Zacks Small-Cap Research
Sponsored – Impartial - Comprehensive

August 26, 2019
David Bautz, PhD
312-265-9471
dbautz@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Chicago, IL 60606

ESSA Pharma Inc. (EPIX-NASDAQ)

EPIX: *Initiating Coverage of ESSA Pharma Inc.; Unique Mechanism Targeting the Androgen Receptor in Prostate Cancer…*

Based on our probability adjusted DCF model that takes into account potential future revenues from EPI-7386, EPIX is valued at $6/share. This model is highly dependent upon continued clinical success of EPI-7386 and will be adjusted accordingly based upon future clinical results.

Current Price (08/26/19)	$2.20
Valuation	**$6.00**

OUTLOOK

We are initiating coverage of ESSA Pharma Inc. (EPIX) with a valuation of $6.00. ESSA is a biopharmaceutical company developing therapies for treatment-resistant prostate cancer. The company is focused on compounds that inhibit activation of the androgen receptor (AR) through binding to the N-terminal domain (NTD), which is a unique mechanism of action compared to currently available prostate cancer treatments that target the AR. ESSA has selected a lead preclinical development candidate and we anticipate the company initiating a Phase 1 clinical trial in patients with metastatic castration-resistant prostate cancer (mCRPC) in the first half of 2020.

SUMMARY DATA

52-Week High	**$4.50**
52-Week Low	**$1.41**
One-Year Return (%)	**-42.86**
Beta	**1.85**
Average Daily Volume (sh)	**18,810**
Shares Outstanding (mil)	**15**
Market Capitalization ($mil)	**$32**
Short Interest Ratio (days)	**1**
Institutional Ownership (%)	**N/A**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2019 Estimate	**N/A**
P/E using 2020 Estimate	**N/A**

Risk Level	**High**
Type of Stock	**Small-Growth**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2018	0 A	0 A	0 A	0 A	0 A
2019	0 A	0 A	0 A	0 E	0 E
2020					0 E
2021					0 E

Earnings per Share

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2018	-$1.40 A	-$0.83 A	-$0.50 A	-$0.39 A	-$2.55 A
2019	-$0.42 A	-$0.54 A	-$0.52 A	-$0.18 E	-$1.33 E
2020					-$0.48 E
2021					-$0.53 E

WHAT'S NEW

Initiating Coverage

We are initiating coverage of ESSA Pharma Inc. (EPIX) with a $6.00 valuation. ESSA is a biopharmaceutical company developing treatments for prostate cancer that are no longer responding to current therapies. The company is developing a series of compounds ('anitens') that disrupt the androgen receptor (AR) signaling pathway through a unique mechanism of action that targets the N-terminal domain (NTD) of the AR, as opposed to the ligand-binding domain (LBD) of the AR that is targeted by all other AR-directed prostate cancer treatments. The company has selected a lead preclinical aniten (EPI-7386) to advance to clinical trials, and we anticipate a Phase 1 clinical trial initiating in the first half of 2020.

Unmet Need in mCRPC

Following initial treatment, approximately one-third of patients with localized prostate cancer will develop recurrent or advanced disease. Many of these patients will undergo androgen ablation through the use of androgen deprivation therapy (ADT). However, most patients' tumors will recur despite the absence of testosterone, and at that point the patient is deemed to have castration-resistant prostate cancer (CPRC). Patients with CPRC are typically treated with anti-androgens that inhibit the synthesis of androgens or the binding of androgens to the AR. Even with new anti-androgen therapies, resistance will develop for most every patient and at this point CPRC remains incurable.

Novel Class of Drugs to Treat Prostate Cancer

All current anti-androgen prostate cancer treatments that target the AR are specific to the ligand binding domain (LBD). These drugs are effective, but positive long-term outcomes are difficult due to various resistance mechanisms that develop. These mechanisms ultimately result in alterations to the AR in the LBD that result in keeping the activity of the AR intact and cause anti-androgen therapies to be ineffective with the cancer progressing. ESSA is developing a novel class of compounds (anitens) that target the N-terminal domain of the AR, where few if any resistance mechanisms are known to occur.

Lead Preclinical Asset Selected

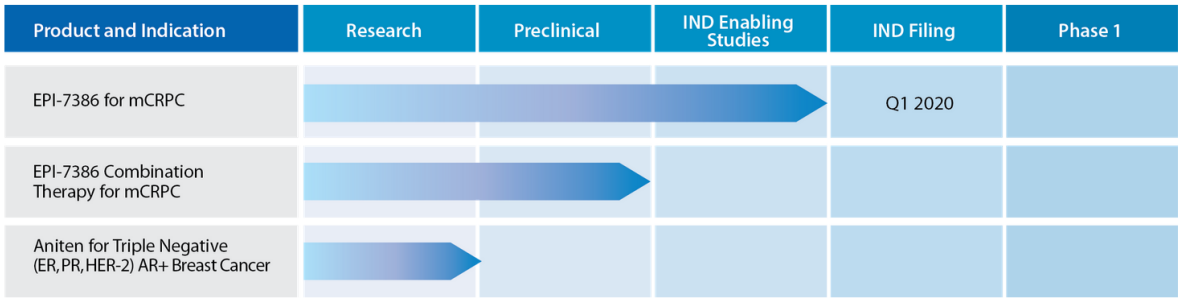
Following completion of a Phase 1 clinical trial with the first-generation aniten compound EPI-506, the company discontinued its development due to an inability to achieve exposures that produced efficacy in animal models. The company then designed, synthesized, and screened a series of more potent and stable next-generation compounds. From these compounds, the company identified a next-generation aniten compound, EPI-7386, that has increased potency and reduced metabolism while maintaining a clean off-target profile. We anticipate a Phase 1 clinical trial of EPI-7386 initiating in the first half of 2020.

Financing Through Multiple Inflection Points

In July 2019, ESSA completed the acquisition of Realm Therapeutics, which gives ESSA access to Realm's estimated net cash amount of $20.5 million. In addition, in August 2019 the company announced a public offering of common stock that is intended to raise gross proceeds of $36 million through the issuance of 18 million common shares. Following the closing of the public offering, we estimate the company will have sufficient financial resources for multiple inflection points, including the completion of the Phase 1 clinical trial of the EPI-7386 in patients with advanced prostate cancer and proof-of-concept data from a Phase 1 trial of EPI-7386 in combination with current anti-androgen therapy in earlier stage mCRPC patients.

INVESTMENT THESIS

ESSA Pharma Inc. (EPIX) is a biopharmaceutical company developing a novel class of compounds, known as 'anitens', to treat prostate cancer in patients that are progressing on standard of care therapy. Anitens target the androgen receptor (AR), which is the main signaling mechanism driving the growth of prostate tumors, through binding of the N-terminal domain (NTD), which is unique compared to other available anti-androgen therapies. The company has completed a Phase 1 trial with a first-generation aniten compound, EPI-506, that confirmed the safety and tolerability of this class of compounds. However, due to its short half-life and other negative pharmaceutical properties, the development of EPI-506 was discontinued while research continued on the development of next-generation anitens. This work led to the discovery of EPI-7386, a next-generation aniten that has a number of advantages compared to first-generation anitens. We anticipate that compound entering Phase 1 clinical testing in the first half of 2020.



Prostate Cancer

Prostate cancer is the most common non-cutaneous cancer diagnosed in men. It is typically a slow growing cancer, although it still accounts for approximately 10% of all cancer related deaths in men. The 2020 estimated incidence of prostate cancer in the U.S. is approximately 550,000 with a prevalence of approximately 3 million (Scher *et al*., 2015). In addition, the disease will be responsible for approximately 30,000 deaths. Prostate cancer is quite rare in men less than 40 years of age, and is still uncommon in men younger than 50. Sixty percent of cases are in men aged 65 or older and the average age of diagnosis is 66. Prevalence rates are significantly higher in African-Americans than in White or Hispanic populations, although the exact reasons for this are unclear (Hoffman *et al*., 2001). In addition to age and race, other risk factors include geography, as most cases occur in North American, Northwestern Europe, Australia, and the Caribbean Islands, and genetics, as prostate cancer appears to run in some families.

