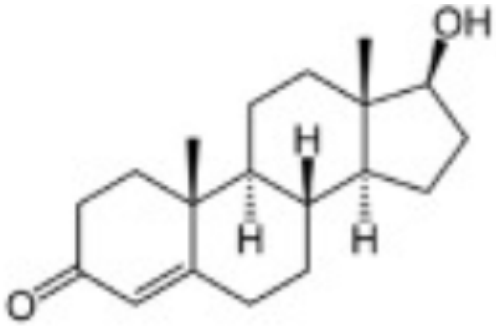
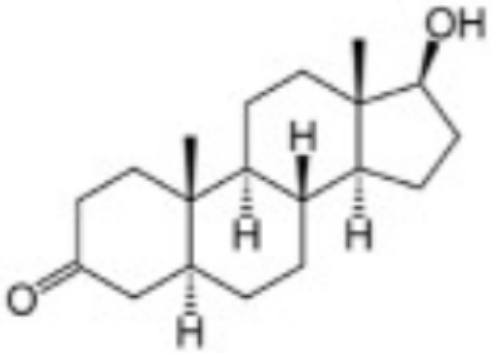


Figure 2 Chemical Structure of Dihydrotestosterone

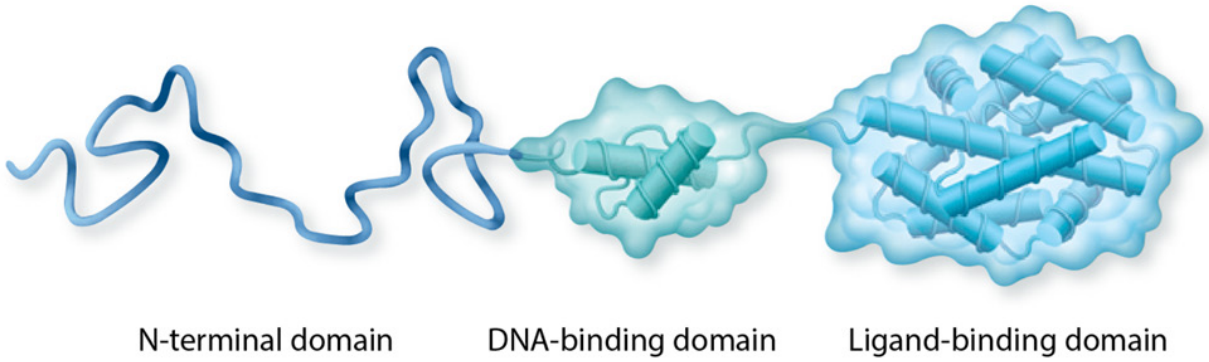


The AR is a ligand-activated transcription factor that plays a central role in male sexual development and in the etiology of prostate cancer (McPhaul, 1999; Gottlieb et al, 1998). It is a member of the steroid and nuclear hormone receptor superfamily, which also includes receptors for glucocorticoids (GR), mineralocorticoids (MR), progesterone (PR), estrogen (ER) and vitamin D (VDR) (Mangelsdorf et al, 1995).

Like other nuclear hormone receptors, the AR protein contains 3 main functional domains (Figure 3):

- NH2-terminal unstructured transcriptional activation domain (NTD),
- Central DNA binding domain (DBD),
- Carboxyl-terminal ligand binding domain (LBD)

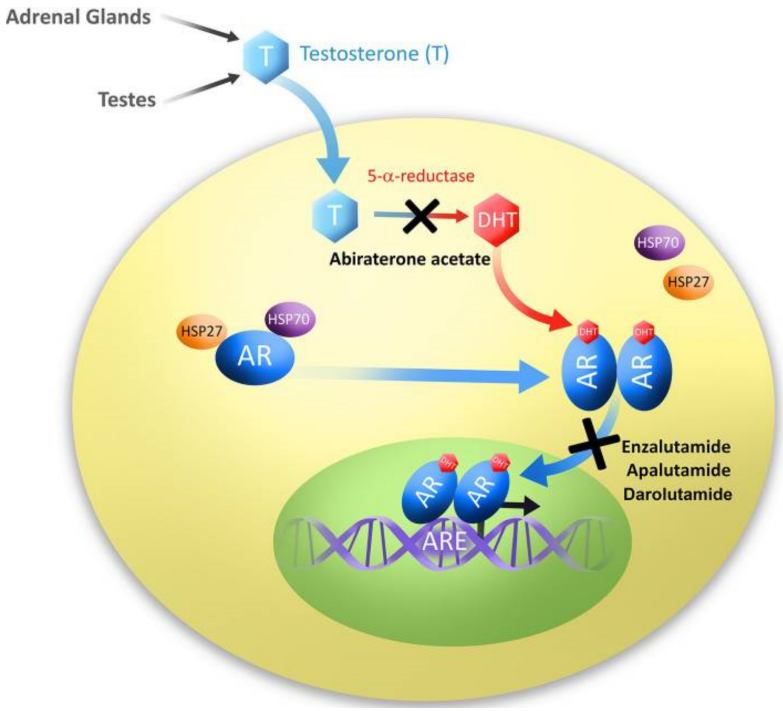
Figure 3 Androgen Receptor Diagram



(ESSA Pharma Website, 2019)

Prior to activation, ARs are located in the cytoplasm bound to several chaperone proteins, members of the heat-shock protein family (HSP). Androgens bind to the AR ligand binding domain releasing AR chaperones which allows AR to homodimerize and translocate to the nucleus where it acts as a transcription factor for androgen responsive genes such as prostate-specific antigen (PSA) and others (Figure 4).
Many aspects of AR signaling allows for therapeutic exploitation, such as sequestration of dihydrotestosterone ligands that activate AR, blockade of AR N-C terminal interaction, disruption of AR coactivator interaction and prevention of AR nuclear translocation (Scher et al, 2005; Andriole et al, 2009).

Figure 4 Diagram of Androgen Signaling through the Androgen Receptor



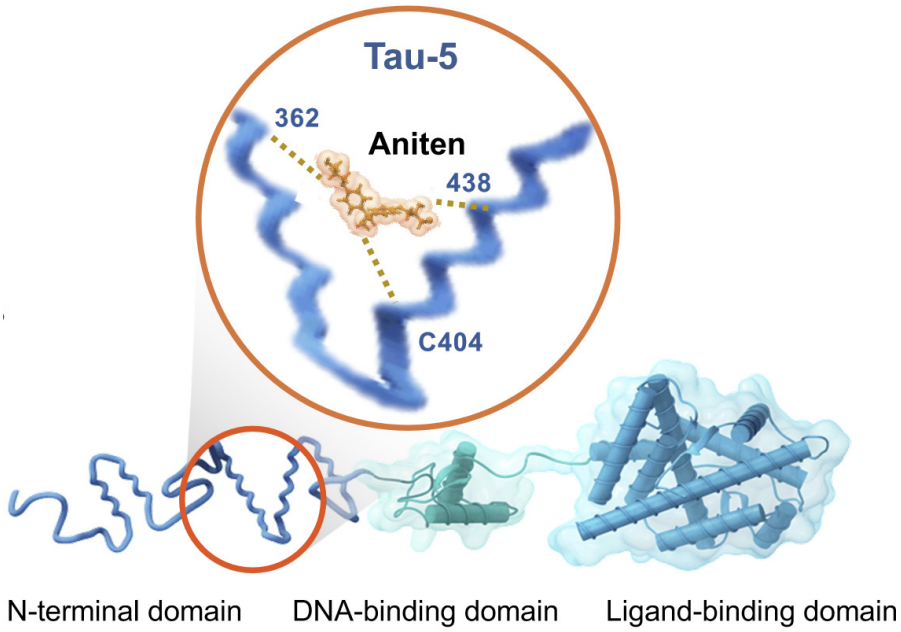
(Rice et al, 2019)

Patients diagnosed early with prostate cancer are treated with surgery or radiotherapy. Unfortunately, these treatments fail in 10–20% of cases. Recurrent patients are exposed to ADT. However, ADT efficacy is time-limited, and most patients undergo disease progression and develop castration-resistant prostate cancer (Watson et al, 2015). In spite of the antitumor efficacy demonstrated by antiandrogen drugs, the emergence of AR resistance mechanisms, are responsible for treatment failure (Guerrini et al, 2014; Ferroni et al, 2017; Howard et al, 2019; Huang et al, 2018; Paschalis et al, 2018). These tumors are often still dependent on ARs and continue to grow in the presence of very low levels of circulating androgens (Huang et al, 2018). Other mechanism underlying failure to these therapies and the continued androgen receptor transactivation activity may be the expression of constitutively active splice variants of androgen receptor that lack ligand binding domain. In this scenario, the development of new drugs represents a critical need.

1.3 ESSA Pharma

ESSA Pharma Inc. (ESSA) is a pharmaceutical company focused on developing novel therapies for the treatment of prostate cancer. ESSA has developed a new class of drugs called anitens that block a novel target on the androgen receptor, the N-terminal domain (Figure 5). The N-terminal domain controls the transcriptional activity of the androgen receptor. This domain is critical for androgen receptor function and is not currently targeted by any other therapy. By blocking androgen receptor-directed biology in this manner, resistance to current hormone therapies may be overcome.

Figure 5 Aniten Targeting of the Androgen Receptor N-Terminal Domain



(ESSA Pharma Slide Deck, 2019)

ESSA's lead product is EPI-7386. It is initially being advanced to treat metastatic castration-resistant prostate cancer. EPI-7386 is currently undergoing Investigational New Drug (IND) application enabling studies. The IND is expected to be filed in early 2020 (Figure 6).

