ESSA Pharma

Innovative Targeting of Androgen Receptor, Potential to Overcome Challenges in Prostate Cancer

Innovative approach to target androgen receptor provides advantages. Androgen receptor plays an important role in the progression of prostate cancer, targeting the amino terminus of androgen receptor to inhibit androgen receptor activity is expected to overcome some of the challenges of resistance, potentially leading to advantages over conventional androgen receptor antagonists

EPI-506 is a novel, oral androgen receptor antagonist. It selectively binds to the amino terminal DNA binding domain of the androgen receptor abrogating its activity in cell lines and animal models. EPI-506 has advantages over conventional androgen receptor antagonists targeting the carboxyl terminus receptor binding domain and has therapeutic potential as single agent, as well as part of combination in androgen receptor mediated cancers

EPI-506 overcomes some of the challenges by targeting the amino terminus of androgen receptor. Historically, efforts to exploit androgen receptor antagonists have been successful given the significant role played by androgen receptor in progression of prostate cancer. But, challenges remain due to development of resistance mechanisms to drugs targeting ligand binding domain of androgen receptor

EPI-506 Phase 1/2 trials are ongoing in prostate cancer with results possible in 1Q17. EPI-506 may provide a novel approach to fulfill unmet need in targeting prostate cancer resistant to conventional androgen receptor antagonists

EPI-506 development supported by Cancer Prevention and Research Institute of Texas (CPRIT) grant. ESSA Pharma has received $12M grant from CPRIT for company relocation to Texas, with a final disbursement of ~$1.4M expected upon completion of Phase 1 trial of EPI-506

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1. Key Investment Considerations

Castrate resistant prostate cancer (CRPC) is not responsive to androgen deprivation therapies: Initially, prostate cancer patients respond to interventions such as surgical castration, radiation, and androgen deprivation therapies. However, disease progression and metastasis occurs and androgen deprivation therapies are not effective, despite castrate levels of testosterone/other androgens, leading to CRPC.

Significant unmet need in CRPC: Less than a third of patients are diagnosed with metastatic CRPC (mCRPC) at presentation. Even though relatively newer options that target androgens and the androgen receptor are available for mCRPC that include Xtandi (enzalutamide, androgen receptor antagonist) and Zytiga (abiraterone, androgen biosynthesis inhibitor), the disease has no cure. Unfortunately, mCRPC continues to evolve over time. With every therapy used, the disease acquires additional and diverse resistance mechanisms.

The androgen receptor signaling axis drives prostate cancer and CRPC: At disease onset, androgen deprivation therapies induces apoptosis of androgen-dependent prostate cancer epithelial cells and regression of androgen-dependent tumors. However, the vast majority of patients with advanced prostate cancer progress and become refractory due to emergence of androgen-independent prostate cancer driven by dysregulated activation of the androgen receptor.

Current therapies target the ligand binding domain (LBD) of the androgen receptor: Androgen biosynthesis inhibitor drugs such as Zytiga, LHRH analogues, anti-androgens (Xtandi) as well as androgen receptor antagonists such as bicalutamide target the LBD of the androgen receptor. Targeting the LBD has limitations.

Several resistant mechanisms in CRPC are related to the LBD: Resistance mechanisms that make androgen deprivation or androgen receptor antagonism approaches ineffective are often (not always) related to the LBD. These include the development of splice variants lacking the LBD or point mutations in the androgen receptor LBD that may make it constitutively active. Current approaches do not address this resistance mechanism.

The significance of the N-terminal domain (NTD) of the androgen receptor: The androgen receptor consists of three domains, the LBD, the DNA-binding domain and the NTD. The NTD is responsible for transcriptional activation of genes that propagate the tumor. Binding of testosterone/androgen to the LBD of the androgen receptor leads to homo-dimerization of the receptor followed by nuclear translocation. In the nucleus, the NTD of the androgen receptor binds to regulatory regions of target genes leading to gene expression including the expression of prostate specific antigen (PSA).
Strong rationale for targeting the NTD of the androgen receptor, significance of splice variants of the androgen receptor: Several lines of evidence implicate splice variants of the androgen receptor that lack the LBD in developing resistance to androgen deprivation therapies in CRPC. Therefore, inhibiting the NTD of the androgen receptor from transcriptional activation of genes that propagate CRPC is a rational drug development approach.

**EPI-506 binds irreversibly and with high selectivity to the NTD:** EPI-506 binds irreversibly and with high selectivity to the NTD and can prevent wild-type androgen receptor and splice variants of the androgen receptor from transcriptional activity. EPI-506 therefore can inhibit androgen receptor driven tumor growth in wild type and splice variant mutations of the androgen receptor.

The mechanism of action EPI-506 provides advantages over other approved or developing therapeutic agents for CRPC: The mechanism of action of some of the approved drugs and drugs in development for CRPC is by antagonizing the binding of ligand to the LBD of androgen receptor. These agents are not effective in inhibiting tumor growth in prostate cancer expressing androgen receptor splice variants, androgen receptor activated independent of the LBD, or have mutations in the LBD that make the androgen receptor constitutively active.

**CRPC may also be attributed to factors other than splice variants that may not be amenable to EPI-506:** Factors include, over expression of androgen receptor, ligand-independent androgen receptor activation such as by glucocorticoid receptor activation, alternative oncogenic pathways, and PD-1/PD-L1 pathways upregulation.

**Pre-clinical efficacy data with EPI-506 is encouraging:** In cell lines expressing androgen receptor splice variants, EP1-506 inhibited growth, but androgen receptor antagonists, enzalutamide (Xtandi) and bicalutamide, were not effective in tumor growth inhibition. In an in vivo xenograft mouse model expressing androgen-independent splice variants that lack the LBD, EP1-506 reduced tumor growth compared to enzalutamide (Xtandi).

**EPI-506 pharmacological profile is attractive:** 100% bioavailability, EPI-506 pro-drug completely converts to active EPI-002 in vivo, no significant inhibition of CYP enzymes in screening assays, no significant drug interaction demonstrated in screening assays, no observed QT prolongation, and no mutagenic potential.

**Phase 1/2 trial ongoing in mCRPC patients:** Phase 1/2 trial is ongoing across 27 clinical sites across US and Canada. The trial enrolls mCRPC patients who experienced disease progression after failing abiraterone, enzalutamide, or both. Patients that have failed one regimen of chemotherapy are also allowed to enroll. The primary endpoint is safety, pharmacokinetics, maximum tolerated dose, and recommendation for Phase 2 dose. The secondary endpoints include PSA response metrics and radiographic response. Topline data from the Phase 1 portion of study is possible in 1Q17.

**Experienced management team:** ESSA is led by a capable team. CEO, David Parkinson is an oncologist with
a strong background in clinical research; roles at the FDA, NIH and NCI; Big Pharma oncology leadership roles; as well as experience at an established venture capital firm. COO, Peter Virsik has extensive experience in drug development, licensing, and from 2000 through 2005, was involved in building Gilead's HIV franchise through acquisition and licensing deals. CFO, David Wood has extensive experience as a finance professional including overseeing several M&A transactions and financing. Frank Perabo, CMO has extensive drug development experience and was previously Executive Director, Oncology at Astellas Pharma Global Development where his role was important in the development of Xtandi. Marianne Sadar, Scientific Co-founder, is an eminent and well published researcher in the area of therapeutics against androgen receptor.