The different stages of prostate cancer include:

Localized disease: This is prostate cancer that has not advanced beyond the prostate. Treatment at this stage depends on a number of factors, including the patient's overall life expectancy and the biological characteristics of the tumor. Treatment options include active surveillance (consistent monitoring of the course of the disease with intervention taken if the tumor progresses), radiation therapy, or radical prostatectomy. Localized prostate cancer is the most common form of the disease and is typically identified through the digital rectal exam or prostate specific antigen (PSA) screening.

Non-metastatic hormone sensitive: Following localized treatment, a rising PSA level is widely thought to signify the onset of advanced disease. When confined to the periprostatic area with no evidence of lymph node or direct metastases, first-line therapy is androgen deprivation therapy (ADT), which is removal of androgens (e.g., testosterone and dihydrotestosterone) either through surgical or chemical castration.

Metastatic hormone sensitive: Once the cancer advances to local lymph nodes or beyond therapy can include both ADT (if the cancer is still responding to anti-androgen therapy) along with the chemotherapy agent docetaxel or Zytiga® (abiraterone acetate).

Non-metastatic castration resistant: When PSA levels begin to rise following ADT, the patient is deemed to have 'castration resistant' disease. When imaging studies remain negative for metastatic lesions, the goal of therapy is to delay the development of metastases, which is accompanied by a poor prognosis. This may include observation, for patients who have slowly rising PSA levels, or treatment with another anti-androgen.

Metastatic castration resistant: Prostate cancer typically metastasizes to bone, but can also be found in lymph nodes, lungs, and liver. Treatment at this stage can include chemotherapy, anti-androgens, bone-targeting agents, and immunotherapy.

Detection of Prostate Cancer

There are currently two screening tests available to detect prostate cancer: the digital rectal exam (DRE) and the prostate specific antigen (PSA) test. There is controversy surrounding their use because, while they do detect cancer earlier, it is unclear at this point whether regular screening using these two tests saves lives. This is because some prostate cancers are slow growing, and many times a patient that has prostate cancer is more likely to die from another cause before they die from prostate cancer due to advanced age or other comorbid conditions.

PSA: Prostate-specific antigen is an enzyme produced by normal prostate cells. The highest amounts of PSA are found in seminal fluid, however some PSA escapes the prostate and can be found in the blood. Increased levels of PSA are associated with prostate cancer. (Stamey *et al*., 1987). The PSA test became commercially available in 1986 and has been utilized to assess response to prostate cancer therapy, determine tumor progression, and screen for prostate cancer. Two large studies on prostate cancer screening were published in 2009: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and The European Randomized Study of Screening for Prostate Cancer (ERSPC). The PLCO study randomized 76,693 men age 55 to 74 to either annual screening with PSA and DRE or usual care (Andriole *et al*., 2009) while the ERSPC study randomized 182,000 men to usual care or DRE and PSA screening every four years (Schroder *et al*., 2009). The PLCO study found approximately 17% more cancers in the screening group, however there was no difference in cancer-related deaths between the groups. The ERSPC study found 39% more cancers in the screening group along with a 20-31% reduction in prostate cancer death in the screening arm compared to control. Both studies found that men with a very low PSA level (0-1.0 ng/mL) are at a low risk of developing a clinically significant prostate cancer within the next few years.

Current screening guidelines from the American Cancer Society notes that testing for PSA may reduce the likelihood of dying from prostate cancer, however there are serious risks associated with the test in regards to treating prostate cancer that would not have caused ill effects if left undetected (Wolf *et al*., 2010).

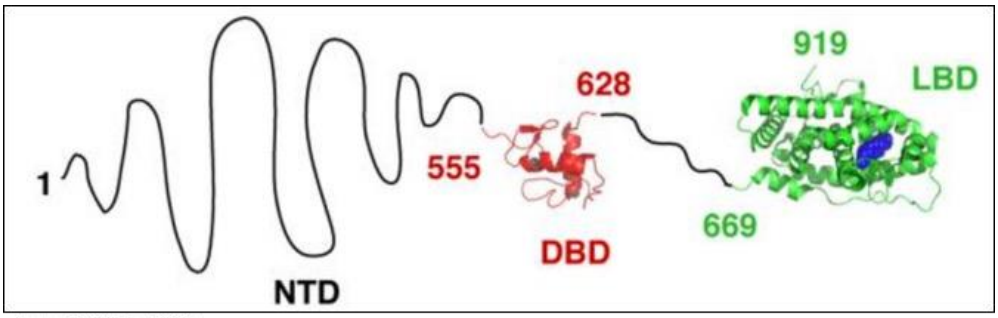
The National Comprehensive Cancer Network (NCCN) has issued updated guidelines in regards to PSA testing:

- Obtain PSA testing in healthy men aged 45 to 70 years and older.
- For men aged 45-49 years with serum PSA levels below 0.7 ng/mL, retest at age 50 years.
- For men aged 45-49 years with serum PSA levels above 0.7 ng/mL, and those aged 50-59 years with serum PSA levels above 0.9 ng/mL, retesting may be performed every 1-2 years.
- Follow-up testing should be performed every 1-2 years for all men with PSA levels above 1.0 ng/mL.
- After age 70 years, PSA testing should be individualized, and indications for biopsy should be carefully evaluated.
- Refer patients for a prostate tissue biopsy when their serum PSA levels exceed 3.0 ng/mL.

Androgen Deprivation Therapy

For patients whose cancer advances despite initial treatment for localized disease, or for those who present initially with more advanced disease, treatment typically begins with ADT. Prostate cells (and subsequently prostate cancer cells) are dependent on androgens (e.g., testosterone and dihydrotestosterone) for growth, as removal of androgens through castration results in apoptosis of prostate epithelial cells.

The androgen receptor (AR) is responsible for mediating the biological effects of androgens (Evans, 1988). It consists of three domains: the N-terminal domain (NTD), the DNA binding domain (DBD), and the ligand binding domain (LBD). The following figure shows the crystal structure of the AR, with the LBD and DBD having well defined structure while the NTD is intrinsically disordered (De Mol *et al*., 2016).

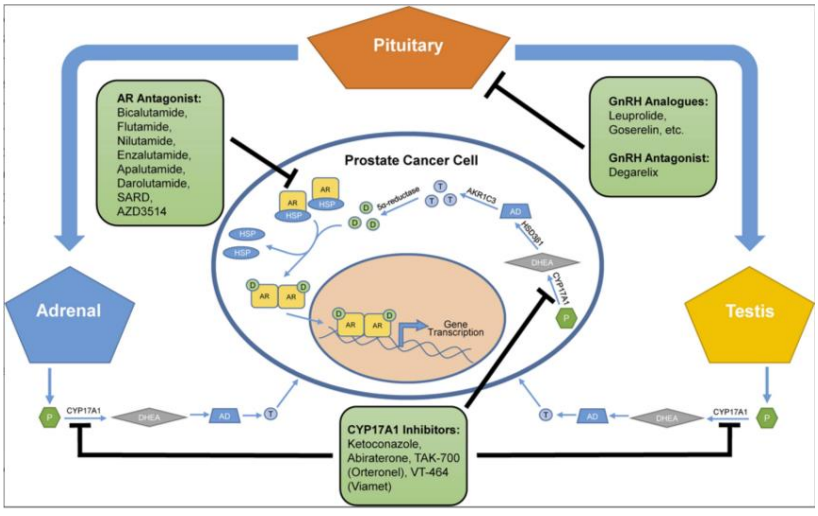


Source: De Mol *et al*., 2016

Androgens bind to the AR in the LBD, at which point the protein undergoes conformational changes, nuclear translocation, and binding to regulatory elements to cause transcription of genes that promote prostate cell growth and survival. The NTD is responsible for transcriptional activity; without it there is no effect on gene expression by the AR. However, the LBD can continue to bind ligands even without the presence of the NTD.