Figure 6 ESSA Pharma Product Pipeline

Product and Indication	Research	Preclinical	IND Enabling Studies	IND Filing	Phase 1
EPI-7386 for mCRPC				Q1 2020	
EPI-7386 Combination Therapy for mCRPC					
Aniten for Triple Negative (ER, PR, HER-2) AR+ Breast Cancer					

(ESSA Pharma Website, 2019)

1.4 Report Objective

The objective of this report is to summarize the information available on the following topics:

- Androgen receptors as a prostate cancer treatment target
- Antiandrogen treatment landscape
- ESSA Pharma's prostate cancer candidate currently in development

This information will then be used to determine the potential future commercial prospects for ESSA Pharma and its products.

2 Literature Search

Pubmed searches (https://www.ncbi.nlm.nih.gov/pubmed) using the following key words were performed by the author in mid-October of 2019:

- Prostate cancer, PC, PCa
- Castration resistant prostate cancer, CRPC
- Metastatic castration resistant prostate cancer, mCRPC
- Prostate cancer treatments
- Androgen deprivation therapy, ADT
- Androgen ablation
- Androgen receptor, AR
- Antiandrogen, anti-androgen
- Androgen
- Aniten

Abstracts were reviewed for their relevance and if available free online, the full article was obtained. The pubmed searches were restricted to information available for humans. No time restrictions were imposed. Additional references, identified through article review, were also included if deemed relevant.

In addition to the pubmed searches, information from the following websites was also reviewed:

- ESSA Pharma - https://www.essapharma.com
- Clinical Trials Government - https://clinicaltrials.gov
- Drug Information Portal - https://druginfo.nlm.nih.gov/drugportal
- U.S. Food and Drug Administration - https://www.fda.gov

A comprehensive list of references used for compiling this report can be found in Section 5.

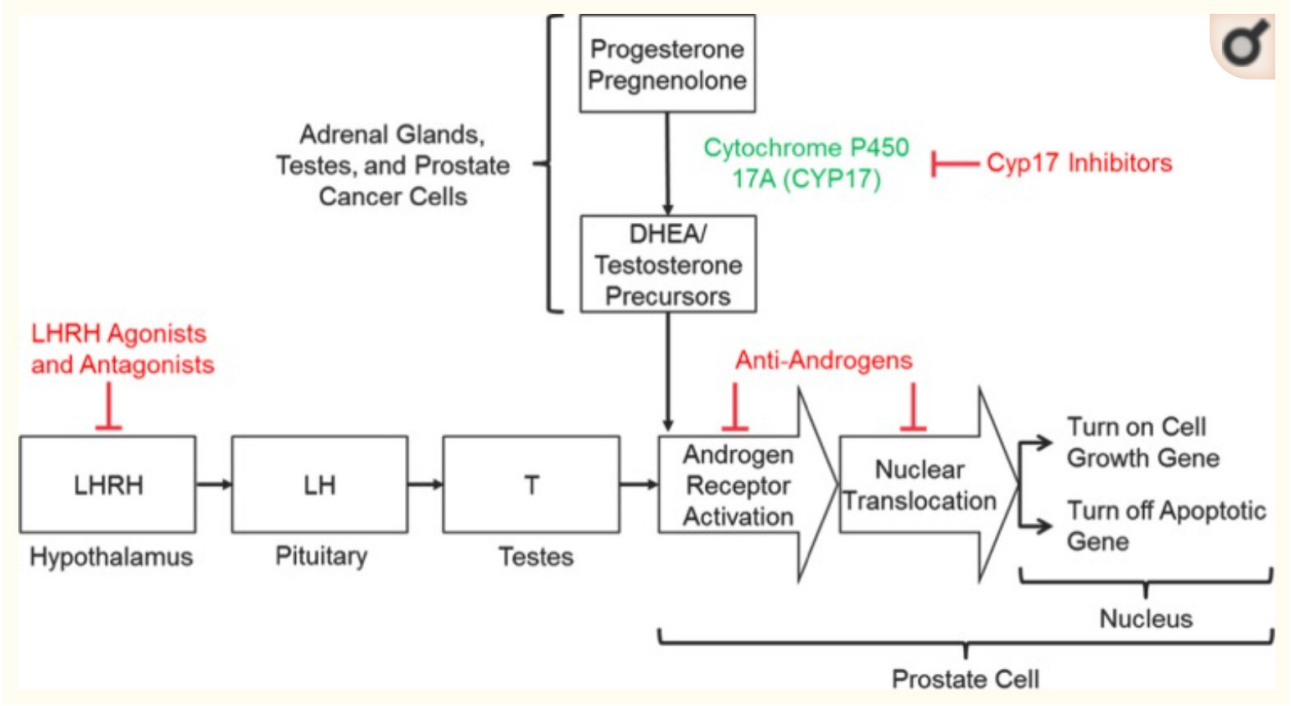
3 Discussion

Androgen deprivation therapy is the standard first-line treatment for advanced prostate cancer (Hellerstedt et al, 2002). In addition to surgical castration, luteinizing hormone-releasing hormone (LHRH) agonists and antagonists block the production of testicular androgens (Figure 7). Although surgical and medical castration can suppress testosterone production in the testes, the adrenal glands can still produce small amounts of androgens (Barnard et al, 2019).

To neutralize the activity of these residual androgens, antiandrogens are used to block AR signaling in prostate cancer cells. Antiandrogens do not prevent androgen production in the body. Instead, the antiandrogens bind to the AR with a relatively high affinity but lack the ability to activate the transcriptional activity of the AR. Therefore, antiandrogens function by competitively blocking testosterone and dihydrotestosterone from binding to the AR (Figure 7) (Vis et al, 2009).

In contrast to androgen receptor blockade, another method of androgen signaling inhibition is the upstream blockade of androgen production. Androgens are processed by the cytochrome p450 enzyme 17α-hydroxylase-17,20-lyase (CYP17). Androgens are then released and circulate through the body. Targeting the biosynthesis mechanism of testosterone through inhibition of CYP17, produced in the testes and adrenal glands, inhibits the production of dihydrotestosterone and decrease endogenous androgen levels (Figure 7) (Maity et al, 2016).

Figure 7 Mechanisms of Androgen Signaling Inhibition



(Crawford et al, 2019)

3.1 LHRH Agonists and Antagonists

LHRH agonists and antagonists were among the first therapies developed to reduce androgen signaling in prostate cancer. The pharmacological target is the LHRH receptor in the anterior pituitary gland. Continuous serum levels of LHRH agonists stimulate the receptor and generate a transient surge in release of luteinizing hormone (LH) and testosterone, followed by downregulation of the receptor over 2–3 weeks with reduction in LH and subsequent suppression of testosterone production by the testes (Cooke et al, 1985). The amplitude of the surge depends on baseline testosterone levels with higher levels leading to greater surges (Damber et al, 2012).

There are several LHRH agonist molecules with a range of drug delivery technologies to effect continuous, controlled release of drug (Table 2). These include intramuscular leuprolide acetate, LUPRON® with a microsphere technology (LUPRON DEPOT® Prescribing Information, 2019) and subcutaneous leuprolide acetate, ELIGARD® that utilizes the ATRIGEL® delivery system (ELIGARD® Prescribing Information, 2019). Subcutaneous and intramuscular leuprolide acetate both have 1-, 3-, 4-, and 6-month formulations. Triptorelin pamoate (TRELSTAR®) also employs microspheres and is available in 1-, 3-, and 6-month intramuscular formulations (TRELSTAR® Prescribing Information, 2018). Goserelin acetate (ZOLADEX®) uses 1- and 3-month subcutaneous implants that require insertion under the supervision of a physician (ZOLADEX® Prescribing Information 10.8 mg, 2019; ZOLADEX® Prescribing Information 3.6 mg, 2019). Although not readily available, histrelin acetate (VANTAS®) is a 12-month subcutaneous implant inserted into the upper arm (VANTAS® Prescribing Information, 2019).

Table 2 LHRH Agonists

Product Name	Drug Delivery	Indication	Reference
Leuprolide Acetate	LUPRON® Intramuscular microsphere technology	Indicated in the palliative treatment of advanced prostatic cancer	LUPRON DEPOT® Prescribing Information, 2019-
	ELIGARD® Subcutaneous ATRIGEL® Delivery System	Indicated for the palliative treatment of advanced prostate cancer	ELIGARD® Prescribing Information, 2019
Triptorelin Pamoate	TRELSTAR® Microsphere technology	Indicated for the palliative treatment of advanced prostate cancer	TRELSTAR® Prescribing Information, 2018

Product Name	Drug Delivery	Indication	Reference
Goserelin Acetate	ZOLADEX® Subcutaneous implants 10.8 mg	Indicated for use in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate	ZOLADEX® Prescribing Information 10.8 mg, 2019
	ZOLADEX® Subcutaneous implants 3.6 mg	Indicated for use in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate	ZOLADEX® Prescribing Information 3.6 mg, 2019
Histrelin Acetate	VANTAS® Subcutaneous implants	Indicated for the palliative treatment of advanced prostate cancer	VANTAS® Prescribing Information, 2019

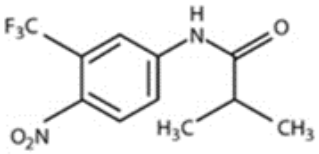
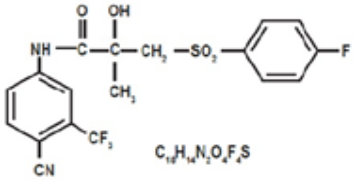
When LHRH agonists are first given, testosterone levels go up briefly before falling to very low levels. This effect is called a flare and results from the complex way in which these drugs work. A flare can be avoided by giving drugs called antiandrogens (discussed below) for a few weeks when starting treatment with LHRH agonists (Vis et al, 2015).