**Intellectual property:** ESSA Pharma has a patent granted for active drug EPI-002, which provides intellectual property protection until July, 2029. The company also has a patent for pro-drug EPI-506, which is valid until April, 2034. ESSA Pharma's intellectual property portfolio covers composition of matter and methods of use. It has 17 filed patent families filed covering various EPI structural motifs, with prosecution ongoing for 14 at present.

**Valuation:** We value ESSA Pharma based on a risk-adjusted net present value (rNPV) of its pipeline. The company is valued at $9/per share over the next year. The main investment driver is EPI-506 for the castrate resistant prostate cancer (CRPC) program in Phase 1/2 trials. The Phase 1 program is projected to report topline results in 1Q 2017 and a Phase 2 trial based on dose from Phase 1 trial is expected to be initiated in 1Q17. Conservatively, we assess a 35% probability of success for the CRPC program given the lack of human efficacy data, androgen receptor is a validated target in prostate cancer, and based on results in pre-clinical models. The market potential for a safe, efficacious, therapeutic for prostate cancer patients progressing on current treatments is large and of significant unmet need. J&J's Zytiga and Astellas's/Medivation's Xtandi together had combined global sales of $4.1B in 2015 and is expected to increase over time as earlier stage patients are treated with these drugs. We conservatively assume that EPI-506 will capture 35% of the estimated $6.74B market in the peak year i.e. ~$2.4B.

**Finances:** ESSA Pharma raised $15M in January, 2015 and $15M in January, 2016 and $5M in March, 2016 from educated biotechnology investors. It has also received $12M dilution-free grant from Cancer Prevention and Research Institute of Texas (CPRIT) for company relocation to Texas, with a final disbursement of ~$1.2M expected upon completion of Phase 1 trial of EPI-506. As of last reporting, for the first quarter ending December 31, 2016, the company had $14.1M in working capital. The company has secured a $10M term loan ($8M drawn down), for a total cash position of $10.8M. We believe the current finances will be sufficient until the end of 2017.
2. Investment Risks

Risk may hinder achievement of price target

Every therapeutic product subject to regulatory approval is subject to regulatory, scientific and clinical challenges. Risk in biotechnology drug development includes overcoming scientific/biologic barriers understanding novel targets/biology, difficulty in recruiting patients for clinical trials, delays in FDA approval, worsening or continuation of the harsh economic environment or the inability to raise additional capital to run operations. These and other factors may hinder reaching our price target. Even after regulatory approval, in the face of stiff competition from other entrenched or novel therapies, the products may not capture a meaningful market share to justify our projections. If the company enters into an agreement with a commercialization partner, revenues from the company's marketed products are still subject to risk. The company's commercialization partner may not allocate the resources to facilitate successful market penetration of its products or the competitive landscape may change with novel medical advances of which we are unaware.

Specific risks to ESSA Pharma's drug development pipeline are listed below:

ESSA Pharma has only one product candidate, EPI-506, which is being developed for prostate cancer. Though EPI-506 has been shown to be safe and well tolerated based on pre-clinical testing in animal models and could be efficacious based on its mechanism of action, first in human studies are ongoing and safety and efficacy data in humans is pending. Clinical data is needed from large patient populations to further mitigate risk. Robust controlled, randomized clinical trials are needed to demonstrate statistically significant efficacy.

The prostate cancer treatment landscape is evolving with the approval of drugs like Zytiga and Xtandi for treatment in earlier stages of prostate cancer. It needs to be seen how the prostate cancer treatment paradigm will evolve and where EPI-506 will fit in the treatment paradigm. There are potential challenges for pricing with the expected approval of generic Zytiga.
3. Pipeline

ESSA Pharma’s pipeline is based on its novel androgen receptor antagonist EPI-506. EPI-506 is a synthetic small molecule which selectively binds to the N-terminal domain (NTD) of the androgen receptor. The NTD of the androgen receptor is responsible for transcriptional activity by binding to the DNA, leading to tumor cell growth.

Though EPI-506 is being developed for prostate cancer at present, the role of the androgen receptor in other cancers such as breast cancer has been documented. There is potential for EPI-506 to be developed in other cancers where dysregulation of the androgen receptor is known to play a role.

Exhibit 1: ESSA Pharma Pipeline.

<table>
<thead>
<tr>
<th>Drug Candidate</th>
<th>Indication</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPI-506</td>
<td>Metastatic castrate-resistant prostate cancer (CRPC) patients with disease progression after failing abiraterone, enzalutamide, or both, could have also failed one regimen of chemotherapy</td>
<td>Phase 1/2 study ongoing with Phase 2 dose expected to be established 1Q17; clinical results following establishment of Phase 2 dose</td>
</tr>
</tbody>
</table>

Source: ESSA Pharma and Noble Life Science Partners

4. Upcoming Milestones

1Q17: Initial EPI-506 Phase 1 results and establish Phase 2 dose

2H17: Updated EPI-506 Phase 1/2 Data

2018: EPI-506 Phase 3 Study Initiation
5. Significant Unmet Need in Prostate Cancer

Prostate cancer impacts a large number of older men and is the second most common cancer in men, in the US, after skin cancer (2). One in seven American men will be afflicted with prostate cancer during his lifetime. The National Institute for Health (NIH) estimates that there will be ~181K new cases of prostate cancer and ~26K patient deaths due to prostate cancer in the US in 2016 (2). There are about 2.9M men with prostate cancer alive today in the US (18).

Treatment options for prostate cancer

On first being diagnosed, treatment options are based on age, other medical conditions or co-morbidity a patient may have, PSA levels, stage of disease, biopsy, and Gleason grade. Low grade (Gleason score less than 6) patients who are low risk (low PSA) may qualify for active surveillance. Active surveillance may also be a good choice for older men with limited life expectancy or if the patient has other serious disease like heart disease, long-standing high blood pressure, or poorly controlled diabetes. If the disease is more aggressive, or risk factors are increased, radical prostatectomy is prescribed, to remove the prostate gland and the surrounding tissue. Another option for early-stage prostate cancer is radiation therapy (brachytherapy, proton therapy, external beam radiation therapy).

Hormone therapy or anti-androgen therapy (also called chemical castration) is used in men with advanced prostate cancer to shrink the tumor and slow the growth of tumors by blocking the supply of androgens. The most prominent androgen is testosterone. In men with early-stage prostate cancer, hormone therapy may be used to shrink tumors before radiation therapy. Hormone therapy includes luteinizing hormone-releasing hormone (LH-RH) that prevents testosterone synthesis by the testes (Lupron, Zoladex). Hormone therapy also includes the use of anti-androgens like bicalutamide (Casodex), flutamide, and nilutamide (Nilandron).