Current ADT Treatments

ADT is designed to completely abrogate all signaling through the AR pathway and has been a mainstay in advanced prostate cancer treatment for over 60 years (Huggins *et al*., 2002). The goal of ADT is to deprive the AR of androgens through inhibition of androgen production or blockage of androgen binding to the AR. The following figure gives an overview of androgen synthesis and the drugs that target each of those pathways (Hahn *et al*., 2018).



Source: Hahn *et al*., 2018

Androgen Synthesis Inhibitors

Zytiga® (abiraterone acetate): This is a pregnenolone-derived 3-pyridyl steroidal agent that selectively and irreversibly inhibits the CYP17A1 enzyme. CYP17A1 inhibition blocks two important steps in testosterone production: the conversion of pregnenolone to 17-OH-pregnenolone and the conversion of 17-OH-pregnenolone to dehydroepiandrosterone. Zytiga® is approved for the treatment of metastatic disease that is both castration resistant and sensitive regardless of chemotherapy status.

Lupron® (leuprolide), Zoladex® (goserelin): These are synthetic versions of gonadotropin-releasing hormone (GnRH) receptor agonists. Agonism of the GnRH receptor causes the pituitary gland to increase production of luteinizing hormone and follicle-stimulating hormone, which initially causes an increase in testosterone levels. However, GnRH receptors eventually become desensitized after several weeks of continuous therapy. To counteract the initial increase in testosterone levels, men with prostate cancer are typically given concurrent therapy with a 5α-reductase inhibitor (e.g., finasteride) to block the downstream effects of testosterone.

Firmagon® (degarelix): This is a synthetic version of a GnRH antagonist, which competes with GnRH for binding to GnRH receptors. Unlike GnRH agonists, there is no initial increase of testosterone following the start of treatment and no need to co-administer an antiandrogen to counteract the effects of an increase in testosterone (van Poppel *et al*., 2008).

AR Antagonists

Casodex® (bicalutamide), Nilandron® (nilutamide), Eulexin® (flutamide): These are first-generation nonsteroidal antiandrogens (NSAAs) that are antagonists of the AR. Of the three, bicalutamide was the most widely prescribed due to its favorable efficacy, tolerability, and safety when compared with nilutamide (potential for interstitial pneumonitis) and flutamide (potential for elevated liver enzymes and hepatotoxicity).

Xtandi® (enzalutamide), Erleada® (apalutamide): These are second-generation NSAAs that are chemically-related molecules, exhibiting a two-atom difference between the two chemical structures. Both show increased efficacy compared to first generation AR antagonists with less risk of elevated liver enzymes or hepatotoxicity. However, both compounds are associated with a small, but increased risk of seizures. Xtandi® exhibits a risk of seizures of 0.4% while Erleada's® seizure risk is 0.2%. Both Xtandi® and Erleada® also exhibit a higher risk of falls (10% and 16%, respectively) and fractures (8% and 12%, respectively). Erleada® treatment is also associated with a higher risk of developing a rash (24%). Xtandi® was first approved by the FDA in 2012 while Erleada® was approved by the FDA in early 2018.

Nubeqa® (darolutamide): This is a newer second-generation NSAA that is structurally distinct from both enzalutamide and apalutamide. In addition, the drug shows much lower central nervous system (CNS) penetration and has CNS side effects, including seizures. The drug was approved by the FDA in July 2019 for the treatment of non-metastatic castration resistant prostate cancer.

Prostate Cancer Treatment Landscape

The prostate cancer treatment landscape is rapidly evolving with numerous clinical trials ongoing, thus the standard of care for each stage is likely to continue to evolve over the next few years. Following initial approvals in late-stage mCRPC patients, anti-androgen therapies are being tested in earlier stage patients. Below we examine currently approved therapies for each stage of prostate cancer along with ongoing clinical trials.

Metastatic Castration Resistant Disease: Current treatment options include Zytiga® (and generic abiraterone), Xtandi®, Provenge®, Xofigo®, and chemotherapy (cabazitaxel/docetaxel). A number of Phase 3 clinical trials are currently underway to test new treatment combinations, including:

Combination Trials of Anti-Androgens and PARP inhibitors:

MAGNITUDE: This is a Phase 3 clinical trial of Zejula® (niraparib) in combination with Zytiga® and prednisone (NCT03748641). Zejula® is a poly ADP ribose polymerase (PARP) inhibitor that is currently approved for the treatment of ovarian cancer.

TALAPRO-2: This is a Phase 3 clinical trial of Talzenna® (talazoparib) in combination with Xtandi® (NCT03395197). Talzenna® is a PARP inhibitor currently approved for the treatment of germline BRCA-mutated, HER2-negative breast cancer.

PROfound: This is a Phase 3 clinical trial comparing Lynparza® (olaparib) to either Zytiga® or Xtandi® (NCT02987543). Lynparza® is a PARP inhibitor that is approved for germline BRCA-mutated ovarian and breast cancer.

TRITON3: This is a Phase 3 clinical trial comparing Rubraca® (rucaparib) to physician's choice (Zytiga® or Xtandi® or docetaxel) (NCT02975934). Rubraca® is a PARP inhibitor that is currently approved for the treatment of ovarian cancer.

Combination Trials of Anti-Androgens and Immunotherapy:

Based upon the Phase 1b/2 KEYNOTE-365 trial, in which Keytruda® (pembrolizumab) was tested in combination with Xtandi®, Lynparza®, or docetaxel/prednisone with encouraging results (ORR of 20% with Xtandi®, 7% with Lynparza®, 14% with docetaxel/prednisone), Merck will be studying each of those combinations in Phase 3 trials: KEYLNK-010 with Lynparza®, KEYNOTE-641 with Xtandi®, and KEYNOTE-921 with docetaxel/prednisone.

Combination Trials of Anti-Androgens and ADT in Earlier Stage Prostate Cancer:

Non-metastatic castration resistant: Current treatment options include Xtandi® and Erleada®. The ARAMIS Phase 3 clinical trial is testing Nubeqa® against placebo (NCT02200614). Nubeqa® was approved based upon an interim analysis of the primary endpoint of metastasis free survival, however the median overall survival (a key secondary endpoint) has not been reached.

Metastatic hormone sensitive: Current treatment options include ADT, Zytiga®, and docetaxel. Ongoing Phase 3 clinical trials in for patients in this stage include: ARCHES - Xtandi® + ADT (NCT02677896); TITAN - Erleada® + ADT (NCT02489318); ARASENS – darolutamide + ADT + docetaxel (NCT02799602).

Non-metastatic hormone sensitive: Current treatment options include ADT and radiotherapy. Many of the next-generation anti-androgens are currently in Phase 3 clinical trials in an effort to expand their labels. These trials include: EMBARK – Xtandi® +/- Lupron® (NCT02319837); Zytiga® + Erleada® + prednisone + ADT vs. ADT only (NCT03777982).

An additional consideration regarding the prostate cancer treatment landscape is that Zytiga® went off patent in 2018 and eight generic abiraterone therapies have been approved so far by the FDA. However, generic abiraterone is only approved for mCRPC due to Johnson and Johnson having data exclusivity in other settings until February 2021.

AR Resistance Mechanisms

Second-generation treatments such as enzalutamide have helped to increase overall survival for patients with mCRPC (Loriot *et al*., 2017), however all patients will invariably develop resistance to treatment and ultimately succumb to the disease. There are a number of molecular mechanisms that underlie this resistance, including:

Tumor derived androgens: CRPC cells are capable of synthesizing their own androgens, thus even under castration conditions serum androgen concentrations may be sufficient to promote AR-driven signaling pathways (Liu *et al*., 2015).