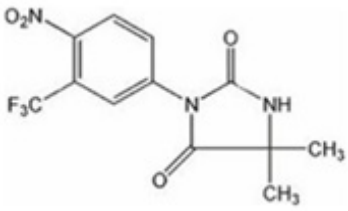
LHRH antagonists competitively and reversibly bind to and block LHRH receptors, inhibiting LH release and testosterone suppression without an initial rise in testosterone. Degarelix (FIRMAGON®) is an LHRH antagonist. It works like the LHRH agonists, but it lowers testosterone levels more quickly and doesn't cause tumor flare like the LHRH agonists do. Treatment with this drug can also be considered a form of medical castration. This drug is used to treat advanced prostate cancer. It is given as a monthly injection under the skin. The most common side effects are problems at the injection site (pain, redness, and swelling) (FIRMAGON Prescribing Information, 2017).

3.2 Antiandrogens

Most prostate cancer cells grow in response to androgens binding to their androgen receptors. Antiandrogens are drugs that also bind to these receptors, keeping the androgens from causing tumor growth. Antiandrogens are also sometimes called androgen receptor antagonists. The first-generation antiandrogens bicalutamide, nilutamide, and flutamide exclusively target AR translocation to the nucleus and prevent downstream signaling (Table 3). Second-generation antiandrogens enzalutamide, apalutamide and darolutamide have further improved upon this mechanism (Table 4).

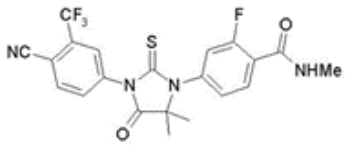
Table 3 First Generation Antiandrogens

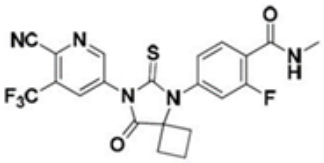
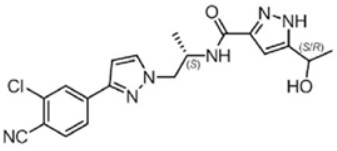
Product Name	Product Structure	Indication	Reference
Flutamide (EULEXIN®)	 Chemical Name - α,α,α-trifluoro-2-methyl-4'-nitrom-propionotoluidide Molecular Formula - $C_{11}H_{11}F_3N_2O_3$	Indicated for use in combination with LHRH-agonists for the management of locally confined Stage B2-C and Stage D2 metastatic carcinoma of the prostate	EULEXIN Prescribing Information, 2014
Bicalutamide (CASODEX®)	 Chemical Name - propanamide, N [4 cyano-3-(trifluoromethy])phenyl]-3-[(4-fluorophenyl) sulfonyl]-2-hydroxy-2-methyl-,(+-) Molecular Formula - $C_{16}H_{14}N_2O_4F_4S$	Indicated for use in combination therapy with a LHRH analog for the treatment of Stage D2 metastatic carcinoma of the prostate	CASODEX Prescribing Information, 2019

Product Name	Product Structure	Indication	Reference
Nilutamide (NILANDRON®)	 Chemical Name - 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-2,4-imidazolidinedione Molecular Formula - $C_{12}H_{10}F_3N_3O_4$	Indicated for use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D2)	NILANDRON Prescribing Information, 2018
LHRH = Luteinizing Hormone-Releasing Hormone			

In addition to treating mCRPC, second-generation antiandrogens are also proving to be effective against metastatic castration sensitive prostate cancer (mCSPC). Apalutamide is Food and Drug Administration (FDA) approved for the treatment of non-metastatic castration-sensitive prostate cancer (nmCRPC), based on the SPARTAN study (Smith et al, 2018). The phase III TITAN trial demonstrated that the addition of apalutamide to lifelong ADT improved overall survival in mCSPC (Chi et al, 2019). Enzalutamide is also FDA approved for the treatment of mCRPC (Scher et al, 2012; Beer et al, 2014; Hussain et al, 2018) however, the benefits of adding enzalutamide to ADT for the treatment of mCSPC patients has recently been established by two phase III studies, ARCHES and ENZAMET (Armstrong et al, 2019; Davis et al, 2019).

Table 4 Second Generation Antiandrogens

Product Name	Product Structure	Indication	Reference
Enzalutamide (XTANDI®)	 Chemical Name - 4-{3-[4-cyano-3-(trifluoromethyl) phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide Molecular Formula - $C_{21}H_{16}F_4N_4O_2S$	Indicated for the treatment of patients with castration-resistant prostate cancer	XTANDI Prescribing Information, 2018

Product Name	Product Structure	Indication	Reference
Apalutamide (ERLEADA®)	 Chemical Name - (4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide) Molecular Formula - $C_{21}H_{15}F_4N_5O_2S$	Indicated for the treatment of patients with • Metastatic castration-sensitive prostate cancer • Non-metastatic castration-resistant prostate cancer	ERLEADA Prescribing Information, 2019
Darolutamide (NUBEQA™)	 Chemical Name - N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl] propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide Molecular Formula - $C_{19}H_{19}Cl\ N_6O_2$	Indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer	NUBEQA Prescribing Information, 2019

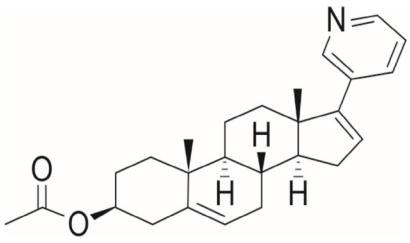
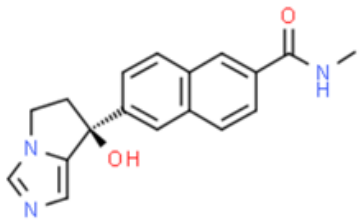
The most utilized mechanism of antiandrogens is blockade of AR signaling by sequestration of AR itself, thus preventing nuclear translocation and subsequent signaling to AR target genes. While first-generation antiandrogens also fit this classification, as a group, second-generation AR blockers no longer exhibit agonist/antagonist switch, androgen withdrawal syndrome, and have decreased patient toxicities. The main new side effect associated with AR blockade is increased risk of seizure. This is due to penetrance of the compounds through the blood-brain barrier (BBB) and subsequent inhibition of the γ-aminobutyric acid receptor ($GABA_AR$). Enzalutamide was the first of the class to be characterized and has the highest risk of seizures at low doses. Apalutamide and darolutamide provide reductions in brain penetrance and reduced association with clinical risk of seizure, demonstrating advances in the field of antiandrogen therapy (Clegg et al 2012; Moilanen et al, 2015; Zurth et al, 2018).

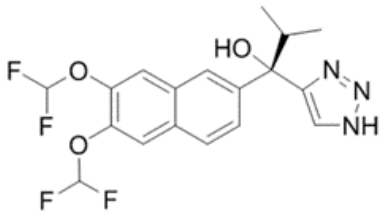
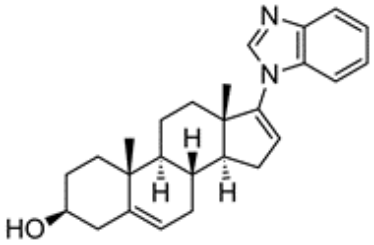
3.3 Androgen Biosynthesis Inhibitors

Abiraterone acetate (ZYTIGA®) is the only androgen biosynthesis inhibitor currently approved by the FDA (ZYTIGA Prescribing Information, 2019). Abiraterone acetate is an irreversible, highly selective CYP17 inhibitor that targets 17α-hydroxylase and C17,20-lyase activities resulting in reduced intratumoral production of androgens, as well as reducing their synthesis in the adrenal glands and the testes. This drug is taken as pills every day. It doesn't stop the testicles from making testosterone, so men who haven't had an orchiectomy need to continue treatment with an LHRH agonist or antagonist. Because abiraterone also lowers the level of some other hormones in the body, prednisone (a corticosteroid drug) needs to be taken during treatment as well to avoid certain side effects.

Next generation CYP17 inhibitors are currently being evaluated in clinical trials for metastatic prostate cancer (Table 5). These inhibitors include Orteronel (TAK 700, Takeda Pharmaceuticals, Deerfield, IL, USA), Seviteronel (VT-464, Viamet Pharmaceuticals, Durham, North Carolina, USA), and Galeterone (TOK-001, Tokai Pharmaceuticals, Boston, MA, USA) (Alex et al, 2016).