The above are treatment options for non-metastatic prostate cancer and must balance the risk of disease progression with the side effects of available therapies.

Following prostatectomy and/or hormone therapy/anti-androgens, the cancer develops resistance and patients have progressive disease despite anti-androgen therapy. This stage of prostate cancer is called as castration resistant prostate cancer. Spread of the cancer leads to metastatic castration-resistant prostate cancer (mCRC) when the cancer has spread from prostate to distal organs and tissues despite lowering androgens either by surgical castration or chemical castration (anti-androgen therapy).

Once the cancer progresses after anti-androgen therapy, treatment options include:

Zytiga: an androgen biosynthesis inhibitor that unlike the other anti-androgens that only decrease androgen in
the testes, also decreases androgen in the adrenals and tumor

Xtandi: an androgen receptor antagonist

Xofigo: alpha particle-emitting radioactive that binds with bone minerals to deliver radiation directly within bones, prevents bone metastasis

Provenge: autologous cellular immunotherapy with antigen presenting cells (APCs) activated \textit{ex vivo} with recombinant prostatic acid phosphatase fused to granulocyte–macrophage colony-stimulating factor

When patients progress on these treatments, the next option is rescue chemotherapy with docetaxel. Zytiga and Xtandi have also been approved for treatment of patients who have progressed on docetaxel. Clinical trials are being conducted to evaluate the optimal sequencing of Xtandi and Zytiga, the possibility of combination therapy, and use of these drugs in earlier stages of the disease.

Exhibit 2: The prostate cancer continuum. Localized disease is treated with surgery or radiation therapy (RT) +/- androgen deprivation therapy (ADT).

Source: Ramalingam MD et al; Oncology Journal, Prostate Cancer September 2015 (http://www.cancernetwork.com/oncology-journal/what-should-we-tell-patients-about-physical-activity-after-prostate-cancer-diagnosis)

Recent drug-development progress in prostate cancer

There have been significant advances in the treatment of prostate cancer in the last several years with the
approval of more effective therapies that slow disease progression and increase survival. Androgen receptor targeted drugs like Zytiga and Xtandi have been approved in pre-chemotherapy and post-chemotherapy patients. Xtandi and Zytiga have led to prolongation of progression free and overall survival of metastatic prostate cancer patients. Provenge, though a commercial failure, may be classified as the first FDA approved immunotherapy for cancer. Provenge is approved for asymptomatic mCRPC.

Despite the prolongation of progression free survival and overall survival, prostate cancer continues to develop resistance mechanisms leading to progression of disease and ultimately leading to death. While prostate cancer may today be managed as a chronic disease for some patients, there remains a significant unmet need for patients that progress on existing therapies. Patients who eventually develop mCRPC are initially diagnosed with localized high-risk disease that usually progresses after treatment (12). Less than a third of patients are diagnosed with mCRPC at presentation. Even though several options are available for mCRPC, including Xtandi and Zytiga, the disease has no cure. mCRPC continues to evolve over time. With every therapy used, the disease acquires additional and diverse resistance mechanisms (12). It has been estimated that 20%-40% of patients have primary resistance to Xtandi and Zytiga, and ultimately all patients develop secondary resistance (12).

Exhibit 3: Treatment landscape for prostate cancer. Zytiga (abiraterone) and Xtandi (enzalutamide) are the relatively new drugs for mCRPC

Substantial and growing market opportunity

The market opportunity for treating prostate cancer patients is substantial and growing. In 2015, Zytiga and Xtandi had combined global sales of $4.1B and sales are expected to grow over time as more patients are...
treated in the earlier stages of the disease and have longer progression free and overall survival. Initially, both Xtandi and Zytiga were approved for treatment of men with metastatic castration-resistant prostate cancer (mCRPC) after chemotherapy, subsequently the label was extended for treatment of chemotherapy-naive mCRPC patients.

Pfizer completed acquisition of Medivation in September of 2016. The terms to acquire Medivation, represented an offer of $81.50 a share in cash for a total of approximately $14B.

Exhibit 4: Global sales of J&J’s Zytiga and Medivation/Astellas’s Xtandi reached $4.1B in 2015.

<table>
<thead>
<tr>
<th>Zytiga and Xtandi 2015 Sales $M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zytiga</strong></td>
</tr>
<tr>
<td>U.S</td>
</tr>
<tr>
<td>OUS</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td><strong>Xtandi</strong></td>
</tr>
<tr>
<td>U.S</td>
</tr>
<tr>
<td>OUS</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td><strong>Zytiga and Xtandi</strong></td>
</tr>
<tr>
<td>U.S</td>
</tr>
<tr>
<td>OUS</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Source: J&J and Medivation press release
6. Landscape for mCRPC drugs

Zytiga (Abiraterone) in combination with prednisone

Zytiga (Abiraterone) is a potent and selective inhibitor of CYP17-α-hydroxylase and C17, 20-lyase (CYP17). CYP17 enzyme is expressed in testicles, adrenal glands and prostate tumor cells and is required for biosynthesis of androgen. Zytiga was first approved in April, 2011 to be used in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer who have previously had docetaxel chemotherapy. In December, 2012, Zytiga prescription label was expanded to be used in combination with prednisone for treatment of metastatic castration-resistant prostate cancer patients who had not received prior docetaxel therapy.

In the Phase 3 (COU-AA-301) trial, Zytiga was evaluated in patients with mCRPC who received prior docetaxel therapy. A total of 797 patients were randomized to 1000mg (four 250 mg tablets) Zytiga once daily plus 5mg prednisone twice daily, 398 patients were randomized to receive placebo plus 5mg prednisone twice daily. Zytiga plus prednisone led to 14.8 months median overall survival compared to 10.9 months with placebo plus prednisone for a 3.9 month difference in median overall survival.

In the Phase 3 (COU-AA-302) trial, Zytiga was evaluated in patients with mCRPC who had not received prior docetaxel therapy. A total of 546 patients were randomized to 1000mg (four 250 mg tablets) Zytiga once daily plus 5mg prednisone twice daily, 542 patients were randomized to receive placebo plus 5mg prednisone twice daily. Zytiga plus prednisone led to 34.7 months median overall survival compared to 30.3 months with placebo plus prednisone for a 4.4 month difference in median overall survival.

Exhibit 5: Zytiga pivotal Phase 3 clinical trials in mCRPC patients with prior chemotherapy and chemo naive patients.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Setting</th>
<th># of Patients</th>
<th>Abiraterone plus prednisone</th>
<th>Prednisone plus placebo</th>
<th>Median Overall Survival</th>
<th>P Value</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>COU-AA-301</td>
<td>mCRPC post docetaxel</td>
<td>1195</td>
<td>797</td>
<td>398</td>
<td>14.8 vs. 10.9 months</td>
<td>P &lt; 0.0001</td>
<td>April, 2011</td>
</tr>
<tr>
<td>COU-AA-302</td>
<td>mCRPC chemotherapy naive</td>
<td>1088</td>
<td>546</td>
<td>542</td>
<td>34.7 vs. 30.3 months</td>
<td>P = .0033</td>
<td>December, 2012</td>
</tr>
</tbody>
</table>

Source: Zytiga prescription information
Medivation’s Xtandi (Enzalutamide/MDV3100)

Xtandi (Enzalutamide/MDV3100) is an androgen receptor antagonist which has increased affinity for the androgen receptor compared to bicalutamide, inhibits androgen receptor nuclear translocation, prevents the androgen receptor from DNA binding, suppresses androgen receptor co-activator recruitment, has pro-apoptotic activity, and does not have agonistic effects (9,14).

