Next Generation Therapeutics for Prostate Cancer
(NASDAQ: EPIX; TSX: EPI)
Rodman & Renshaw 19th Annual Global Investment Conference
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The ESSA Mission

Address a major unmet medical need in the therapy of prostate cancer through novel mechanisms of inhibiting of androgen driven biology.
Investment Highlights

• Through EPI-506, the clinical safety and benefit established for inhibition of the N-terminal domain of the androgen receptor in mCRPC patients
• Promising next-generation Aniten compounds are designed to improve potency and other pharmaceutical properties compared to EPI-506
  • Rapidly advancing toward the clinic for mCRPC
• mCRPC represents a significant market opportunity – 160,000 new cases of prostate cancer annually
• Company to implemented a corporate restructuring plan to focus its resources on rapidly advancing the lead Aniten compound into the clinic
  • Annual cash savings of approximately $7M
• Highly experienced management team with significant oncology experience
# Management Team and Board of Directors

## Management

**David R. Parkinson, MD**
- President & Chief Executive Officer, Director
- Nodality, Novartis, Amgen, Biogen Idec, National Cancer Institute

**Peter Virsik, MS, MBA**
- Executive Vice President and Chief Operating Officer
- XenoPort, Gilead Sciences, J.P. Morgan, Genentech

**Frank Perabo, MD, PhD, FEBU**
- Chief Medical Officer & Executive Vice President of Clinical Development
- Astellas Global, Oncology World GmbH, P & S Partner Consulting, Bonn University

**David S. Wood, MBA, CPA, CMA**
- Chief Financial Officer
- Celator Pharmaceuticals, Cubist Pharmaceuticals, TerraGen Discovery

## Board of Directors

**Richard Glickman, LLD (Chairman)**
- Chairman of the Board, Aurinia, Aspreva, StressGen

**David R. Parkinson, MD**

**Marianne Sadar, PhD**
- BC Cancer Agency, UBC, ESSA Co-Founder

**Raymond Anderson, PhD**
- UBC, ESSA Co-Founder, Aquinox, Inflazyme

**Gary Sollis, LLD**
- Dentons

**Franklin Berger, CFA**
- JP Morgan, Salomon Smith Barney, Five Prime

**Scott Requadt, JD, MBA**
- Clarus Ventures, TransForm Pharma, Davis Polk
Prostate Cancer: Unmet Medical Need

• Prostate cancer is 2nd most common cause of death in men \(^1\)
  o Yearly, there are ~160,000 new prostate cancer cases and ~26,000 US deaths due to the disease
• In 2015, Zytiga® (abiraterone, approved 2011) and Xtandi® (enzalutamide, approved 2012) generated global sales of over $4B
• Disease progression strongly driven by androgen receptor (AR) signaling \(^2,3,4\)
  o An estimated ~60% of mCRPC tumors post-Xandi or Zytiga failure may still be AR-driven \(^5\)
• Despite new therapies, development of resistance limits treatment options and survival \(^6,7\)

\(^1\) Surveillance Research, American Cancer Society, 2016
\(^5\) Wyatt, JAMA, 2016
\(^7\) Attard, G, et al. ASCO Annual Meeting, 2017
Evolution of Prostate Cancer Therapeutics: Improvements with Higher Anti-AR Potencies and Earlier Combination Therapy

• Enzalutamide (ENZ) is a LBD inhibitor similar in pharmaceutical class to bicalutamide (BIC) but with higher affinity and in vivo potency

• ENZ vs. BIC clinical studies indicate more robust and thorough AR inhibition can lead to improvements in PFS in early CRPC:
  o TERRAIN (M1): PFS advantage of 9.9 months for ENZ compared to BIC
  o STRIVE (M0, M1): PFS advantage of 13.7 months for ENZ compared to BIC

• Limited clinical response to enzalutamide after progression on abiraterone (ABI)
  o PLATO clinical trial (abiraterone + ADT): Attard et al: J Clin Oncol 2017.35.15_suppl.5004
  o Astellas ENZ post ABI study: de Bono JS et al: Eur Urol 2017.07.035

• Major clinical benefit of early combination anti-hormonal therapy in castration-sensitive prostate cancer
  • LATITUDE trial; Fizazi K et al: NEJM 2017 377: 352
Prostate Cancer: Role of the Androgen Receptor