Table 5 Androgen Biosynthesis Inhibitors

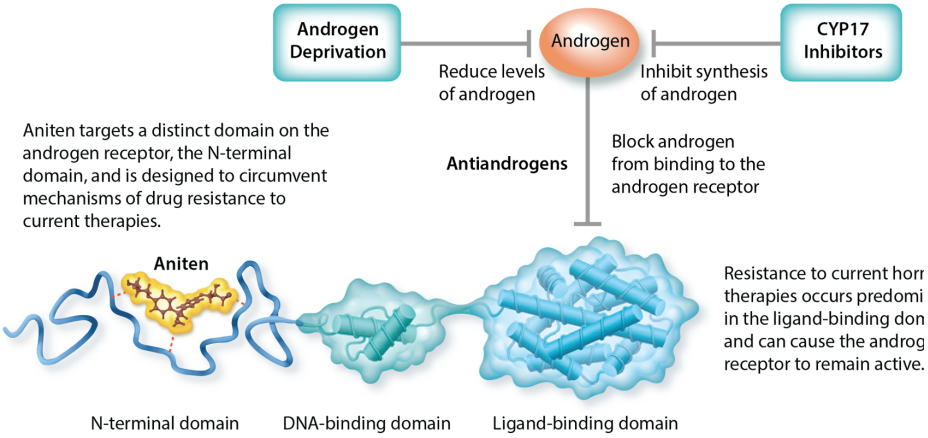
Product Name	Product Structure	Indication	Reference
Abiraterone acetate (ZYTIGA®)	 Chemical Name - 17-(Pyridin-3-yl)androsta-5,16-dien-3β-yl acetate Molecular Formula – $C_{26}H_{33}NO_2$	Indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer	ZYTIGA Prescribing Information, 2019
Orteronel	 Chemical Name – 6-(7-Hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl)-N-methylnaphthalene-2-carboxamide Molecular Formula – $C_{18}H_{17}N_3O_2$	Development terminated (Takeda News Release, 2014)	Van Hook et al, 2014 (review)

Product Name	Product Structure	Indication	Reference
Seviteronel	 Chemical Name - (S)-1-(6,7-bis(difluoromethoxy) naphthalen-2-yl)-2-methyl-1-(1H-1,2,3-triazol-5-yl)propan-1-ol Molecular Formula - $C_{18}H_{17}F_4N_3O_3$	In development, not yet FDA approved	Gupta et al, 2018 (review)
Galeterone	 Chemical Name - (3S,8R,9S,10R,13S,14S)-17-(benzimidazol-1-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15-decahydro-1H-cyclopenta[a]phenanthren-3-ol Molecular Formula - $C_{26}H_{32}N_2O$	In development, not yet FDA approved	Bastos et al, 2016 (review)
FDA = Food and Drug Administration			

3.4 Anitens

As discussed previously, the androgen receptor is a large multi-domain protein composed of globular ligand and DNA-binding domains and an N-terminal transactivation domain that is intrinsically disordered (ID) (Reid et al, 2006; Lavery et al, 2008). Currently all conventional therapies have concentrated on androgen-dependent activation of the AR through its C-terminal ligand binding domain (Figure 8).

Figure 8 Site of Action for Conventional Prostate Cancer Therapies



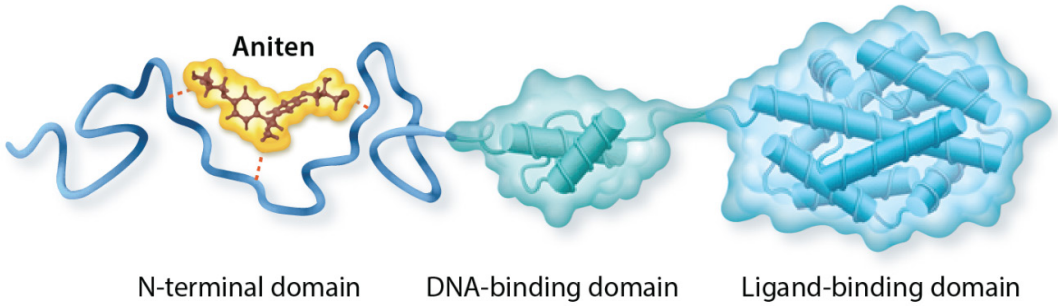
Previous results have shown that although these therapies are initially effective, they eventually fail due to (Guerrini et al, 2014; Ferroni et al, 2017; Howard et al, 2019; Huang et al, 2018; Paschalis et al, 2018):

- AR gain-of-function mutations with increased sensitivity to androgens or increased recruitment of AR co-activators,
- AR amplification/overexpression,
- Androgen independent AR activation,
- Expression of constitutively active AR splice variants,
- Intratumoral conversion of adrenal androgens and androgen production.

The function of the AR N-terminal domain (residues 1 to 558) is to recruit the basal transcription machinery by binding to general transcription factors either directly or assisted by transcriptional co-activators (Gelmann, 2002). These protein-protein interactions are thought to cause the folding of binding motifs in a region of the N-terminal domain called activation function 1 (AF-1) that has not yet been characterized at high resolution (Lavery et al, 2008). Inhibiting these interactions is considered a potential therapeutic approach for both prostate cancer and CRPC (Quayle et al, 2007), but the N-terminal domain has not been considered a suitable target for drug discovery due to its apparent lack of persistent secondary and tertiary structure. However, over the last few years development of drugs that interact with ID regions has met with some success (Lamberto et al, 2011; Krishnan et al, 2014) and has shown that targeting them with small molecules may be a viable therapeutic approach (Metallo, 2010; Heller et al, 2015).

ESSA is developing aniten compounds that directly inhibit the N-terminal domain of the androgen receptor, bypassing resistance mechanisms to current antiandrogen hormonal treatment of prostate cancer (Figure 9).

Figure 9 Site of Action for Aniten Prostate Cancer Therapy



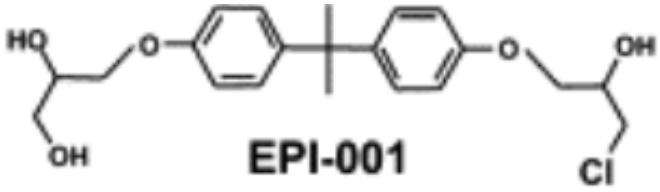
Anitens offer a novel approach to the treatment of prostate cancer since they (Sadar, 2011; Sader, 2012):

- Do not cause nuclear translocation of the AR in the absence of ligands unlike antiandrogens,
- Do not cause the AR to bind androgen-response elements,
- Inhibit protein-protein interactions that are necessary for transcription, and
- Are the only known direct inhibitor of all AR species, including constitutively active forms.

3.4.1 EPI-001

The first aniten compound (EPI-001) was identified by screening a library of marine sponge extracts for inhibition of both ligand-dependent and ligand-independent activation of the AR by blocking transactivation of the AR N-terminal domain (Figure 10) (Andersen et al, 2010).

Figure 10 Chemical Structure of EPI-001



(Andersen et al, 2010)

It was found that EPI-001 selectively interacts with a partially folded region of the transactivation domain of the AR, known as transactivation unit 5 (Tau-5). Tau-5 is key for the ability of prostate cells to proliferate in the absence of androgens (De Mol et al, 2016) which is a distinctive feature of CRPC.

EPI-001 is able to block transactivation of the N-terminal domain and is specific for inhibition of AR without attenuating transcriptional activities of related steroid receptors (GR, MR, PR, ER and VDR). EPI-001 interacts with the AF-1 region, inhibits protein-protein interactions with AR and reduced AR interaction with androgen-response elements on target genes. Importantly, EPI-001 blocks androgen-induced proliferation and caused cytoreduction of CRPC in xenografts dependent on AR for growth and survival without causing toxicity (Andersen et al, 2010).

EPI-001 has two stereogenic centers and can therefore be found as four stereoisomers. To investigate whether the interaction between EPI-001 and Tau-5 was stereospecific the four stereoisomers were synthesized and their interaction with AF-1 studied. The results indicated that the four compounds all interacted with the N-terminal domain of AR and thus the interaction appeared to occur with little or no stereoselectivity. These results agree with the results obtained in vivo by Myung et al (2013), who found that, although one of the stereoisomers tested (EPI-002) was more active than the others, the inhibitory activity of the four stereoisomers were similar.

3.4.2 EPI-506/EPI-002

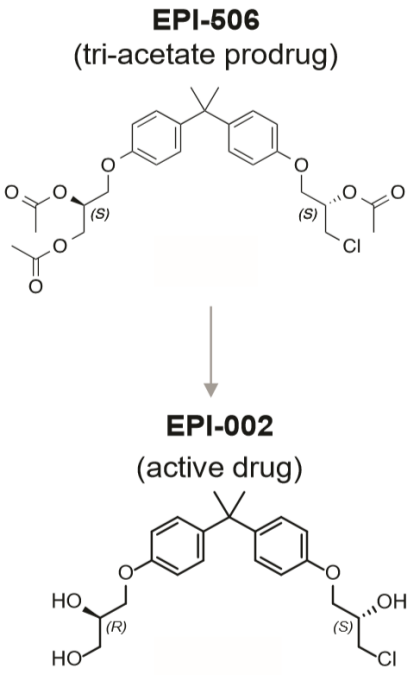
EP-002 is the most potent of EPI-001's four stereoisomers and has improved properties compared with the other's including (Myung et al, 2013):

- EPI-002 inhibits a constitutively active AR splice variant that lacks ligand binding domain,
- Oral delivery of EPI-002 reduces the growth of CRPC xenografts expressing AR variants, and

- AR transcriptional program is blocked *in vivo* by EPI-002.

To be able to move EPI-002 into clinical development, ESSA developed a triacetate prodrug of EPI-002 called EPI-506 (Figure 11) (Antonarakis et al, 2016).

Figure 11 Chemical Structure of EPI-002 and EPI-506



(Le Moigne et al, 2019a)

EPI-506 was tested in a phase 1/2 open-label study to assess the safety, pharmacokinetics (PK) and anti-tumor activity of oral EPI-506 in patients with mCRPC (NCT02606123). A brief overview of the study can be found in Table 6.

Table 6 Overview of Clinical Trial NCT02606123

Overview of Clinical Trial NCT02606123 (ClinicalTrials.gov)	
Title	Safety and Anti-Tumor Study of Oral EPI-506 for Patients with Metastatic Castration-Resistant Prostate Cancer
Condition	Prostatic Neoplasms Genital Neoplasms, Male Genital Diseases, Male Prostatic Diseases
Intervention	Drug: EPI-506 Patients will receive EPI-506 as an oral softgel capsule. Part 1: Approximately six dose levels of EPI-506 will be studied, beginning at 80 mg/day. During the Single-Dose Period, patients will first receive a dose of EPI-506 in the fasted state followed by 2 days of washout, and then patients will receive a second dose of EPI-506 in the fed state followed by 2 days of washout. Patients will then enter the Multiple Dosing and Long-term Dosing Period where they will receive once or twice daily dosing in a fed or fasted state until they meet discontinuation criteria. Part 2: The dose in Part 2 will be determined in Part 1 of the study. Patients will receive the Part 2 dose daily until they meet discontinuation criteria.