In the Phase 3 AFFIRM trial, Xtandi was evaluated in mCRPC patients who has previously received docetaxel chemotherapy. A total of 800 patients were randomized to receive 160mg Xtandi daily and 390 patients to receive placebo. The trial evaluated overall survival as the primary endpoint. Xtandi treatment led to 37% reduction in risk of death compared to placebo. The median overall survival was 18.4 months for Xtandi treated patients compared to 13.6 months for placebo treated patients.

In the Phase 3 PREVAIL study, Xtandi was evaluated in mCRPC patients who had disease progression on gonadotropin-releasing hormone (GnRH) therapy or after surgical removal of both testicles. The trial evaluated radiographic progression free survival and overall survival as co-primary endpoints. Secondary endpoints included time to initiation of chemotherapy, time to first skeletal-related event, soft tissue response rate, PSA response rate and time to PSA progression. A total of 872 patients were randomized to receive Xtandi 160mg with GnRH therapy or after bilateral orchiectomy. A total of 845 patients were randomized to receive placebo with GnRH therapy or after bilateral orchiectomy. Patients were treated until confirmed radiographic disease progression or skeletal-related event and initiation of cytotoxic chemotherapy or other agent or until unacceptable toxicity or withdrawal.

There was an 83% reduction in risk of radiographic progression or death in patients treated with Xtandi compared to placebo treated patients. Median radiographic progression-free survival was not reached for patients receiving Xtandi vs 3.7 months for placebo treated patients. Median overall survival was 35.3 months for Xtandi patients vs. 31.3 months for placebo treated patients with a 23% reduction in risk of death.

Exhibit 6: Xtandi pivotal Phase 3 clinical trials is mCRPC patients with prior chemotherapy and chemo naive patients.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Setting</th>
<th># of Patients</th>
<th>Xtandi</th>
<th>Placebo</th>
<th>Median Overall Survival</th>
<th>P Value</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFFIRM</td>
<td>mCRPC post docetaxel</td>
<td>1196</td>
<td>800</td>
<td>399</td>
<td>18.4 vs. 13.6 months</td>
<td>P &lt; 0.0001</td>
<td>August, 2012</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>mCRPC chemotherapy naïve</td>
<td>1717</td>
<td>872</td>
<td>845</td>
<td>25.3 vs. 21.3 months</td>
<td>P &lt; 0.0001 at interim analysis</td>
<td>September, 2014</td>
</tr>
</tbody>
</table>

Source: Xtandi prescription information
Provenge (Sipuleucel-T)

Provenge (sipuleucel-T) is approved for treatment of prostate cancer patients with asymptomatic or minimally symptomatic mCRPC. Provenge is an autologous cellular immunotherapy, which consists of peripheral blood mononuclear cells, including antigen presenting cells (APCs) activated ex vivo with recombinant fusion protein PA2024. PA2024 is prostate antigen, prostatic acid phosphatase fused to granulocyte–macrophage colony-stimulating factor. Patients undergo three leukapheresis procedure, followed by infusion of Provenge after three days. Provenge is prepared at a central facility by culturing patients APCs for 36 to 44 hours at 37°C in media containing PA2024. It is administered intravenously every two weeks for three infusions.

In the Phase 3 IMPACT trial, Provenge was evaluated in comparison to placebo in mCRPC patients who had asymptomatic or minimally symptomatic disease. Provenge led to relative reduction of 22% in the risk of death compared to placebo treated patients leading to 4.1 month improvement in median survival based on 25.8 months median survival for Provenge compared to 21.7 months for placebo.

Some of the challenges with Provenge include high cost of treatment, need for patients to go for leukapheresis, which take 3 to 4 hours, and infusion for a total of six visits. On launch Provenge was priced at $31K per infusion for a full treatment cost of $93K.

Exhibit 7: Provenge Phase 3 IMPACT trial.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Setting</th>
<th># of Patients</th>
<th>Sipuleucel-T</th>
<th>Placebo</th>
<th>Median Overall Survival</th>
<th>P Value</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT</td>
<td>Asymptomatic or minimally symptomatic mCRPC</td>
<td>512</td>
<td>341</td>
<td>171</td>
<td>25.8 vs 21.7 months</td>
<td>0.032</td>
<td>April, 2010</td>
</tr>
</tbody>
</table>

Source: Provenge label

Orteronel (TAK-700)

In late 2014, Takeda Pharmaceuticals voluntarily decided to end the developmental program for Orteronel (TAK-700) following the results of two Phase 3 clinical trials. TAK-700 is a non-steroidal anti-androgen, which selectively inhibits CYP17A in metastatic, castration resistant prostate cancer patients.

Although the studies found the combination of TAK-700 plus prednisone could extend time patient’s lives before the progression of their cancer, there was no evidence of overall extension of survival in the patient tested. The decision to discontinue the trial were based off of results from two Phase 3 trials, ELM-PC4 and ELM-PC5. ELM-PC4 found the combination of TAK-700 plus prednisone improved radiographic progression free survival (rPFS)
compared to prednisone alone. However, the results did not show a statistically significant improvement in the second primary endpoint of overall survival (OS). ELM-PC5 found that TAK-700 plus prednisone would likely not meet the primary endpoint of improved overall survival when compared to the control arm. The interim analysis did show an advantage for TAK-700 plus prednisone for the secondary endpoint, radiographic progression-free survival over the control arm. There were no significant safety concerns in either study.

**Xofigo (Radium-223)**

Bayer’s Xofigo is approved for treatment of prostate cancer resistant to treatments that lower testosterone and has metastasized to the bones. In clinical trials Xofigo extended overall survival by 30%. Xofigo is an alpha particle-emitting radioactive isotope that binds with bone minerals to deliver radiation directly within bones preventing bone metastasis.

In the Phase 3 ALSYMPCA trial, Xofigo on top of best standard of care was evaluated compared to placebo plus best standard of care in CRPC patients with symptomatic bone metastases but no visceral metastases. A total of 614 patients were randomized to Xofigo and 307 were randomized to placebo. Xofigo led to median overall survival of 14.9 months compared to 11.3 months for placebo.