Androgen

Cytoplasm

Nucleus

Gene transcription

Cell proliferation

ARE = Androgen responsive elements
Current Therapies Target the AR Ligand Binding Domain

- AR is comprised of 3 distinct, independently acting domains
- Current therapies target the ligand-binding domain (LBD) of the AR

Zytiga® (abiraterone acetate)
Eligard™, Lupron® (leuprolide)
Zoladex® (goserelin)
Firmagon® (degarelix)

Xtandi® (enzalutamide)
Casodex® (bicalutamide)
Eulexin® (flutamide)
Nilandron® (nilutamide)

N-terminal domain  DNA-binding domain  Ligand-binding domain
Mechanisms of AR Resistance Occur in the Ligand Binding Domain

AR Amplification

Gain-of-function mutations

Splice variants

Promiscuous activation (i.e., glucocorticoids, progesterone)

Androgen Receptor

N-terminal domain (NTD) DNA-binding domain Ligand-binding domain (LBD)

“Anitens”: Novel Mechanisms of AR Inhibition with EPI Compounds

• Medical Need:
  o AR pathway active and relevant even after failure of current anti-androgens
  o Alternative mechanisms of AR pathway inhibition are required to address mechanisms of resistance
  o Successful development of new agents may lead to both salvage therapy strategies but also combination therapy strategies in earlier stage patients for better outcomes

• Anitens:
  o Initial compound result of natural product discovery
  o Granted unique USAN drug stem of “Aniten” as an N-terminal inhibitor of AR
  o AR inhibition through a completely novel mechanism: N-terminal domain inhibition
  o First generation EPI-506 has completed Phase I study
  o More potent next generation compounds being prepared for clinical development
Targeting the AR NTD: Novel Transcription Factor Inhibition of Androgen-driven Prostate Cancer Biology

- Proposed binding of EPI compounds to Tau-5 region of AF1
- EPI compounds inhibit wild-type, LBD mutant, and splice-variant AR activity
- EPI compounds inhibits AR transcriptional activity by blocking interaction with key transcriptional proteins (RAP74 & CBP)

Preclinical EPI-506/002 Activity in AR Splice Variant Driven Tumors

- LNCaP95 has a high level of expression of AR-V7 splice variant and is enzalutamide (ENZ) resistant
- EPI is active in inhibiting cellular proliferation while ENZ is not active
- EPI effectively reduces AR splice-variant driven tumor growth compared to ENZ and control

Adapted from Fig. 5A in Yang YC, et al. Clin Cancer Res, 2016
# First-Generation EPI-506 Phase 1/2 study in Patients w/ mCRPC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>An adaptive Phase 1/2 first-in-man dose escalation/dose expansion study</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Oral once-daily as a soft-gel capsule</td>
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<tr>
<td><strong>Population</strong></td>
<td>mCRPC patients who have experienced disease progression after abiraterone, enzalutamide, or both; allowed to have also failed one regimen of docetaxel chemotherapy</td>
</tr>
</tbody>
</table>
| **Study Size**  | Phase 1: ~36 patients  
    Phase 2: planned 120 patients                                                                                                        |
| **Endpoints**   | Phase 1: safety, PK, maximum tolerated dose, recommended Phase 2 dose, biomarkers (CTCs)                                               |
|                 | Phase 2: PSA response parameters, radiographic response, pain, biomarkers (CTCs, cfDNA)                                               |
| **Study Status**| Phase 1 study ongoing at 5 sites in US and Canada  
    Anticipated 27+/- clinical sites in US, Canada, and EU for Phase 2                                                                      |
# First-Generation EPI-506 Phase 1 Pharmacokinetic Data