Overview of Clinical Trial NCT02606123 (ClinicalTrials.gov)	
Primary Outcomes	Part 1: Safety and tolerability assessed by vital signs, laboratory measurements, and frequency and severity of treatment-related AEs [Time Frame: 12 weeks] Part 2: PSA response rate [Time Frame: 12 weeks]
Phase	Phase 1 Phase 2
Sponsor	ESSA Pharmaceuticals
Status	Terminated at the end of Part 1
AE = Adverse Event; PSA = Prostate-specific Antigen	

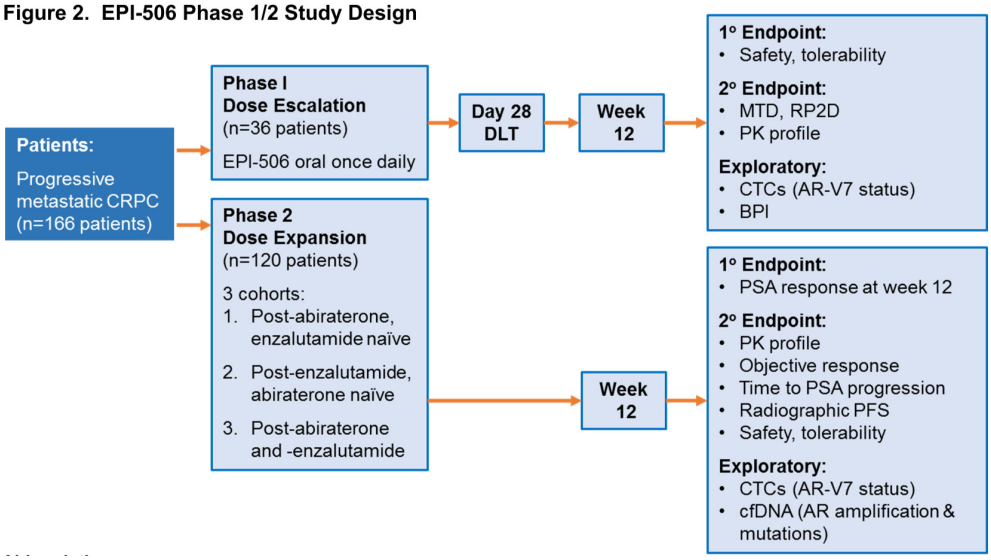
The study design consisted of two parts, a dose escalation phase and a dose expansion phase (Figure 12).

In Part 1, patients were to participate in single, multiple, and long-term dosing periods using EPI-506 to determine safety, PK, the maximum tolerated dose (MTD) and preliminary indications of anti-tumor activity. Part 1 was an open-label, adaptive 3 + 3 design, dose-escalation study. Approximately six dose levels of EPI-506 were to be studied, beginning at 80 mg/day. Enrolled patients could escalate to a subsequent dose cohort after their initial twelve weeks.

In Part 2, three patient populations; post-abiraterone mCRPC but enzalutamide-naïve, post-enzalutamide mCRPC but abiraterone-naïve, and post-abiraterone and enzalutamide mCRPC were to be studied at the dose determined in Part 1 over 12 weeks of daily dosing. Approximately 120 patients (40 in each cohort) were to be enrolled.

Figure 12 EPI-506 Clinical Trial Study Design

Figure 2. EPI-506 Phase 1/2 Study Design



(Chi et al, 2017)

This trial was the first to evaluate a compound targeting the AR N-terminal domain. The results indicated that EPI-506 was well-tolerated with an acceptable safety profile. However, the study was terminated at the end of Part 1 because of an excessively high pill burden on patients (18 capsules/day). Information on patient disposition for Part 1 of the EPI-506 trial can be found in Table 7.

Table 7 EPI-506 Clinical Trial Patient Disposition

Patient Disposition	
Enrolled	21
Dose Level 80 mg 160 mg 320 mg 640 mg 1280 mg 2400 mg	 3 3 3 6 3 3
Discontinued Due to adverse events Due to progressive disease Due to withdrawal of consent	17 2 13 2

(Chi et al, 2017)
Safety information for some patients in Part 1 of the EPI-506 trial has been summarized in Table 8 and Table 9.

Table 8 Commonly Reported Adverse Events Following EPI-506 Administration

Most Commonly Reported Adverse Events (any cause)	All Grades, N (%)
Diarrhea	8 (38%)
Nausea	7 (33%)
Pain in extremities	6 (29%)
Decreased appetite	4 (19%)
Fatigue	4 (19%)
Anemia	3 (14%)
Arthralgia	2 (10%)
Dizziness	2 (10%)
Fall	2 (10%)
N = Number	

(Chi et al, 2017)

Table 9 Adverse Events ≥ Grade 3 Following EPI-506 Administration

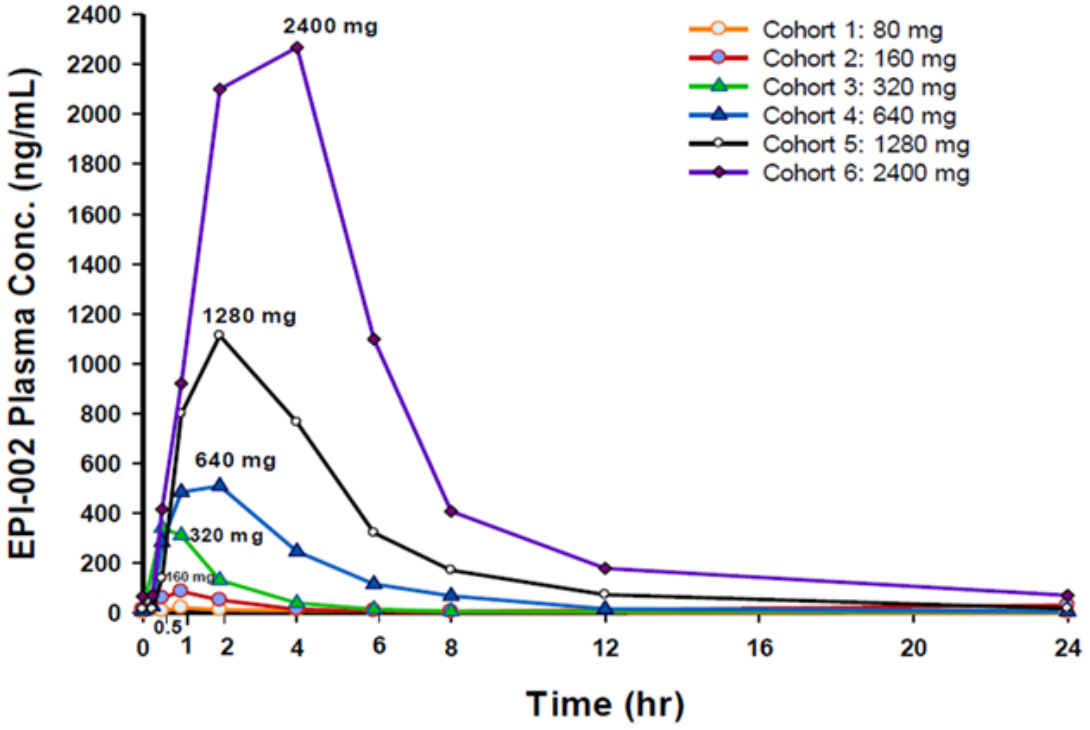
Adverse Events ≥ Grade 3	N (%)	Relationship to Study Drug
Anemia	3 (14%)	Not related
Neutropenia	2 (10%)	Not related
Arthralgia	1 (5%)	Not related
AST elevated	1 (5%) DLT	Possibly related
Amylase Elevated	1 (5%)	Possibly related
Gastrointestinal hemorrhage	1 (5%)	Not related
Urinary retention	1 (5%)	Not related

Adverse Events ≥ Grade 3	N (%)	Relationship to Study Drug
Syncope	1 (5%)	Not related
Thrombocytopenia	1 (5%)	Not related
AST = Aspartate Aminotransferase; DLT = Dose-limiting Toxicities; N = Number		

(Chi et al, 2017)

EPI-002 the active moiety of EPI-506 prodrug was measured in plasma of treated patients. The plasma profiles indicate dose-proportionality for the maximum concentration (C_{max}) and area under the concentration curve (AUC) following once-daily administration of 80 mg through 2400 mg EPI-506 (Figure 13 and Table 10). The EPI-506 prodrug was not detected in plasma at any measured time point across dose groups.