**Exhibit 8: Xofigo Phase 3 ALSYMPCA trial.**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Setting</th>
<th># of Patients</th>
<th>Xofigo</th>
<th>Placebo</th>
<th>Median Overall Survival</th>
<th>P Value</th>
<th>FDA Approval</th>
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</thead>
<tbody>
<tr>
<td>ALSYMPCA</td>
<td>CRPC with symptomatic bone metastases and no known visceral metastatic disease</td>
<td>921</td>
<td>614</td>
<td>307</td>
<td>14.0 vs. 11.2 months</td>
<td>0.00185 at interim analysis</td>
<td>May, 2013</td>
</tr>
</tbody>
</table>

Source: Xofigo label

**BAY1841788 (ODM-201)**

BAY1841788 (ODM-201) is a novel androgen receptor inhibitor. It has high affinity for the androgen receptor and inhibits testosterone induced nuclear translocation of the androgen receptor. It also has activity against androgen receptor mutants like F876L, which are resistant to Xtandi and ARN-509 (discussed below). ODM-201 leads to reduction in growth of androgen receptor over expressing VCaP prostate cancer cells both* in vitro* and also in mouse xenograft model. BAY1841788 is being developed by Bayer in collaboration with Orion. Phase 3
ARAMIS clinical trial of BAY1841788 in high-risk non-metastatic CRPC is ongoing in 1,500 patients with data expected in March, 2018.

**TOK-001 (Galeterone)**

Galeterone is a small molecule, steroidal antiandrogen with dual mechanism of action. It targets the androgen receptor as an antagonist and is also a CYP17A1 inhibitor.

Galeterone was in a Phase 3 trial (ARMOR3-SV) in mCRPC in patients expressing AR-V7 variant of androgen receptor and was being compared with Xtandi. This trial was expected to enroll patients with metastatic disease on androgen deprivation therapy. The study was looking at radiographic progression-free survival as the primary endpoint and secondary endpoints include overall survival and time to initiation of cytotoxic chemotherapy. As of July 26, 2016, a data monitoring committee determined that the trial was unlikely to meet its primary endpoint. This news led the company to discontinue the Phase 3 trial of Galeterone, even though no safety-related concerns were attributed with galeterone by the data monitoring committee.

**JNJ-56021927 (ARN-509)**

JNJ-56021927 (ARN-509) is a second-generation, small molecule androgen receptor antagonist which lacks the agonist activity shown by bicalutamide. In mouse xenograft models of human CRPC, ARN-509 showed comparatively better efficacy than Xtandi. JNJ-56021927 is in multiple Phase 3 trials in prostate cancer.
7. Castration-Resistant or Hormone-Refractory Disease

Castrate-resistant prostate cancer (CRPC) overcomes the effects of androgen deprivation therapy and has been hypothesized to develop following development of mutations in prostate cancer cells to evade effects of androgen deprivation therapy. Some of the characteristics of CRPC that make it refractory to anti-androgen therapy are:

- Over expression of androgen receptor
- Mutations in the ligand binding domain of androgen receptor following treatment with anti-androgens targeting the ligand binding domain
- Ligand-independent androgen receptor activation
- Expression of androgen receptor splice variants lacking carboxyl terminus which contains the ligand binding domain

8. Targeting the Androgen Receptor Signaling Pathway

The androgen receptor plays an important role in prostate cancer

Research has shown that the androgen receptor plays a central role in the progression of prostate cancer. Treatments have been developed to target certain aspects of activation of the androgen receptor involved in the progression of prostate cancer. As scientists further understand the role of androgen receptor, treatments are being developed targeting other aspects of androgen receptor function, which may have been overlooked but play a role in the progression of cancer. Androgen-deprivation therapy has played an important role in the treatment of prostate cancer and advancements have been made in the development of effective therapeutic agents including agents targeting androgen synthesis pathways.

Androgen receptor structure and function

The androgen receptor is a nuclear receptor with three domains, the DNA binding domain, carboxyl terminal ligand binding domain and the amino terminal domain containing the transactivation domain. A flexible hinge region connects the ligand binding domain to the DNA binding domain. The amino terminal domain containing the transactivation domain is unique for the androgen receptor compared to other nuclear receptors.
Exhibit 9: Androgen receptor structure, depicting the carboxyl terminal ligand binding, DNA-binding, and N-terminal domains.

Source: ESSA Pharma

Under normal conditions, the androgen receptor is regulated by the binding of ligands, testosterone or dihydrotestosterone (DHT). Binding of ligand to the ligand binding domain of the androgen receptor leads to homodimerization of the receptor followed by nuclear translocation. In the nucleus, the androgen receptor binds to regulatory regions of target genes leading to gene expression including the expression of prostate specific antigen (PSA). PSA levels are used as a screening marker for prostate cancer diagnosis.

**Amino terminal domain of androgen receptor essential for transcriptional activity**

The amino terminal domain of the androgen receptor is essential for transcriptional activity of the androgen receptor both in a ligand-dependent and ligand-independent manner (3). Some of the androgen receptor related mechanisms of resistance include persistence of intratumoral androgen by *in situ* synthesis and metabolism, androgen receptor gene amplification or message/protein over expression, development of androgen receptor splice variants.
Exhibit 10: The androgen receptor and its mechanisms of reactivation leading to resistance and CRPC. Reactivation mechanisms include 1. Androgen dependent reactivation by intra-tumoral androgen production 2. Ligand hypersensitization which includes androgen receptor amplification, cofactor dysregulation, growth factor cross talk and androgen receptor tyrosine phosphorylation and 3. Androgen independent mechanism like alternative androgen receptor splicing and androgen receptor mutation.

9. Development of Resistance to Anti-androgen Therapies in mCRPC

Prostate cancer patients develop resistance and progress on Zytiga or Xtandi therapy. For example, patients progressing on Xtandi display rising PSA levels indicating that the tumor cells continue to be driven by androgen receptor activity (11). Androgen receptor splice variants play an important role in progression of prostate cancer and newer treatments are needed which target the mechanism of resistance and progression of the cancer.
There are several mechanisms involved in development of resistance to anti-androgen therapies.

**Exhibit 11: Mechanisms of resistance to anti-androgen therapies.** Resistance mechanisms include A. Androgen receptor/ CYP17 upregulation B. Androgen receptor splice variants C. Androgen receptor point mutations D. Glucocorticoid receptor upregulation E. Alternative oncogenic signaling pathways F. PD-L1/PD-1 upregulation

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**Androgen receptor and CYP17 upregulation**

Studies have shown that androgen deprivation therapy leads to androgen receptor gene amplification and protein over expression. 80% of CRPC has high levels of androgen receptor expression. Androgen receptor gene amplification and protein over expression is also involved in resistance to Zytiga and Xtandi. Studies in human CRPC xenograft models show that treatment with Zytiga lead to more than three times increase in expression of both full-length and truncated splice variants. LNCaP cells resistant to Xtandi have been showed to have higher levels of expression of both full-length androgen receptor and truncated splice variants in comparison to CRPC LNCaP cells (12).
Androgen receptor splice variants

Several studies had led to the identification of approximately 22 androgen receptor splice variants with focus on AR-V7 and AR\(^{\text{v567es}}\). Splice variants of androgen receptor have been hypothesized as one of the mechanisms of resistance to both Xtandi and Zytiga. Truncated androgen receptor protein encoded by splice variant mRNA lack the carboxyl terminal ligand binding domain but still has the trans-activating amino terminal domain. Despite the inability to bind ligand, these truncated proteins are constitutively active as transcription factors and are able to activate androgen receptor target genes in a ligand independent manner. Studies have shown that inhibition of the androgen receptor pathway by Xtandi and Zytiga leads to upregulation of AR-V7 and AR\(^{\text{v567es}}\) splice variants. Based on data from pre-clinical models, splice variants seem to play a clinically meaningful role in resistance to Xtandi and Zytiga.