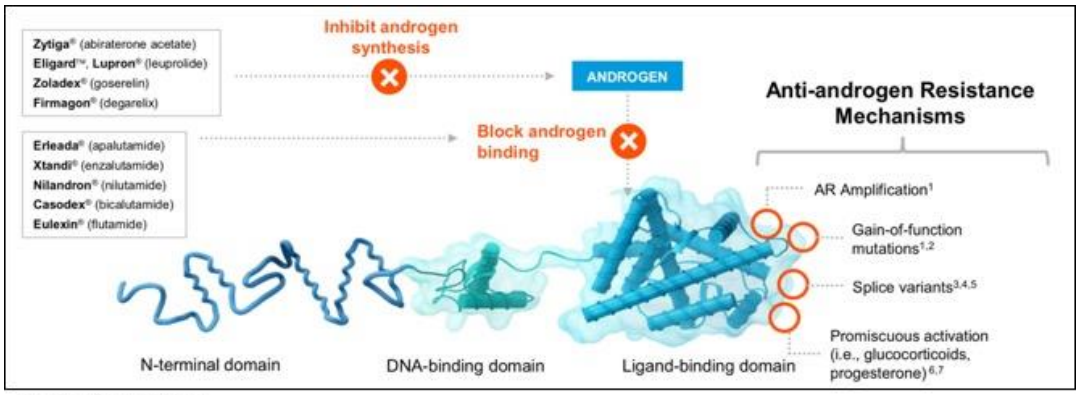
AR amplification: Receptor-ligand interactions are governed by the relative abundance of each of the components of that interaction. Sequencing of CRPC samples shows that the majority of patients show AR gene amplification (Robinson *et al*., 2015). Increased concentration of the AR may make treatments that target it unable to antagonize all of the protein present in the tumor.

AR Mutations: A number of mutations in the AR have been characterized, including those that convert first-generation antiandrogens from antagonists to agonists (Veldscholte *et al*., 1992; Beltran *et al*., 2013). However, each mutation that confers resistance to a particular treatment still leaves the cancer vulnerable to other treatments in the same class (Joseph *et al*., 2013).

AR Variants: Following ADT treatment a number of AR splice variants (AR-V) can be identified in tumor samples, with the most common being AR-V7, which lacks the LBD (Guo *et al*., 2009). The presence of AR-Vs correlate with poor survival, progression, and resistance to antiandrogen therapy (Sun *et al*., 2010; Antonarakis *et al*., 2014). AR-V7 is found in <1% of primary prostate tumors, however it is identified in 75% of patients following ADT and is negatively associated with OS (74.3 vs 25.2 months, HR 0.23 [0.07-0.79], *P*=0.02) (Sharp *et al*., 2019).

Promiscuous Activation: Aberrant activation of the AR has been demonstrated through signaling by insulin-like growth factor I (IGF-I), keratinocyte growth factor (KGF), and epidermal growth factor (EGF) in the absence of androgens (Culig *et al*., 1994). In addition, abiraterone treatment increases the production of progesterone, which can activate a mutant AR with a T878A mutation (Chen *et al*., 2015).

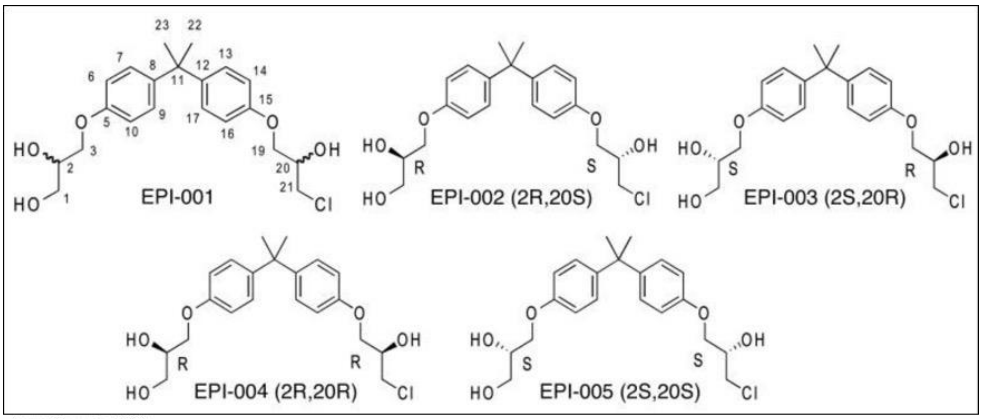
In summary, there are a number of mechanisms involving alterations in AR signaling that ultimately confer resistance to ADT in patients with prostate cancer. These mechanisms continue to drive AR-dependent signaling in the majority of patients even in the absence of androgens. Interestingly, resistance mechanisms are all confined to the LBD, thus targeting a different region of the AR may offer a novel means by which to overcome these resistance mechanisms.



Source: ESSA Pharma Inc.

Anitens to Target the NTD of the AR

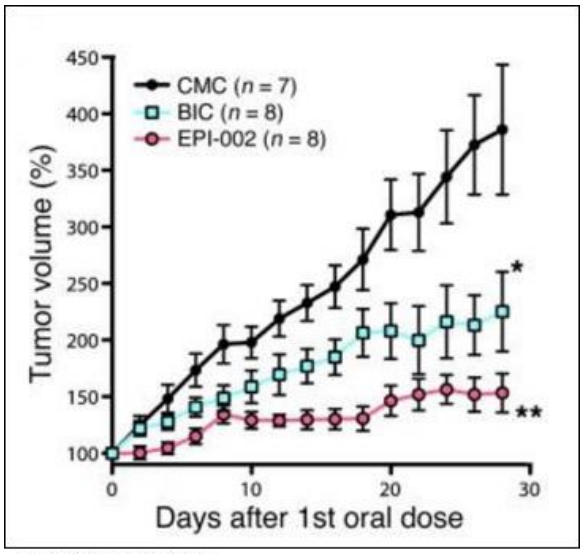
An analysis of a library of extracts from the marine sponge *Geodia lindgreni* was performed to identify compounds that inhibited both ligand-dependent and ligand-independent activation of the AR (Andersen *et al*., 2010). This assay resulted in the identification of compounds that were ultimately determined to be of industrial origin given their resemblance to BADGE (Bisphenol A Diglycidic Ether). Approximately 20 BADGE analogs were tested, with the analog EPI-001 having the most potent activity. Interestingly, additional BADGE analogs had previously been tested and shown to bind the AR (Satoh *et al*., 2004). EPI-001 is a mixture of four stereoisomers (EPI-002, EPI-003, EPI-004, EPI-005), as shown below.



Source: Myung *et al.*, 2013

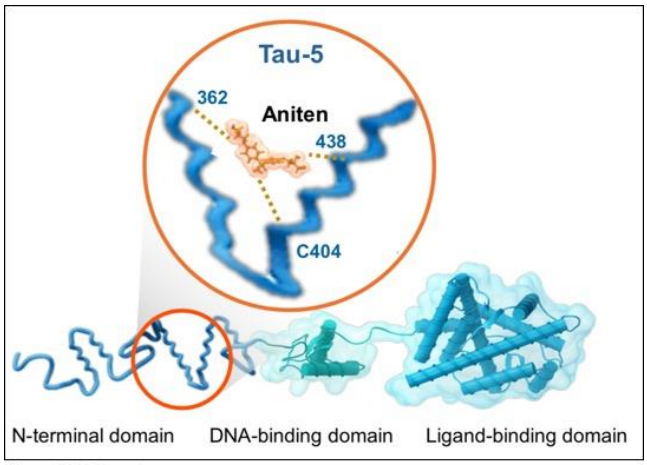
EPI-001 was shown to inhibit both ligand-dependent and ligand-independent AR activity, inhibited activity of an AR deletion mutant that did not contain the LBD, did not inhibit the activity of the progesterone receptor or the glucocorticoid receptor, did not prevent ligand binding to the AR, bound to the NTD of the AR, inhibited protein-protein interactions between the AR and its binding partners, significantly reduced the weights of prostates in intact mice, and significantly reduced the growth of prostate cancer xenografts in mice (Andersen *et al.*, 2010).

Of the four stereoisomers of EPI-001, EPI-002 had the greatest *in vivo* anti-tumor activity, although all the other isomers exhibited some anti-tumor activity as well. Using a VCaP prostate cancer xenograft model, EPI-002 (200 mg/kg) inhibited tumor growth greater than bicalutamide (10 mg/kg), as shown in the following figure. VCaP cells were derived from a skeletal metastasis and are known to have five additional copies of the AR gene and 11-fold more AR mRNA than LNCaP cells (Liu *et al.*, 2008; Makkonen *et al.*, 2011).