## Mean Steady-State EPI-002 Plasma Pharmacokinetics

<table>
<thead>
<tr>
<th>EPI-002 Pharmacokinetics (Mean ± S.D.) on Day 8</th>
<th>PK Parameter</th>
<th>Cohort 6 2,400 mg QD (n=3)</th>
<th>Cohort 7 1,800 mg BID (n=2)</th>
<th>Cohort 8 3,600 mg QD (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>2,372 ± 813</td>
<td>3,057 ± 159</td>
<td>8,397 ± 1396</td>
<td></td>
</tr>
<tr>
<td>**t&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>4.00 (2.00 - 4.00)</td>
<td>2.00 (2.00 - 2.00)</td>
<td>2.50 (1.00 - 4.00)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;last&lt;/sub&gt; (ng/mL)</td>
<td>70 ± 25</td>
<td>208 ± 85</td>
<td>195 ± 185</td>
<td></td>
</tr>
<tr>
<td>**AUC&lt;sub&gt;0-24h&lt;/sub&gt; (ng*h/mL)</td>
<td>13,829 ± 6,758</td>
<td>23,524 ± 5,380</td>
<td>42,988 ± 24,841</td>
<td></td>
</tr>
</tbody>
</table>

**t<sub>max</sub> reported as median (min – max)
First-Generation EPI-506 Phase 1 Interim Exposure and Treatment Duration Data (N=28)

Data as of Aug 28, 2017

Median # exposure days = 87

- Continuing on study drug
- Discontinued
- Time of best PSA decline

Doses Received (mg)
- 160, 320, 640, 1280, 2400
- 640, 1280
- 2400
- 80, 160
- 2400
- 320
- 640, 1280
- 640
- 2400
- 320
- 1280
- 1280
- 80
- 1280
- 80
- 1800 (BID)
- 160
- 160
- 3600
- 1800 (BID)
- 320
- 640
- 3600
- 640
- 1800 (BID)
- 3600
- 1800 (BID)
## Safety / Tolerability Profile

<table>
<thead>
<tr>
<th>Most Commonly Reported Adverse Events &gt; 10%</th>
<th>All Grades, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea, nausea</td>
<td>13 (46%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>Decreased appetite, pain in extremity</td>
<td>6 (21%), each</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Abdominal distension, anemia, arthralgia, musculoskeletal pain, UTI</td>
<td>3 (11%), each</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events ≥ Grade 3</th>
<th>N (%)</th>
<th>Relationship to study drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>3 (11%)</td>
<td>Not related</td>
</tr>
<tr>
<td>AST elevated</td>
<td>2 (7%)</td>
<td>Probably related, Possibly related</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (7%)</td>
<td>Not related</td>
</tr>
<tr>
<td>Abdominal pain, diarrhea</td>
<td>1 (4%), each</td>
<td>Possibly related</td>
</tr>
<tr>
<td>ALT elevated, amylase elevated, angina, hypertension, dizziness postural</td>
<td>1 (4%), each</td>
<td>Probably related</td>
</tr>
<tr>
<td>Arthralgia, gastrointestinal hemorrhage, pain in extremity, syncope, thrombocytopenia, urinary retention</td>
<td>1 (4%), each</td>
<td>Not related</td>
</tr>
</tbody>
</table>
First-Generation EPI-506 Interim PSA Response - Maximal PSA Change at Any Time from Start of Multi-dose Period (N=25*)

*Of 28 enrolled pts: 25 were evaluable (had at least a WK4 PSA reading), 1 has not reached WK4, 2 discontinued before reaching WK4

Data as of Aug 28, 2017
EPI-506/002: Preclinical and Clinical Summary

• **Preclinical proof-of-concept established:**
  o Inhibition of AR transcription in vitro and in vivo
  o Dose-dependent tumor growth inhibition
  o More profound AR inhibition by combining NTD inhibitors with LBD inhibitors

• **Clinical data from the Phase 1 trial indicates:**
  o Modest efficacy in refractory mCRPC patients with minor PSA declines and some evidence of stable disease in this difficult-to-treat population
  o Favorable safety profile: mostly mild-moderate adverse events
  o Significant pharmaceutical limitations to EPI-506:
    » Potency, bioavailability, formulation, stability
Improving Upon the Limitations of EPI-002: Next-Generation Aniten Target Product Profile

Next-Generation Aniten Goals

• Increase *in vitro* and *in vivo* potency (≤1 μM IC$_{50}$ potency)
  o Verify oral activity *in vivo*

• Clean off-target profile

• Improved ADME profile
  o Block anticipated metabolism/resistance
  o Short, efficient, and scalable synthesis
  o Drug substance/product stability

• Strong IP – novel composition of matter
Several years of SAR effort led to the next-generation compounds