Androgen receptor point mutations

Studies have shown high incidence of point mutations in androgen receptor gene in CRPC patients with progressive disease despite treatment with hormonal therapy and anti-androgens. Mutations in androgen receptor could potential lead to loss of function, gain of function, increased or decreased androgen receptor signaling. Gain of function mutations have been shown to lead to nonspecific activation of androgen receptor ligand binding domain by weak androgens, progestins, glucocorticoids, estrogens and even antiandrogens. Androgen receptor gene point mutations seem to provide survival advantage and leads to resistance against Xtandi and Zytiga.

Glucocorticoid receptor upregulation

Glucocorticoid receptor and androgen receptor belong to class I nuclear steroid receptors and share similarities in structure and mechanism of action. Studies have shown that glucocorticoid receptor may be able to bind to androgen receptor promoter elements and potentially lead to resistance to antiandrogen therapy (15). In mouse LNCaP xenograft tumor models resistant to Xtandi and ARN-509, common gene targets of androgen receptor and glucocorticoid receptor were upregulated and glucocorticoid receptor mRNA and protein levels were elevated (15). These and other data support the role of glucocorticoid receptor in resistance against novel antiandrogens.

Other oncogenic signaling pathways

Studies have shown upregulation of other oncogenic signaling pathways that promote transcriptional activities of androgen receptor following androgen deprivation and androgen receptor inhibition (16). Steroid receptor coactivator-1 (Src-1) and interleukin-6 (IL-6) have been shown to promote androgen receptor activation in the absence of androgens (16). Other oncogenic signaling pathways seem to play a role in activating androgen receptor pathway and thereby leading to resistance against novel antiandrogens.
Neuroendocrine/small cell trans-differentiation

Based on cases of development of neuroendocrine prostate cancer and small cell prostate cancer following hormone therapy, it has been hypothesized that these transformations may be linked to resistance to androgen receptor signaling (12).

Programmed death-ligand 1/Programmed death-1 upregulation

Xtandi resistant prostate cancer cell lines show elevated expression of programmed death-ligand 1 (PD-L1) (17). Preclinical data shows increased amounts of circulating PD-L1/2-positive dendritic cells and increased levels of tumor-intrinsic PD-L1 in mice with enzalutamide-resistant tumors (17). Upregulation of PD-L1 could potentially be a mechanism developed by prostate cancer cells to gain resistance to Xtandi.
10. EPI-506 Program

Approved therapies for CRPC target either directly or indirectly the carboxyl terminal of the androgen receptor where ligand binds. Research has shown the important role played by the amino terminal of the androgen receptor in development of resistance to existing treatments and progression of disease. The EPI-506 program is focused on targeting the amino terminus of androgen receptor for treating advanced prostate cancer and overcoming some of the resistance mechanisms leading to progression on Xtandi and Zytiga.

EPI-506 is a novel small molecule and is a pro-drug of EPI-002. EPI-002 binds irreversibly, with high selectivity to the amino terminal domain of both wild-type as well as splice-variant androgen receptor (that lack the LBD) and prevents activation. EPI-002 is differentiated from other androgen receptor targeting drugs by its ability to not impact the activity of other steroid receptors and its ability to target truncated splice variants of androgen receptor, which play an important role in resistance and progression of prostate cancer.

EPI-506 is the first small molecule targeting the amino terminal domain of androgen receptor. The amino terminal domain of the androgen receptor has high flexibility and is intrinsically disordered, therefore it is difficult to develop drugs targeting it.
Exhibit 12: EPI-506 binds to the amino terminal domain of the androgen receptor which is involved in activation of the androgen receptor. EPI-506 prevents transactivation of the amino terminus of the androgen receptor in prostate cancer cells.

Source: ESSA Pharma
**Structure of EPI-001**

EPI-001 was identified by screening marine sponge extracts for inhibition of both ligand-dependent and ligand-independent activation of the androgen receptor (3). EPI-001 has 2 chiral centers and is a mixture of 4 stereoisomers, EPI-002 (2R, 20S), EPI-003 (2S, 20R), EPI-004 (2R, 20R), and EPI-005 (2S, 20S) (6).

Exhibit 13: Structures of EPI-001 mixture and stereoisomers.

EPI-002 has the best anti-tumor activity among EPI analogues

In *in vitro* experiments EPI-002 and EPI-005, which are 20S chlorohydrin stereoisomers, had comparatively better efficacy in blocking the androgen receptor transcriptional activity than the 20R stereoisomers (6). EPI-002 also had best anti-tumor activity *in vitro* compared to other stereoisomers and the EPI-001 mixture, potentially due to differences in impact on transcriptional program.

Exhibit 14: EPI-002 had best anti-tumor activity *in vitro* compared to other stereoisomers and the EPI-001 mixture.

EPI-506 is a small molecule pro-drug of EPI-002 and has better potency when dosed orally

EPI-506 is a small molecule pro-drug of EPI-002 and has better potency when dosed orally. EPI-506 completely converts to EPI-002 \textit{in vivo}.

Exhibit 15: EPI-506 is a small molecule pro-drug of EPI-002. EPI-002 binds to the amino terminal domain of androgen receptor.

EPI-001 analogs, mechanism of binding to androgen receptor

EPI-001 analogs provide an unique mechanism to target progression and resistance of prostate cancer, unlike the existing approved drugs like Xtandi and Zytiga, by its ability to target the amino terminal domain of the androgen receptor and thereby targeting both the full length androgen receptor as well as the truncated splice variants of androgen receptor, which play an important role on the progression of disease by their ability to activate the androgen receptor pathway even in the absence of ligands like testosterone.

The AF-1 region in the amino-terminal domain (NTD) of androgen receptor predominantly drives the transcriptional activity. EPI-001 analogs interact with the AF-1 region, leading to inhibition of protein-protein interactions with the androgen receptor, and reduce androgen receptor interaction with androgen-response elements on target genes (3).

Experiments have demonstrated that EPI compounds target the NTD and prevent androgen driven activity. In pre-clinical models, it was shown that inhibition of androgen receptor activity could not be competed away with increasing concentrations of androgens, which bind to the ligand binding domain and activate the androgen
receptor. LNCaP human prostate cancer cells were transfected with an androgen receptor-driven PSA(6.1kb)-luciferase reporter, which is induced by the synthetic androgen, R1881 (3).

Exhibit 16: EPI compounds target the NTD of androgen receptor. B. Androgen receptor transcriptional activity was measured in LNCaP cells transiently transfected with the PSA (6.1kb)-luciferase reporter and treated with vehicle (DMSO), 10 μM bicalutamide (BIC), or 25 μM EPI-001 for 1 hour followed by increasing concentrations of synthetic androgen, R1881 for 48 hours. C. Effect of bicalutamide (0.1–3.5 μM) and EPI-001 (1–35 μM), alone or in combination (1:10 ratio), on androgen-induced AR transactivation in LNCaP cells transfected with the PSA(6.1kb)-luciferase reporter.