Source: Myung *et al.*, 2013

While EPI-001 was shown to bind to the NTD of the AR, a detailed study was undertaken to determine the mechanism of that interaction. The NTD of the AR is intrinsically disordered, with its function being to bind general transcription factors in a region of the NTD called activation function 1 (AF-1). In addition, the Tau5 region (residues 360-485) is considered to be important for activity in the absence of androgen (Dehm *et al.*, 2007). To investigate the interaction of EPI-001 with the AR NTD, NMR analysis was used in conjunction with a synthetic AF-1 peptide. The results showed that EPI-001 interacts specifically with the Tau5 region of AF-1 and that the interaction is not stereospecific (De Mol *et al.*, 2016). A cartoon representation of the binding of EPI-001 and the NTD of the AR is shown below.



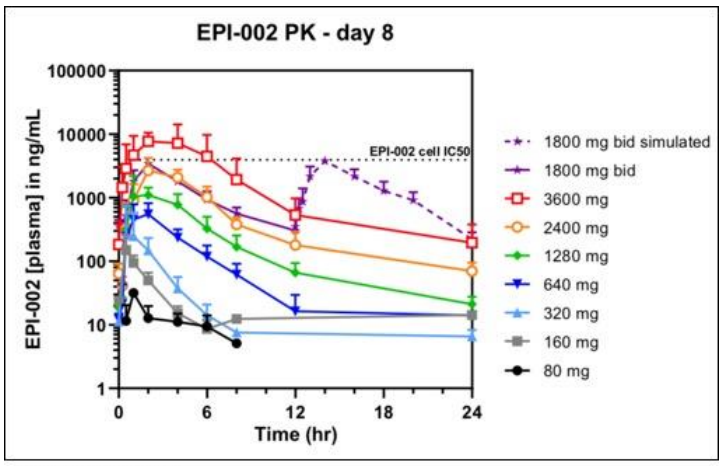
Source: ESSA Pharma Inc.

Binding to the NTD of the AR is a unique mechanism of action, as all current prostate cancer therapeutics that target the AR bind to the LBD. The unique mechanism of action led to the United States Adopted Names (USAN) council to assign the unique drug stem of “aniten” as an N-terminal inhibitor of the AR.

Phase 1 Trial of a First-Generation Aniten

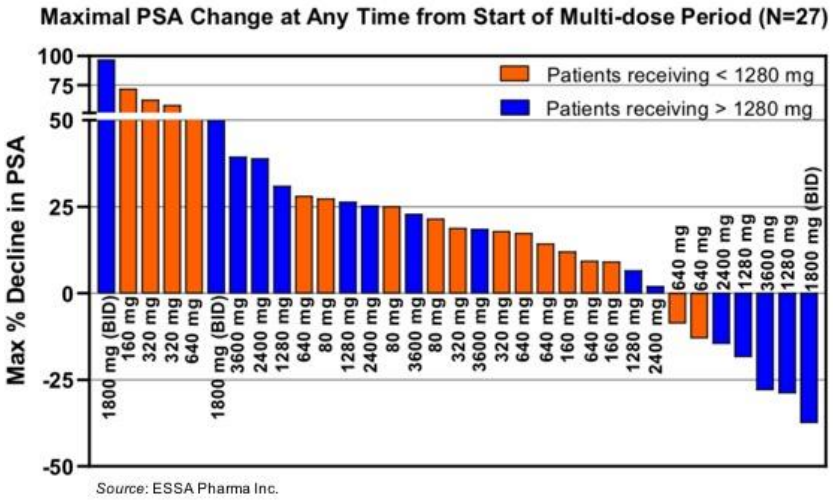
Based on the encouraging preclinical results of the EPI compounds, ESSA developed EPI-506, a tri-acetate prodrug of EPI-002, and tested it in a Phase 1 clinical trial in patients with mCRPC that were progressing after abiraterone or enzalutamide with serially rising PSAs (NCT02606123). This was an open label, single arm study in 28 patients to evaluate the safety, pharmacokinetics (PK), maximum tolerated dose, and recommended Phase 2 dose for EPI-506.

The following graph shows the PK profile for EPI-002 following dosing for eight days. The dashed line shows the target plasma concentration of the drug based on the IC50 of cell based assays. Only one of the doses (3600 mg) was able to achieve plasma concentrations above that target. The reason for this turned out to be much higher first pass metabolism of the drug than was seen in animal models.



Source: ESSA Pharma Inc.

The short half-life and minimal therapeutic exposure of the drug led to suboptimal results. The following graph shows the maximal change in PSA, with the majority of the patients showing an increase in PSA. While there were some patients with a decrease in PSA, the results were not sufficiently robust or sustained to be clinically meaningful. In addition, in order to achieve dosing of > 1280 mg/day, patients would have been required to take up to 18 pills/day, which is not a sustainable dosing regimen.



Source: ESSA Pharma Inc.

While the efficacy in the Phase 1 trial was not highly encouraging, the observed PSA decreases were consistent with confirmation of the proof-of-concept. In addition, the drug was shown to be safe and well tolerated up to very high doses. The following table shows that the highest reported adverse events were fatigue and gastrointestinal (GI) related and the number of Grade 3 or greater adverse events was very low. The GI effects were thought to be due to the excipient (i.e., castor oil) rather than EPI-506.

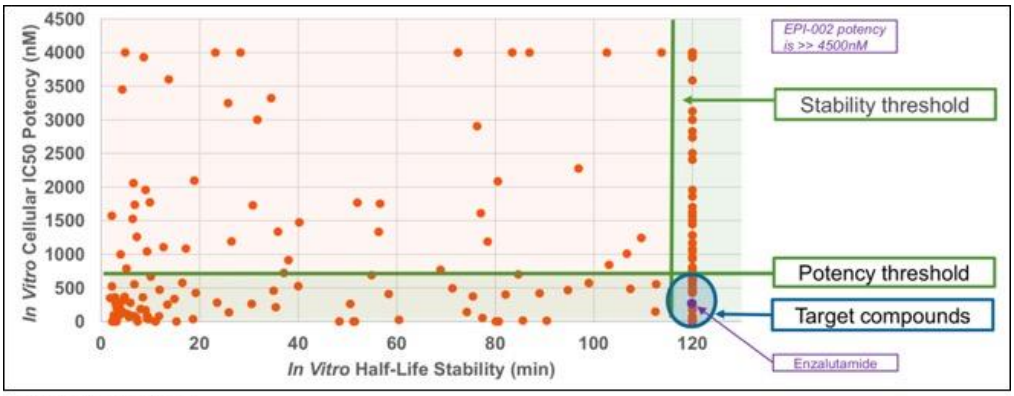
Most Commonly Reported Adverse Event > 10%		All Grades, N (%)
Diarrhea, nausea		**13 (46%)**
Fatigue		7 (25%)
Decreased appetite, pain in extremity		6 (21%), each
Vomiting		5 (18%)
Back Pain		4 (14%)
Abdominal distension, anemia, arthralgia, musculoskeletal pain, UTI		3 (11%), each
Adverse Events ≥ Grade 3	**N (%)**	**Relationship to Study Drug**
Anemia	3 (11%)	Not related.
AST elevated	2 (7%)	Probably related, Possibly related.
Neutropenia	2 (7%)	Not related.
Abdominal pain, diarrhea	1 (4%), each	Possibly related.
ALT elevated, amylase elevated, angina, hypertension, dizziness postural	1 (4%), each	Probably related.
Arthralgia, gastrointestinal hemorrhage, pain in extremity, syncope, thrombocytopenia, urinary retention	1 (4%), each	Not related.

Source: ESSA Pharma Inc.

While the PK and efficacy results were disappointing, the Phase 1 study of EPI-506 did reveal some important lessons that the company could utilize to develop next-generation aniten compounds. Included in those are the requirement for higher potency, reduced first-pass metabolism, maintaining on-target specificity, and having a simple manufacturing process. With those ideas in mind, in 2018 ESSA embarked on a new discovery effort to develop next-generation antien's. Following the synthesis of >300 compounds the company selected EPI-7386 as the lead IND candidate.