Figure 13 Mean EPI-002 plasma concentration-time profiles across EPI-506 dose cohorts



(Chi et al, 2017)

Table 10 EPI-002 Pharmacokinetics Following Once-Daily EPI-506 Administration (Mean ± SD)

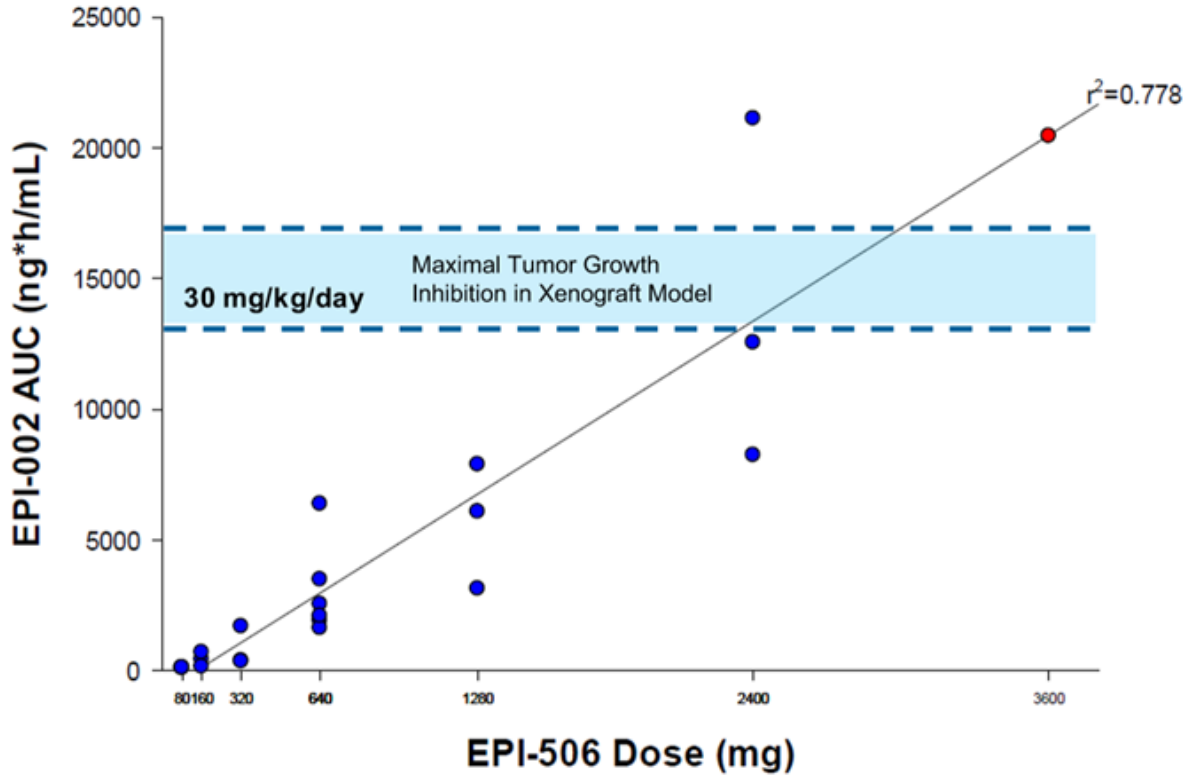
PK Parameter	Cohort 1 80 mg (N=3)	Cohort 2 160 mg (N=3+1 IPDE)	Cohort 3 320 mg (N=3)	Cohort 4 640 mg (N=6)	Cohort 5 1280 mg (N=3+3 IPDE)	Cohort 6 2400 mg (N=3)
C_{max} (ng/mL)	26 ± 9.3	131 ± 90	393 ± 515	763 ± 426	1547 ± 880	2372 ± 813
T_{max} (hr)	1.00 (1.0 - 4.0)	0.75 (0.5 - 4.0)	1.00 (0.5 - 3.0)	1.50 (0.5 - 4.0)	1.50 (1.0 - 4.0)	4.00 (2.0 - 4.0)
C_{last} (ng/mL)	8.4 ± 9.6	19 ± 19.9	5.8 ± 2.0	8.4 ± 5.8	21 ± 6.5	70 ± 25
$AUC_{0\text{-}24hr}$ (ng*hr/mL)	100 ± 18	415 ± 226	815 ± 765	2541 ± 819	5722 ± 1703	13829 ± 6758

PK Parameter	Cohort 1 80 mg (N=3)	Cohort 2 160 mg (N=3+1 IPDE)	Cohort 3 320 mg (N=3)	Cohort 4 640 mg (N=6)	Cohort 5 1280 mg (N=3+3 IPDE)	Cohort 6 2400 mg (N=3)
AUC = Area Under the Concentration Curve; C_{last} = Last Concentration; C_{max} = Maximum Concentration; hr = Hour; IPDE = Intra-patient Dose Escalation; PK = Pharmacokinetics; SD = Standard Deviation						

(Chi et al, 2017)

When treated with high levels of EPI-506, human exposures correlated to the exposure ranges that demonstrated tumor regression in a preclinical LNCaP xenograft mouse model (Figure 14).

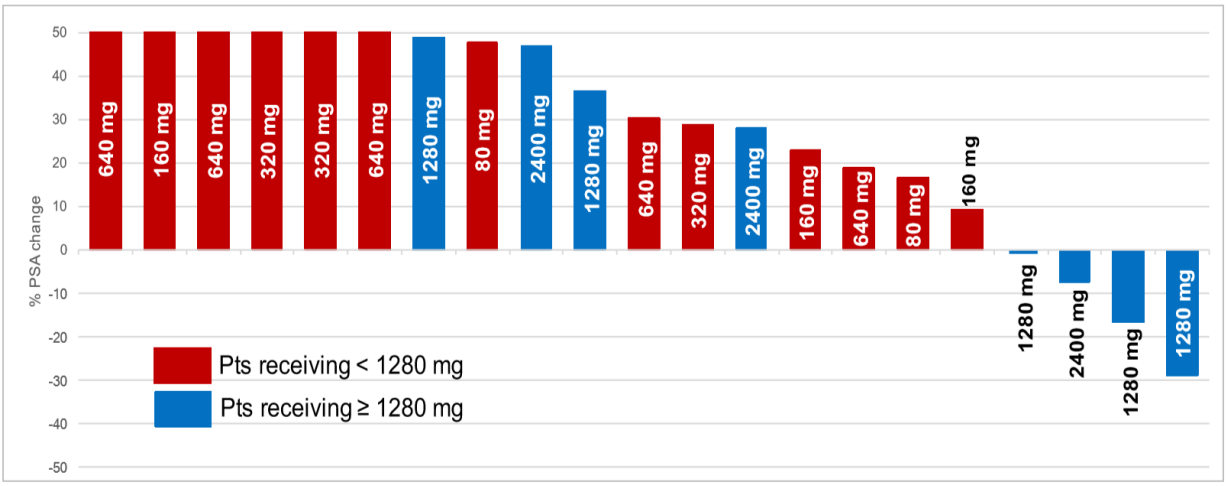
Figure 14 Comparison of EPI-002 Plasma AUC and Effective Xenograft Model AUC Range



(Chi et al, 2017)

PSA levels declined (ranging from 4-29%) and stable disease (unchanged PSA) were observed in patients treated in the higher dose cohorts (>1,280 mg) (Figure 15).

Figure 15 Maximal PSA change at any time from baseline



(Chi et al, 2017)

In summary this trial was the first to evaluate targeting the AR N-terminal domain, a region critical for transcriptional function of all known AR species. The results from the trial indicate that:

- EPI-506 was well-tolerated with an acceptable safety profile,
- PK data support dose-proportionality,
- PSA declined and stable disease was observed in higher dose cohorts, and
- Human exposures at higher dose levels correlate to the exposure ranges that demonstrated tumor regression in a preclinical LNCaP xenograft mouse model.

The overall conclusion was that more stable and potent compounds were needed to address EPI-506/EPI-002's limitations.

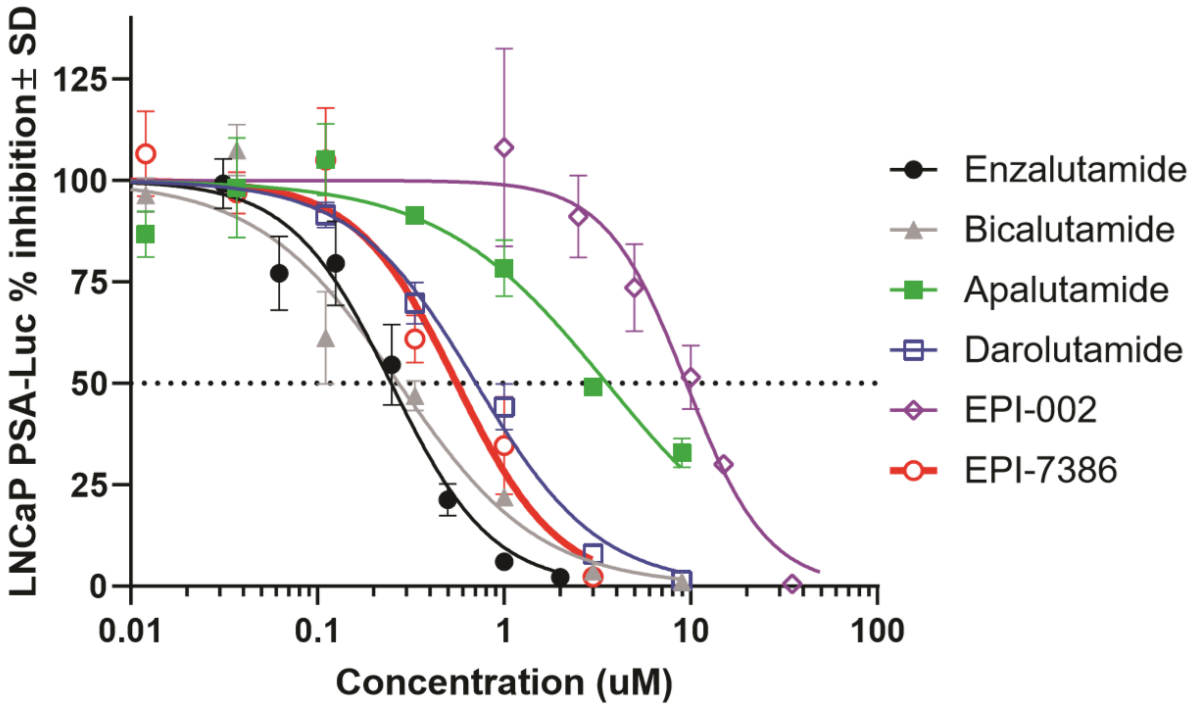
3.4.3 EPI-7386

ESSA has identified and developed several anitens with improved cellular potency compared to EPI-506/EPI-002 and which are also metabolically stable.