**EPI-001 inhibits androgen receptor activity both in the presence as well as absence of ligand**

EPI-001 is a potent inhibitor of the function of the amino terminal domain of the androgen receptor. Since the amino terminal domain of the androgen receptor is responsible for the activation of the androgen receptor blocking the amino terminal domain function should lead to blocking of the androgen receptor both in ligand-dependent and ligand-independent manner (3).

Forskolin (FSK) is able to transactivate the amino-terminal domain of androgen receptor in a ligand independent manner in the absence of both serum and androgen. It stimulates protein kinase A (PKA) activity, or IL-6.
Exhibit 17: EPI-001 inhibits transactivation of androgen receptor (AR) amino terminal domain (NTD) in transactivation assays performed in LNCaP cells. In the experiment, LNCaP cells were cotransfected with an expression vector for a chimeric protein encoding amino acids 1–558 of the human AR NTD fused to the Gal4DBD with a reporter gene containing the Gal4-binding site. The chimera cannot be activated by ligand bicalutamide (BIC) due to lack of ligand binding domain. 185-9-1 is an analog of EPI-001 without activity and was used as control. EPI-001 is able to inhibit both Forskolin (FSK) induced and IL-6-induced transactivation of the AR NTD to baseline levels. EPI-001 does not inhibit FSK-induction of transactivation of the Gal4DBD-CREB fusion protein, indicating that the inhibitory effects of EPI-001 is targeted thorough the AR NTD and do not involve the Gal4DBD.


EPI-001 inhibits endogenous androgen receptor mediated gene expression

Androgen receptor induces prostate-specific antigen (PSA) and Transmembrane Protease, Serine 2 (TMPRSS2) mRNAs in LNCaP cells. TMPRSS22 is a serine protease, which is upregulated by androgenic hormones in prostate cancer cells. EPI-001 led to inhibition of endogenous PSA and TMPRSS2 mRNA in LNCaP cells. EPI-001 did not inhibit mRNA of genes not activated by androgen receptor. This data shows that EPI-001 is able to inhibit the transcriptional activity of androgen receptor and attenuate the upregulation of genes activated by androgen receptor.
Exhibit 18: EPI-001 inhibited endogenous expression of androgen regulated genes in LNCaP cells. (A and B) EPI-001 inhibited endogenous expression of PSA (A) and TMPRSS2 (B). LNCaP cells were pretreated with EPI-001 prior to incubation for 16 or 24 hr with R1881 and harvesting total RNA. Levels of PSA and TMPRSS2 mRNAs were measured by qRT-PCR and normalized to GAPDH mRNA.

EPI-001 inhibited serum PSA and growth of prostate cancer xenografts

EPI-001 administration led to inhibition of serum PSA and growth of orthotopic LNCaP xenografts in castrated mice. This data shows the ability of EPI-001 to inhibit androgen receptor driven gene expression and proliferation of cells.

Exhibit 19: EPI-001 inhibited serum PSA and growth of orthotopic LNCaP xenografts in castrated mice.
(A) Mice were administered 50 mg/kg body weight EPI-001 by i.v. every other day for a total of 8 doses. Serum PSA was measured 2 days after the last dose when the prostates were harvested and tumor volume measured. Initial serum PSA: 69 ± 11 (control) and 60 ± 13 ng/ml (EPI-001), p = 0.36. Serum PSA is represented as the percentage drop from the start of the experiment. Error bars represent the mean ± SEM. (B) Tumor volumes and photographs of representative prostates with LNCaP tumors from mice administered DMSO or EPI-001. Bars represent the mean ± SEM.

Source: Anderson et. al (3)
EPI-002 inhibits androgen receptor splice variant driven tumor growth

In an experiment conducted in mouse xenograft LNCaP95 model, expressing androgen-independent AR splice variants without the ligand binding domain and resistant to Xtandi, EPI-506 was able to reduce splice-variant driven tumor growth in comparison to Xtandi and control with oral daily dosing. This pre-clinical model highlights the differentiated profile of EPI-506 and its potential to be efficacious in prostate cancer patients who do not respond to Xtandi.

Exhibit 20: EPI-002 reduces tumor volume in mouse model expressing androgen-independent AR splice variants (lack LBD) which are resistant to Xtandi. EPI-002 was dosed daily in a LNCaP95 model.

Source: ESSA Pharma
EPI-002 inhibits cells expressing androgen receptor splice variants

In an experiment conducted with LNCaP95 cells, expressing androgen receptor splice variants. EPI-002 was able to inhibit growth of the cells in comparison to ENZ (Xtandi) and bicalutamide.

Exhibit 21: EPI-002 inhibited growth of variant androgen receptor expressing LNCaP95 cells, in contrast to Xtandi and Bicalutamide.

EPI-506 has good safety and toxicity profile

Toxicology studies in rat and dog at 28 days shows that EPI-506 is safe at much higher dose levels than the equivalent being tested in humans. At high doses of 110 and 221 mg/kg/day in rat and 88 mg/kg/day and higher in dogs there were moderate toxicities of weight loss and renal effects of elevated serum creatinine and blood urea nitrogen (BUN), which were reversible.
11. EPI-506 Prostate Cancer Clinical Program

Phase 1/2 study of EPI-506 in patients with metastatic castration-resistant prostate cancer is ongoing. This Phase 1 part of the trial will include ~36 patients, whom will be dosed for 12 weeks, to evaluate safety, pharmacokinetics, maximum tolerated dose and will have dose escalation and dose expansion to find the recommended dose for the Phase 2 part of the trial. The Phase 1 trial enrolled the first patient in November, 2015. The open-label study will test up to six dose level of EPI-506, with the starting dose approved for use at 80 mg.

The Phase 2 part of the trial is expected to enroll 120 patients and is expected to begin in 1Q17. The study will look at three patient populations (~40 in each cohort); post-abiraterone metastatic castration-resistant prostate cancer (mCRPC) but enzalutamide-naive, post-enzalutamide mCRPC but abiraterone-naive, as well as post-abiraterone and enzalutamide mCRPC. The Phase 2 trial will look at prostate specific antigen (PSA) response parameters and radiographic response.

EPI-506 is differentiated from other approved drugs and drugs under development

EPI-506 is differentiated from other approved drugs and drugs under development by the ability to target the amino terminal domain of the androgen receptor. Targeting the amino terminal domain permits EPI-506 to be effective against splice variants lacking the ligand binding domain. This method of targeting also makes EPI-506 effective in CRPC that is refractory to anti-androgen therapies, which are based on targeting the ligand binding domain.
Exhibit 22: Mode of action of various drugs approved and being developed for treatment of prostate cancer.