EPI-7386 Selected as the Lead Next-Generation Aniten

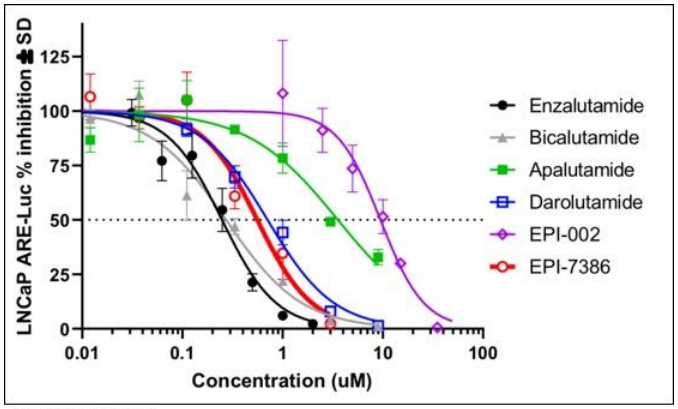
As part of the effort to develop a next-generation aniten compound, scientists at ESSA synthesized > 300 compounds and tested these for potency and stability. The following graph shows the results of these studies, with each dot on the graph representing a unique aniten compound. The company was hoping to identify a drug that had high potency (<750 nM IC50) and very high stability (half-life >115 min). As shown on the graph, only a very small portion of all the synthesized compounds met this threshold. This is in comparison to the first-generation aniten EPI-002, which is not featured on the chart due to its potency being ~9500 nM. Also of note is that enzalutamide falls within the 'target zone' of potency and stability where the company hoped to select for a next-generation aniten.



Source: ESSA Pharma Inc.

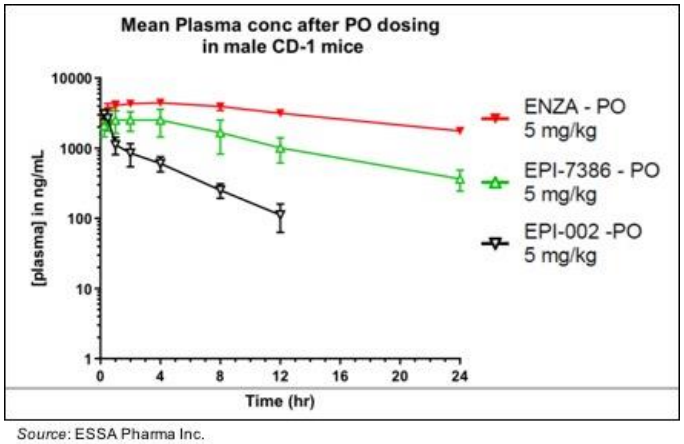
The company selected EPI-7386 as the lead next-generation aniten development candidate due to it possessing a number of positive attributes compared to EPI-002, including:

- **Increased potency**: the following chart shows a cellular inhibition assay in which various AR antagonists were tested along with EPI-002 and EPI-7386. The results show that EPI-7386 has a similar IC50 value compared with enzalutamide, bicalutamide, and darolutamide while EPI-002 had an IC50 value 20X higher than EPI-7386.



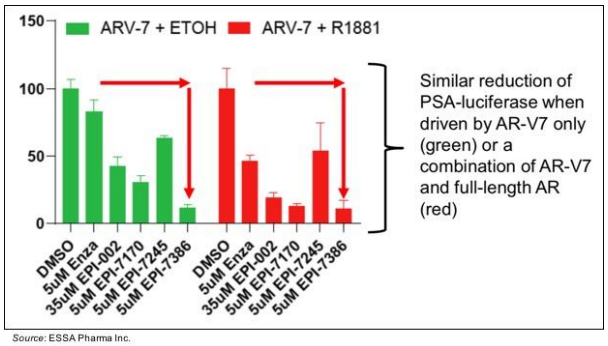
Source: ESSA Pharma Inc.

- **Reduced *in vitro* metabolism**: EPI-7386 exhibits *in vitro* hepatocyte stability that is approximately 10X greater than EPI-002 based on half-life and similar to what is seen with enzalutamide. In addition, the following graph shows that the PK profile in mice for EPI-7386 is similar to enzalutamide while EPI-002 showed a rapid reduction in plasma concentration over 12 hours.



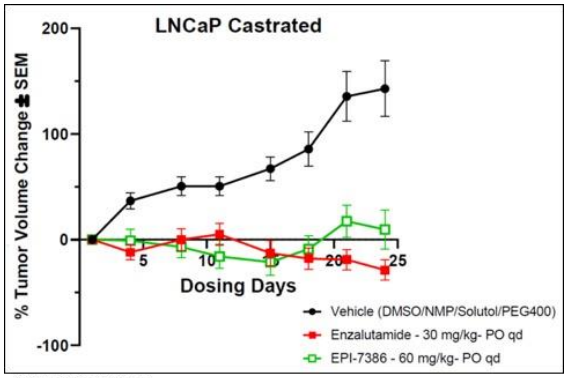
Source: ESSA Pharma Inc.

- **Activity against AR-V7 in *in vitro* models**: The following chart shows the results of an AR activity assay in which PSA is coupled to a luciferase reporter and tested against enzalutamide, EPI-002, and next-generation aniten compounds including EPI-7386. The assay was performed using the AR splice variant AR-V7, which shows androgen-independent activity (green bars) and using a combination of AR-V7 and full-length AR (R1881). The results show that EPI-7386 inhibits the activity of both full-length AR and the AR-V7 splice variant. This is in contrast to enzalutamide, which only shows activity against the full-length AR (red bars) but not against AR-V7, where activity is similar to that seen with only vehicle (DMSO) present.



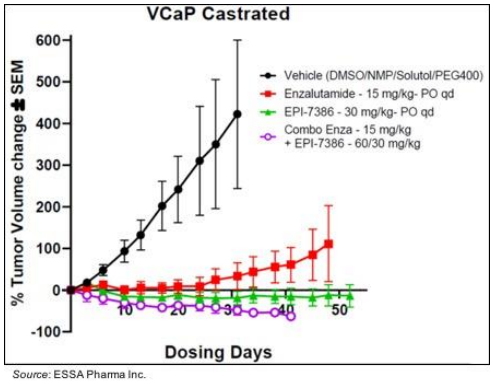
Source: ESSA Pharma Inc.

- **Similar activity to enzalutamide in LNCaP xenograft models**: The following graph shows the activity of both EPI-7386 and enzalutamide in an LNCaP xenograft model, which is driven by a full-length AR. Both drugs similarly inhibit the growth of the tumor in that model.



Source: ESSA Pharma Inc.

- **Enhanced activity in VCaP xenograft model**: The VCaP model is initially driven by full-length AR but is then followed by AR-V7-driven growth. The following graph shows that EPI-7386 shows significant and sustained antitumor activity in this model, while enzalutamide treated tumors show resistance to treatment after day 24. Interestingly, the combination of EPI-7386 and enzalutamide shows even greater activity than either drug on its own.



Source: ESSA Pharma Inc.

EPI-7386 Development Plan

The company is currently conducting IND-enabling studies with EPI-7386 and we anticipate an IND being filed in the first quarter of 2020 such that a Phase 1 clinical trial can initiate soon thereafter. The Phase 1 trial is likely to be a dose escalation trial with patients who are progressing on anti-androgen therapy. Results of the trial will include an appropriate dose for Phase 2 trials along with detailed molecular characterization of each patients' tumors. A combined Phase 1/2 trial is possible, which will allow the company to move directly into a Phase 2 trial with the dose determined in the Phase 1 dose escalation portion of the trial. In addition, since these are end-stage patients who are no longer responding to treatment, there is the potential for accelerated approval strategies with superior results.

Market Opportunity in mCRPC

Initial Opportunity

ESSA will be initially focusing on patients with mCRPC who are no longer responding to therapy. We estimate that there are approximately 30,000 and 80,000 patients in the U.S. and E.U., respectively, who fit these criteria based on the number of deaths attributed to prostate cancer each year. These patients would likely be treated with EPI-7386 as a monotherapy since all other treatment options are no longer working.