EPI-7386 demonstrates a 20-fold improvement in AR-driven cellular potency, while being highly stable in human and animal hepatocytes. In vitro proliferation assays demonstrated on-target activity across a panel of prostate cancer cell lines, with activity in AR-V7-driven cellular models. EPI-7386 was able to control tumor growth and induce tumor regressions in several CRPC xenografts, including enzalutamide resistant models. In addition, the combination of enzalutamide with EPI-7386 demonstrated a more robust and more homogeneous antitumor response (Le Moigne et al, 2019b).

EPI-7386 has similar in vitro potency to several antiandrogens in a full-length AR models (Figure 16 and Table 11).

Figure 16 EPI-7386 Inhibition of Androgen Induced Transcriptional Activity



(Le Moigne et al, 2019b)

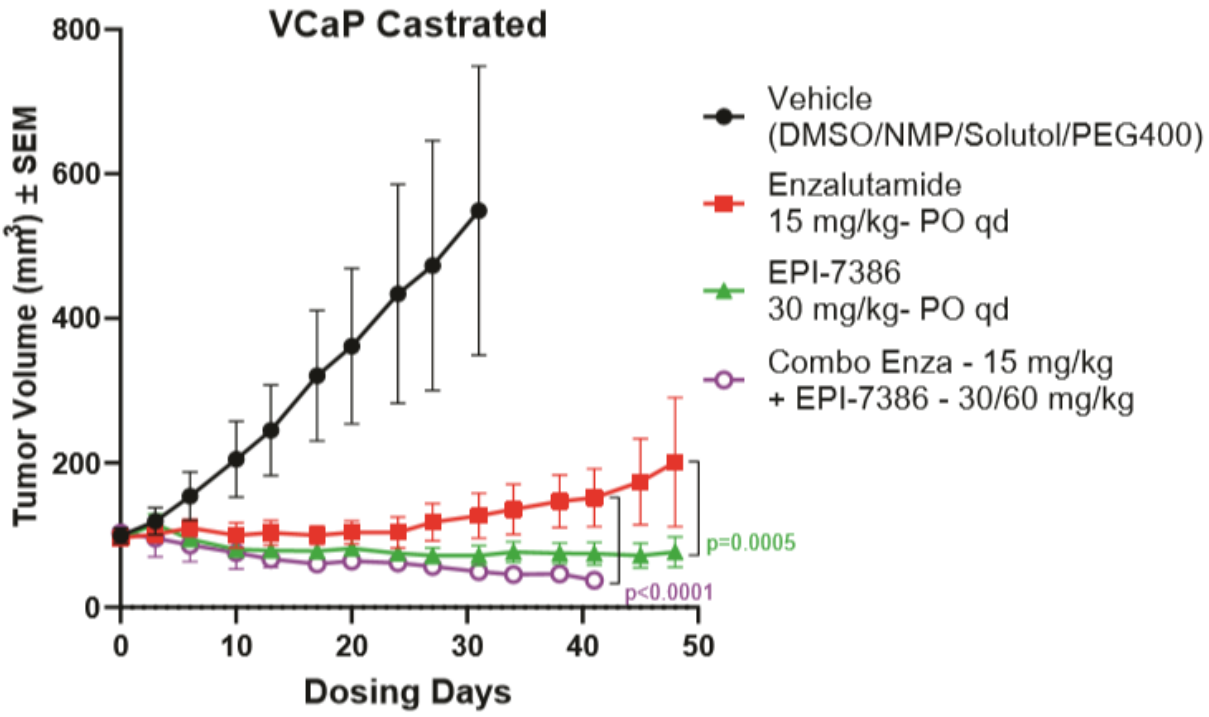
Table 11 EPI-7386 IC_{50} for Androgen Induced Transcriptional Activity

Compound	IC_{50} (nM)	N
EPI-002	9580	2
EPI-7386	421	5
Enzalutamide	154	5
Bicalutmide	242	7
Apalutamide	4540	3
Darolutamide	616	3
IC_{50} = Inhibitory Concentration 50%; N = Number		

(Le Moigne et al, 2019b)

EPI-7386 showed superior activity to enzalutamide as a single agent for reduction in tumor volume in the VCaP xenograft tumor model (Figure 17).

Figure 17 Effect of EPI-7386 on Tumor Volume in Castrated Male Mice Bearing VCaP Tumors



(Le Moigne et al, 2019b)

EPI-7386 showed similar activity to enzalutamide as a single agent for disease progression in the VCaP xenograft tumor model (Table 12).

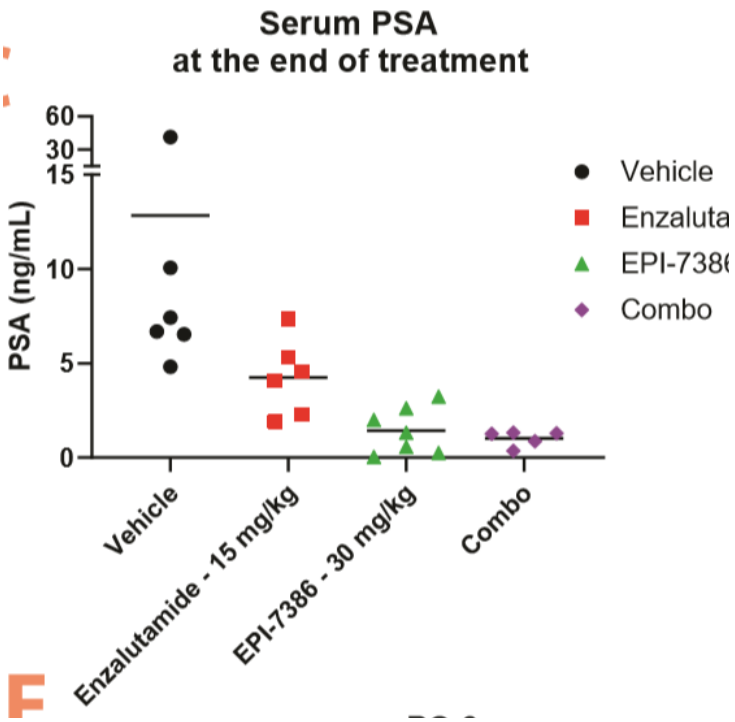
Table 12 Effect of EPI-7386 on Disease Progression in Castrated Male Mice Bearing VCaP Tumors

ARM	Progressive Disease	Stable Disease	Partial Response	Complete Response
ENZ (15 mg/kg)	4 (57%)	3 (43%)	0 (0%)	0 (0%)
EPI-7386 (30 mg/kg)	1 (14%)	5 (71%)	0 (0%)	1 (14%)
ENZ + EPI-7386	0 (0%)	1 (20%)	4 (80%)	0 (0%)
ENZ = Enzalutamide				

(Le Moigne et al, 2019b)

EPI-7386 showed superior activity to enzalutamide as a single agent on serum PSA levels at the end of treatment in the VCaP xenograft tumor model (Figure 18).

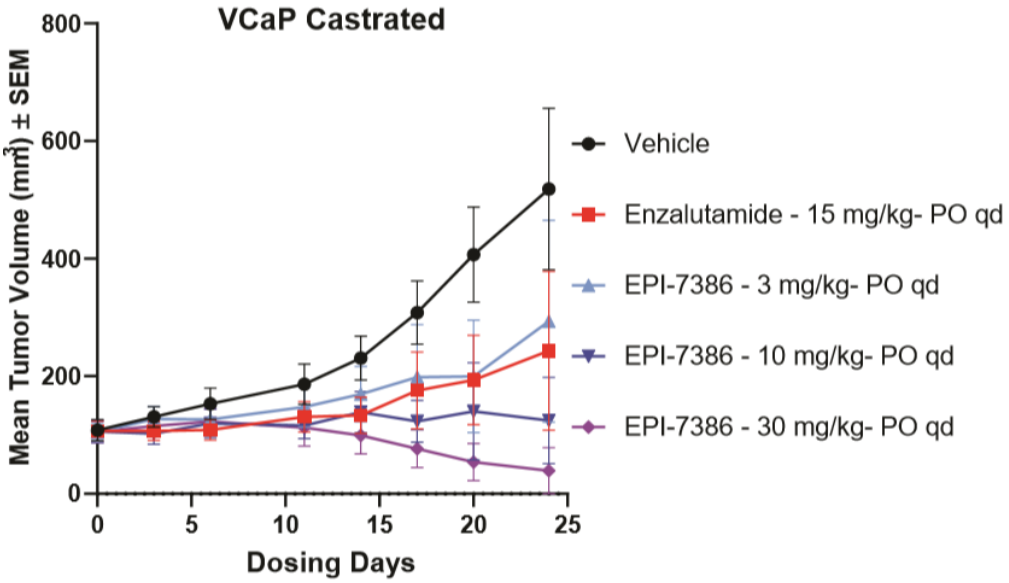
Figure 18 Effect of EPI-7386 on Serum PSA Levels in Castrated Male Mice Bearing VCaP Tumors



(Le Moigne et al, 2019b)

EPI-7386 showed a dose response inhibition on tumor volume in the castrated VCaP xenograft tumor model (Figure 19).