<table>
<thead>
<tr>
<th>MOA</th>
<th>Approved</th>
<th>Agents in Clinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enzalutamide</td>
<td>Abiraterone</td>
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<tr>
<td>CYP17 Inhibitor</td>
<td>X</td>
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<tr>
<td>AR IBD Antagonist</td>
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<td>AR Degrader</td>
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<td>AR NTD inhibitor</td>
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<tr>
<td>Effective against splice variants</td>
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</table>

Source: ESSA Pharma

Collaboration efforts with Epic Sciences

ESSA Pharma entered into a collaboration with Epic Sciences. The usage of the circulating tumor cells (CTC) platform is seen as a powerful tool in understanding various cancer phenotypes. With ongoing collaboration efforts are on to develop new procedures and improve on current technologies in cancer management, the goal is to provide utility in the management of cancer and provide a way to make the CTC platform clinically useful.

We believe ESSA stands to benefit from the impact of the collaboration with Epic Sciences. EPI-506 is designed as the first small molecule targeting the amino terminal domain of androgen receptor. The amino terminal domain of the androgen receptor has high flexibility and is intrinsically disordered, therefore it is difficult to develop drugs targeting it. As past diagnostic assays result in such limitations as the results being narrow in nature, with a single test offering limited information of the targeted biomarker. These limitations have resulted in multiple tests having to be carried out in order to determine the efficacy of the drug, increasing the length of the trial. To address the limited view of cellular heterogeneity, the use of the CTC platform may offer more efficient ways to detect specific circulating tumor cells and the relevant immune cells. As the collaboration continues to grow, we believe such advantages as addressing the issue of the cellular heterogeneity in cancer will aide in distinguishing between different genetic mutations of cancer cells. Will help develop clinical trials, which more directly target the specific androgen receptor being tested to achieve favorable results sooner, enabling the company to better match therapies to the right patients.
References:


18. American Cancer Society. www.cancer.org; Key Statistics for Prostate Cancer
Company Profile

ESSA Pharma is a clinical stage biopharmaceutical company developing treatments for castration-resistant prostate cancer (CRPC). Its lead compound EPI-506, is a small molecule oral drug that selectively blocks the amino-terminal domain of the androgen receptor, thereby has potential to overcome some of the known androgen receptor dependent resistance mechanisms of CRPC. EPI-506 is in Phase 1/2 trial for the treatment of castration-resistant prostate cancer and based on it differentiated mechanism of action could potentially lead to increased progression-free and overall survival compared to the drugs approved for treatment of CRPC.

Valuation Summary

We value ESSA Pharma based on a risk-adjusted net present value (rNPV) of its pipeline. The company is valued at $9/per share over the next year. The main investment driver is EPI-506 for castrate resistant prostate cancer (CRPC) program in Phase 1/2 trial. The Phase 1 program is projected to report top-line results in 1Q 2017 and Phase 2 is possible in 1Q 2017, as well, at the dose established from the Phase 1 trial. Conservatively, we assess a 35% probability of success for the CRPC program given the lack of human efficacy data, androgen receptor is a validated target in prostate cancer, and based on results in pre-clinical models. The market potential for a safe, efficacious, therapeutic for prostate cancer patients progressing on current treatments is large and of significant unmet need. J&J's Zytiga and Astellas's/Medivation's Xtandi together had combined global sales of $4.1B in 2015 and is expected to increase over time as earlier stage patients are treated with these drugs. We conservatively assume that EPI-506 will capture 35% of the estimated $6.74B market in the peak year i.e. ~$2.4B.

Calculation of risk-adjusted NPV of company drug pipeline:

We calculate rNPV of the company's drug pipeline using the following factors:

* Time and risk for clinical development and market launch
* Based on Tufts Center for the Study of Drug Development historical probability of regulatory success based on the current clinical trial stage - 10% for drugs in pre-clinical, 25% for Phase 1, 40% for Phase 2, 67% for drug entering/ in Phase 3, around 81% for a drug in regulatory review. A later study conducted by BIO and BioMed tracker may be more comprehensive and concludes that the probability of success is lower - 9% for Phase 1, 15% for Phase 2, 44% for Phase 3, and 80% for a drug in regulatory review. Our analysis makes subjective adjustments to risk based on other criteria - biologics, vaccines (cancer or infectious disease), novel chemical entity, novel mechanism or known target, robustness of previous clinical data, predictive value
of pre-clinical or early human data etc. to arrive at a probability

- Risk-adjusted remaining R&D expenses (based on clinical trial stage).
- Discount rate of 10% for cash flows generated in the future. This is in addition to clinical and regulatory risk.
- The rNPV is calculated based on the years-to-peak market potential, risk adjusted revenues, and subtracting the risk adjusted R&D expenses. A drawback of this method is that it does not include cumulative revenues in the years prior to peak year - may make it conservative.

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<th>WW peak sales, royalties, milestones potential ($M)</th>
<th>On Market/Peak sales year</th>
<th>Remaining risk-adjusted R&amp;D expenses ($M)</th>
<th>Risk adjusted net present value (NPV) ($M)</th>
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<td>$2.359</td>
<td>2021/2025</td>
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Assumptions: The market potential for a safe, efficacious, therapeutic for prostate cancer patients progressing on current treatments is large and of significant unmet need. J&J’s Zytiga and Astellas/Pfizer’s Xtandi together had combined global sales of $4.1B in 2015 and is expected to increase over time as earlier stage patients are treated with these drugs. We conservatively assume that EPI-506 will capture 35% of the estimated $6.745B market in the peak year i.e. $2.359M.

Calculated based on 32M shares outstanding.
### EPIX INCOME STATEMENT (US$)

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<tr>
<td>Other Items</td>
<td></td>
<td>6,000</td>
<td>6,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net Income (Loss)</strong></td>
<td>(6,676,587)</td>
<td>(12,988,516)</td>
<td>(12,461,561)</td>
<td>1,446,000</td>
<td>(3,597,450)</td>
<td>(5,029,323)</td>
<td>(5,208,789)</td>
</tr>
<tr>
<td>Income tax expense</td>
<td>(151,272)</td>
<td>18,000</td>
<td>18,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative translation adjustment</td>
<td>(1,665,212)</td>
<td>(337,763)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net income (loss) to common stockholders</strong></td>
<td>(11,341,790)</td>
<td>(13,477,551)</td>
<td>(12,443,564)</td>
<td>1,446,000</td>
<td>(3,597,450)</td>
<td>(5,029,323)</td>
<td>(5,208,789)</td>
</tr>
<tr>
<td>Basic Net Income (Loss) Per Share (in Dollars Per Share)</td>
<td>($0.53)</td>
<td>($0.49)</td>
<td>($0.38)</td>
<td>0.05</td>
<td>($0.11)</td>
<td>($0.15)</td>
<td>($0.18)</td>
</tr>
<tr>
<td>Number of common shares outstanding, diluted (in Shares)</td>
<td>18,353,018</td>
<td>26,903,834</td>
<td>32,821,075</td>
<td>31,852,690</td>
<td>32,493,744</td>
<td>33,139,539</td>
<td>33,902,329</td>
</tr>
</tbody>
</table>
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Report ID: 9156