The following chart shows some of the top prostate cancer drugs, which all together constitute a $9.7 billion market in 2018 (EvaluatePharma). Erleada® was launched in late 2018, however it is expected to become a blockbuster drug with peak sales >$1 billion. Thus, if EPI-7386 were to win approval for late-stage prostate cancer we believe it would also have the potential to become a blockbuster drug.

Product	Mechanism	2018 Revenues ($M)
Zytiga	CYP17A Inhibitor	$3,498
Xtandi	AR Antagonist	$3,004
Zoladex	GnRH Analog	$508
Lupron	GnRH Analog	$491
Erleada	AR Antagonist	$20

Source: EvaluatePharma, Zacks SCR

Opportunity as a Combination Therapy

While not an immediate focus of the company, we believe that ESSA will work to attain approval for EPI-7386 in earlier stages of the disease as part of a combination therapy with other available treatments. All recent prostate cancer therapies have first gained approval in late-stage patients while testing as an earlier line therapy continued. For example, Xtandi® was first approved for the treatment of late-stage mCPRC patients in 2012 and then received approval for the treatment of non-metastatic CRPC in 2018. Similarly, Zytiga® was first approved in 2011 for the treatment of mCRPC and in 2018 was approved for the treatment of metastatic hormone sensitive PC. We believe that EPI-7386 is an excellent candidate for combination therapy with one or more approved therapies in earlier stage patients given its differentiated mechanism of action compared with all other available prostate cancer therapies. This would also vastly expand the market opportunity for EPI-7386, as we estimate that the number of earlier stage patients with either non-metastatic CRPC, metastatic hormone sensitive PC, or ADT-failing metastatic CRPC is approximately 160,000 (Scher *et al*., 2015).

Financials and Cap Structure

On August 14 2019, ESSA announced financial results for the third quarter of fiscal year 2019 that ended June 30, 2019. The company reported a net loss of $3.3 million, or $0.52 per share, for the third quarter of fiscal year 2019, compared to a net loss of $2.9 million, or $0.50 per share, for the third quarter of fiscal year 2018. R&D expenses during the quarter ending June 30, 2019 were $2.0 million compared to $1.0 million for the quarter ending June 30, 2018. The increase in R&D expenses was primarily related to the company's efforts in preparing an IND for EPI-7386. G&A expenses for the third quarter of fiscal year 2019 were $1.2 million compared to $1.6 million for the quarter ending June 30, 2018. The decrease in expenses was primarily due to decreased professional fees, rent, and share-based payments.

As of June 30, 2019, the company had approximately $4.9 million in cash and cash equivalents. In July 2019, the company completed the acquisition of Realm Therapeutics, which included the approximately $20.5 million of Realm's cash. A total of 6,718,156 shares were issued as part of the acquisition. In August 2019, the company announced a public offering of 18 million shares (or pre-funded warrants in lieu of common shares) at a price of $2.00 per share for gross proceeds of $36 million. Following the acquisition of Realm and the public offering, we believe ESSA has sufficient capital to fund operations for at least the next few years.

As of June 30, 2019, ESSA had 7,963,628 common shares outstanding. Following the acquisition of Realm and the public offering we estimate the company currently has approximately 32.7 million shares outstanding. When factoring in the 1.2 million stock options and the 0.5 million warrants the company has a fully diluted share count of 34.3 million, although we note that 0.23 million of those warrants are priced at either $42.80 or $66 per share.

Risks to Consider

Clinical Risk: While preclinical results for EPI-7386 have been encouraging, the compound has never been tested in humans, thus there is no guarantee that the results seen in animal models will be recapitulated in patients. In addition, there is the possibility that unforeseen serious adverse events could occur from treatment with EPI-7386 that would force the company to discontinue development of the compound. In addition, clinical testing could reveal that the compound is not suitable for continued development.

Development Risk: ESSA currently only has one lead compound in development (EPI-7386), thus if its development were to be stopped for any reason the company would be materially harmed. The biopharmaceutical industry is highly competitive and there are a large number of compounds under development for the treatment of prostate cancer, thus even if successful in clinical testing there is no guarantee that the drug would be accepted by physicians, patients, or payers. In addition, competitors may develop more effective therapies that could render ESSA's products obsolete.

Stock Risk: ESSA's shares currently trade on the Nasdaq under the ticker symbol EPIX. However, the stock has very limited liquidity with a three-month average trading volume of only 18,590 shares per day. Thus, large block purchases of shares could have a significant effect on the stock price and the lack of liquidity may make it difficult to exit a position.

MANAGEMENT PROFILES

David R. Parkinson, MD – President and Chief Executive Officer

Dr. Parkinson has served as President and Chief Executive Officer of ESSA Pharma Inc. since January 2016, and as a Director of the company since June 2015. Prior to joining ESSA, he was a Venture Partner at New Enterprise Associates, Inc. From 2007 until 2012, Dr. Parkinson served as President and CEO of Nodality, Inc., a biotechnology company focused on the biological characterization of signaling pathways in patients with malignancy. Until October 2007 he was SVP, Oncology Research and Development at Biogen Idec, where he oversaw all oncology discovery research efforts and the development of the oncology pipeline. Previously he had served as VP, Oncology Development, at Amgen and VP, Global Clinical Oncology Development, at Novartis. In those roles he oversaw the successful clinical development of a series of cancer therapeutics, including Gleevec, Zometa, Femara, and Vectibix. He currently serves as Director on the Boards of Tocagen Inc (TOCA), 3SBio Inc (1530.HK), CTI Biopharma, Inc (CTIC), and is a Co-Founder and Director of Refuge Biotech, Inc. He has held academic positions both at Tufts and at the University of Texas MD Anderson Cancer Center, and has authored over 100 peer-reviewed publications.

Peter Virsik – Executive Vice President and Chief Operating Officer

Mr. Virsik has served as Executive Vice President and Chief Operating Officer since August 2016. He has over 20 years of experience in corporate development, strategy, new product planning, alliance management, and finance. During his career, Mr. Virsik has completed over 30 licensing, M&A and financial transactions, totaling over $3 billion in value. Most recently, he served as Senior Vice President, Corporate Development for XenoPort (acquired by Arbor Pharmaceuticals), leading licensing, strategy, new product planning and alliance management for the company. During his tenure at XenoPort, Mr. Virsik played an integral role in the licensing and commercialization of Horizant® (gabapentin enacarbil). Prior to XenoPort, Mr. Virsik worked for Gilead Sciences from 2000 through 2005 in Corporate Development, where he was involved in building Gilead's HIV franchise through the acquisition of Triangle Pharmaceuticals and the licensing of Vitekta® (elvitegravir). Before joining Gilead, Mr. Virsik worked at J.P. Morgan in the biotechnology equity research group and as a consultant for Ernst and Young. Mr. Virsik began his career in R&D at Genentech. Mr. Virsik received an MBA from the Kellogg Graduate School of Management at Northwestern University, an MS in Microbiology from the University of Michigan, Ann Arbor, and a BA in Molecular and Cellular Biology from the University of California, Berkeley.

Alessandra Cesano – MD, PhD – Chief Medical Officer

Dr. Cesano has served as Chief Medical Officer since July 2019. She has extensive experience in drug discovery and development as exemplified through her key roles at Amgen in the approval of Vectibix® and Kepivance®. Prior to joining ESSA, Dr. Cesano was the CMO at NanoString Technologies, Inc., CMO at Cleave Biosciences, Inc., and CMO and COO at Nodality, Inc. She spent 12 years researching tumor immunology, including nine years at the Wistar Institute of the University of Pennsylvania. Dr. Cesano received an MD, a Board Certification in Oncology, and a PhD in Tumor Immunology from the University of Turin.