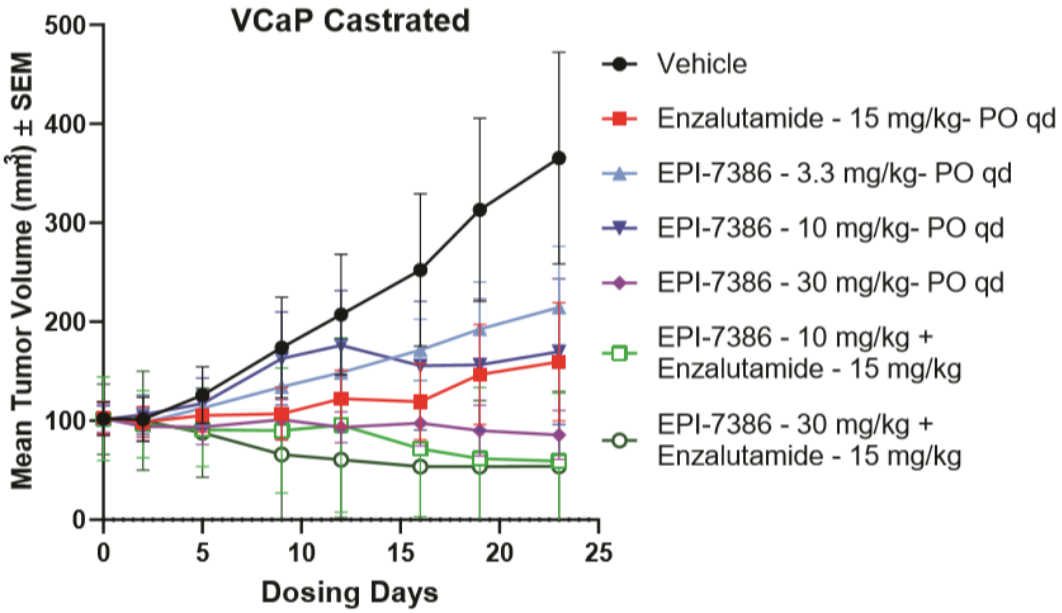
Figure 19 EPI-7386 Dose Response in Castrated VCaP Model



(Le Moigne et al, 2019b)

EPI-7386 alone or in combination with enzalutamide showed a dose response inhibition of tumor volume in the castrated VCaP xenograft tumor model (Figure 20).

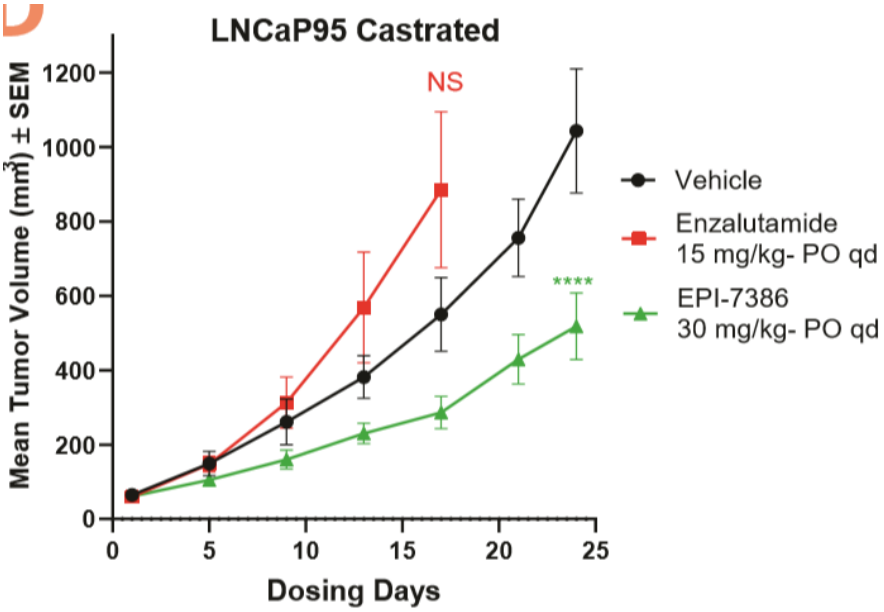
Figure 20 Combination Enzalutamide and EPI-7386 Dose Response in Castrated VCaP Model



(Le Moigne et al, 2019b)

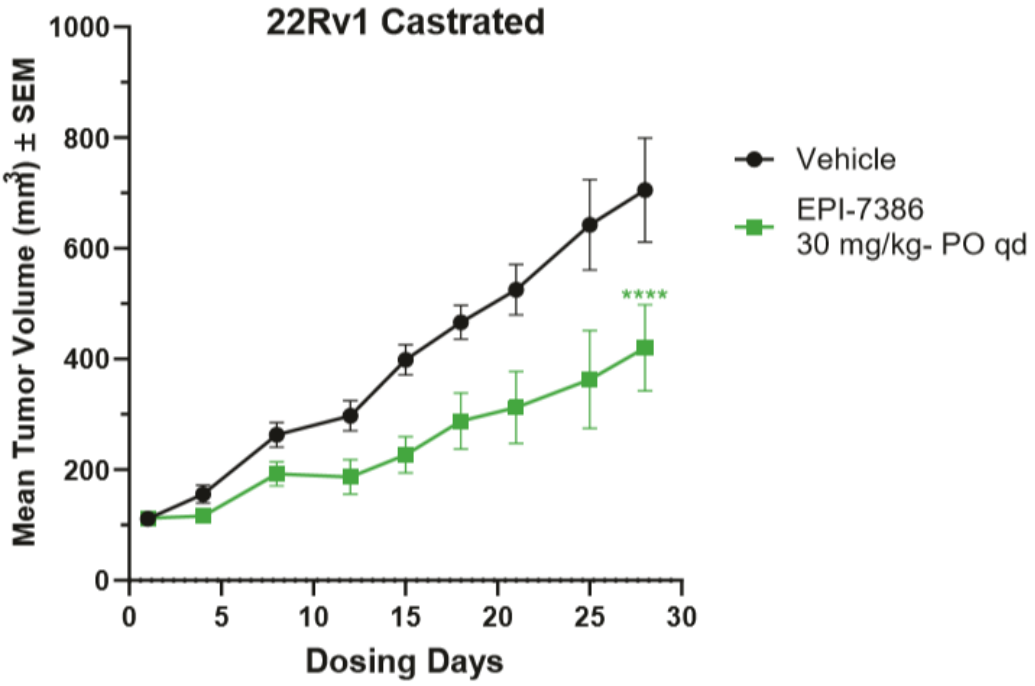
EPI-7386 was also active in two enzalutamide-resistant mouse models (Figure 21 and Figure 22).

Figure 21 Effect of EPI-7386 on Tumor Volume in an Enzalutamide Resistant LNCaP95 Castrated Mouse Model



(Le Moigne et al, 2019b)

Figure 22 Effect of EPI-7386 on Tumor Volume in an Enzalutamide Resistant 22Rv1 Castrated Mouse Model



(Le Moigne et al, 2019b)

EPI-7386 represents a new generation of anitens and has been selected as ESSA's next clinical candidate. The proposed design for a Phase 1 clinical trial has been briefly outlined below. The clinical study will consist of two parts, a dose escalation phase and a dose expansion phase.

Part 1a – Dose Escalation

- Primary objectives
  - Safety and tolerability of orally administered EPI-7386
- Secondary objectives
  - To determine the MTD and the recommended Phase II dose,
  - To evaluate the PK of EPI-7386 and to measure PSA as a pharmacodynamic (PD) marker of response

Part 1b – Dose Expansion

- Primary objective is to further evaluate the safety, tolerability, PK and preliminary anti-tumor activity of the MTD or RP2D of EPI-7386 (as measured by PSA changes over time).

IND filing for EPI-7386 is expected in 1Q of 2020 and the Phase 1 study will start shortly thereafter.

4 Conclusions

The prognosis and treatment options for prostate cancer depends on the stage of the cancer, the patient's age, and whether the cancer has just been diagnosed or has recurred. Radical prostatectomy and/or radiation are the standard primary treatments for patients with localized prostate cancer. For recurrent disease and/or advanced stage prostate cancer, the main therapy is androgen deprivation therapy. Androgen deprivation therapy includes surgical castration, medical castration, antiandrogens and androgen biosynthesis inhibitors.

These therapies relieve symptoms, reduce tumor burden, and prolong patient survival, while having relatively modest side effects. Unfortunately, hormone deprivation therapy rarely cures the cancer itself. Prostate cancer almost always recurs, resulting in deadly castration-resistant prostate cancer.

Many aspects of androgen receptor signaling allows for therapeutic exploitation. Conventional antiandrogen therapies have concentrated on androgen-dependent activation of the androgen receptor through its C-terminal ligand binding domain. However, ESSA is developing a new class of drugs called anitens that block a novel target on the androgen receptor, the N-terminal domain. This domain is critical for androgen receptor function and is not currently targeted by any other therapy.

ESSA has identified and developed several anitens including EPI-001, EPI-002, EPI-506 and EPI-7386. Their second-generation compound EPI-7386 demonstrates a 20-fold improvement in androgen receptor-driven cellular potency, while being highly stable in human and animal hepatocytes. In vitro proliferation assays demonstrated on-target activity across a panel of prostate cancer cell lines, with activity in AR-V7-driven cellular models. EPI-7386 was able to control tumor growth and induce tumor regressions in several castration-resistant prostate cancer xenografts, including antiandrogen resistant models. A combination of antiandrogen with EPI-7386 has demonstrated a more robust and homogeneous antitumor response.

ESSA has selected EPI-7386 as its next clinical candidate. EPI-7386 is currently undergoing IND enabling studies. The expected IND filing date is in 1Q of 2020 with a Phase 1 study scheduled to start shortly thereafter. If successful in clinical trials, EPI-7386 offers a unique opportunity to expand and/or improve upon conventional CRPC therapies.

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