David S. Wood – Chief Financial Officer

Mr. Wood has been CFO of ESSA since October 2013. He is responsible for managing all financial aspects of ESSA's business and matters related to compliance and corporate governance. Mr. Wood has over 30 years of experience in management of both large and early stage companies in North America and the U.K. From 2003 to 2013, he was Head of Finance, Secretary and Treasurer at Celator Pharmaceuticals Inc. Prior to 2003, he was Managing Director of Cubist Pharmaceuticals (UK) Ltd., and Finance Director at TerraGen Discovery, Inc. During 18 years in the biopharmaceutical industry, Mr. Wood has overseen several M&A transactions and numerous financings, raising over $100 million. Mr. Wood began his career in the finance and exploration departments of Chevron Corp. He received a B.Sc. in Biology from Queen's University, an M.B.A. from University of Western Ontario and holds a CPA, CMA accounting designation. He served on the governing body of the National Research Council of Canada from 2008 to 2014.

VALUATION

We are initiating coverage of ESSA Pharma Inc. (EPIX) with a valuation of $6.00. ESSA is a biopharmaceutical company developing treatments for prostate cancer that are no longer responding to current therapies. The company is developing a series of compounds ('anitens') that disrupt the androgen receptor (AR) signaling pathway through a unique mechanism of action that targets the N-terminal domain (NTD) of the AR, as opposed to the ligand-binding domain (LBD) of the AR that is targeted by all other AR-directed prostate cancer treatments. The company has selected a lead preclinical aniten (EPI-7386) to advance to clinical trials, and we anticipate a Phase 1 clinical trial initiating in the first half of 2020.

EPI-7386

EPI-7386 is the lead next-generation aniten development candidate that has a number of superior attributes compared to first-generation aniten compounds, including increased potency, reduced first-pass metabolism, activity against AR-V7 in *in vitro* models, similar activity to enzalutamide in LNCaP xenograft models, and enhanced activity in the VCaP xenograft model. However, the drug maintains the unique mechanism of action of binding to the NTD of the AR, which distinguishes it from all other AR-targeted prostate cancer therapies.

IND-enabling studies are continuing for EPI-7386 and we anticipate the compound entering the clinic in the first half of 2020. We believe the company will initiate a Phase 1 trial involving metastatic prostate cancer patients who are progressing on anti-androgen therapy, with the goal being to determine an appropriate dose to take into Phase 2 testing. A combined Phase 1/2 trial is possible, which will allow for the company to move directly into the Phase 2 trial once a proper dose is determined. While initially EPI-7386 will be tested as a monotherapy, we believe the drug's unique mechanism of action makes it highly suitable for combination therapies and that the company will look to initiate studies of EPI-7386 plus anti-androgen therapy in the near future.

Valuation

We value ESSA using a probability adjusted discounted cash flow model that takes into account potential future revenues for EPI-7386. We model for ESSA to partner the asset and to receive a 15% royalty on net sales.

For EPI-7386, we estimate that the company will initiate a Phase 1 trial in 2020, a Phase 3 trial in 2023, and file for approval in 2025. While the opportunity could exist for accelerated approval with exceptional results, we believe our timeframe is a bit more conservative of an estimate. For the initial indication, which is patients with mCRPC who are no longer responding to therapy, we estimate there are approximately 30,000 in the U.S. and 80,000 in the E.U. who would be eligible for treatment based on the number of deaths attributed to prostate cancer each year. While this represents a potential billion dollar opportunity on its own, we believe the much larger opportunity exists in combination therapy with earlier stage patients. We estimate there are approximately 160,000 patients who have either non-metastatic CRPC, metastatic hormone sensitive PC, or ADT-failing metastatic CRPC. When including these patients in our model we believe EPI-7386 could achieve peak sales of $4 billion worldwide. Using a 25% chance of approval along with a 13.5% discount rate leads to a net present value for EPI-7386 of $154 million. Combining the net present value of EPI-7386 with the company's current estimated cash balance and dividing by an estimated fully diluted share count of 34.1 million (excluding warrants that are priced at $42.80 and $66 per share) leads to a valuation of approximately $6 per share.

PROJECTED FINANCIALS

ESSA Pharma Inc.	2018 A	Q1 A	Q2 A	Q3 A	Q4 E	2019 E	2020 E	2021 E
EPI-7386	$0	$0	$0	$0	$0	$0	$0	$0
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$4.9	$1.3	$1.5	$2.0	$1.6	$6.3	$8.0	$10.0
Financing Costs	$0.9	$0.2	$0.2	$0.1	$0.2	$0.7	$0.8	$0.8
General & Administrative	$5.9	$1.2	$1.8	$1.2	$1.8	$6.0	$7.0	$7.3
Other (Income) Expense	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($11.7)	($2.7)	($3.4)	($3.3)	($3.6)	($13.0)	($15.8)	($18.1)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.1	($0.0)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($11.6)	($2.7)	($3.4)	($3.3)	($3.6)	($13.0)	($15.8)	($18.1)
Income Taxes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($11.6)**	**($2.7)**	**($3.4)**	**($3.3)**	**($3.6)**	**($13.0)**	**($15.8)**	**($18.1)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($2.55)**	**($0.43)**	**($0.54)**	**($0.52)**	**($0.18)**	**($1.33)**	**($0.48)**	**($0.53)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	4.6	6.3	6.3	6.4	20.0	9.8	33.0	34.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

HISTORICAL STOCK PRICE

DISCLOSURES

The following disclosures relate to relationships between Zacks Small-Cap Research ("Zacks SCR"), a division of Zacks Investment Research ("ZIR"), and the issuers covered by the Zacks SCR Analysts in the Small-Cap Universe.

ANALYST DISCLOSURES

I, David Bautz, PhD, hereby certify that the view expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the recommendations or views expressed in this research report. I believe the information used for the creation of this report has been obtained from sources I considered to be reliable, but I can neither guarantee nor represent the completeness or accuracy of the information herewith. Such information and the opinions expressed are subject to change without notice.

INVESTMENT BANKING AND FEES FOR SERVICES

Zacks SCR does not provide investment banking services nor has it received compensation for investment banking services from the issuers of the securities covered in this report or article.
Zacks SCR has received compensation from the issuer directly or from an investor relations consulting firm engaged by the issuer for providing non-investment banking services to this issuer and expects to receive additional compensation for such non-investment banking services provided to this issuer. The non-investment banking services provided to the issuer includes the preparation of this report, investor relations services, investment software, financial database analysis, organization of non-deal road shows, and attendance fees for conferences sponsored or co-sponsored by Zacks SCR. The fees for these services vary on a per-client basis and are subject to the number and types of services contracted. Fees typically range between ten thousand and fifty thousand dollars per annum. Details of fees paid by this issuer are available upon request.

POLICY DISCLOSURES

This report provides an objective valuation of the issuer today and expected valuations of the issuer at various future dates based on applying standard investment valuation methodologies to the revenue and EPS forecasts made by the SCR Analyst of the issuer's business.
SCR Analysts are restricted from holding or trading securities in the issuers that they cover. ZIR and Zacks SCR do not make a market in any security followed by SCR nor do they act as dealers in these securities. Each Zacks SCR Analyst has full discretion over the valuation of the issuer included in this report based on his or her own due diligence. SCR Analysts are paid based on the number of companies they cover. SCR Analyst compensation is not, was not, nor will be, directly or indirectly, related to the specific valuations or views expressed in any report or article.

ADDITIONAL INFORMATION

Additional information is available upon request. Zacks SCR reports and articles are based on data obtained from sources that it believes to be reliable, but are not guaranteed to be accurate nor do they purport to be complete. Because of individual financial or investment objectives and/or financial circumstances, this report or article should not be construed as advice designed to meet the particular investment needs of any investor. Investing involves risk. Any opinions expressed by Zacks SCR Analysts are subject to change without notice. Reports or articles or tweets are not to be construed as an offer or solicitation of an offer to buy or sell the securities herein mentioned.

This research report is a product of Zacks SCR and prepared by a research analyst who is employed by or is a consultant to Zacks SCR. The research analyst preparing the research report is a resident outside of Canada and is not an associated person of any Canadian registered adviser and/or dealer and, therefore, the analyst is not subject to supervision by a Canadian registered adviser and/or dealer, and is not required to satisfy the regulatory licensing requirements of any Canadian provincial securities regulators, the Investment Industry Regulatory Organization of Canada and is not required to otherwise comply with Canadian rules or regulations.