Screening data indicate these compounds are considerably more potent than EPI-002

Next-generation compounds also being targeted to provide improved ADME profile vs. EPI-506/002

- Potential for improved formulation, absorption, stability

Additional improvements in pharmaceutical properties:

- Crystal formation suggests solid form possibility, unlike EPI-506/002 which is difficult to formulation
  - Increases the likelihood of developing fixed-dose formulations in the future with other agents

Further preclinical characterization underway

Strong IP protection covering all Aniten filed broadly
Next-Generation Aniten Program Status

<table>
<thead>
<tr>
<th>TPP Criteria</th>
<th>Status</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase potency</td>
<td>✓</td>
<td>In vitro potency goal achieved; potency similar to ENZ and considerably more potent than EPI-002</td>
</tr>
<tr>
<td>• Oral activity <em>in vivo</em></td>
<td>✓</td>
<td>One compound tested in xenograft LNCaP model; orally active at lower doses than EPI-002</td>
</tr>
<tr>
<td>Clean off-target profile</td>
<td>✓</td>
<td>CEREP screening initiated; initial screening on a few compounds indicate that at least one compound has minimal off-target binding</td>
</tr>
<tr>
<td>Improved ADME profile</td>
<td><em>TBD</em></td>
<td>Screening initiated</td>
</tr>
<tr>
<td>• Block metabolism</td>
<td><em>TBD</em></td>
<td>New chemical structures designed to minimize potential metabolism</td>
</tr>
<tr>
<td>• Simple synthesis</td>
<td>✓</td>
<td>Simple 5-step process developed</td>
</tr>
<tr>
<td>• Chemical stability</td>
<td>✓</td>
<td>Initial stability appears greatly improved over EPI-506</td>
</tr>
<tr>
<td>Strong IP</td>
<td>✓</td>
<td>Worldwide IP filings made</td>
</tr>
</tbody>
</table>

- IND filing is targeted for early 2019
Emerging Potential Clinical Applications for NTD Inhibitors

• Salvage of anti-androgen refractory mCRPC patients
  o Majority were AR amplification or mutations
  o Other pathway genes affected: FOXA1, NCOR1/2, SPOP ZBTB16

• In combination with second generation anti-androgens in earlier mCRPC patients
  o In vitro data (Sadar lab, BCCA)
  o Preclinical in vivo (Mostaghel et al, unpublished)

• In combination with other agents
  o e.g. mTOR, PARP inhibitors (Sadar lab, BCCA)
More Complete AR Inhibition by Combining NTD & LBD Inhibitors in both Full Length and Splice Variant AR

**In Vitro AR Inhibition with Full-Length AR***

<table>
<thead>
<tr>
<th></th>
<th>EPI-002</th>
<th>ENZ</th>
<th>EPI-002 + ENZ</th>
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<tbody>
<tr>
<td>LNCaP fl-AR 100%</td>
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<tr>
<td>90%</td>
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<td></td>
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<td>80%</td>
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<td>0%</td>
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**In Vitro AR Inhibition with Resistant Cell Line***

<table>
<thead>
<tr>
<th></th>
<th>EPI-002</th>
<th>ENZ</th>
<th>EPI-002 + ENZ</th>
</tr>
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<tbody>
<tr>
<td>LNCaP95 w/ High Ectopic AR-V7 100%</td>
<td></td>
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<tr>
<td>90%</td>
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<tr>
<td>0%</td>
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- Similar effect seen in an *in vivo* VCaP xenograft model conducted independently which studied adding EPI to abiraterone or enzalutamide
- Together, these data indicate that both CYP17a lyase inhibitors and direct AR LBD antagonists may be worthwhile combinations with EPI in early and late-stage prostate cancer patients

Situation:
- Strengthening preclinical evidence for a therapeutic benefit from AR NTD inhibition
- Recognition that the agent is not a covalent binder: implications
- Phase I trial of EPI-506: safe, hints of efficacy but revealing of 506’s limitations
- Development of next generation Anitens preserves MOA but significantly improves potency, pharmaceutical properties

Choice:

Switch to EPI-002 (Active Drug):
- Reformulate
- Conduct bridging PK study
- Move to phase 2 study

-or-

Switch to Aniten:
- Select higher potency compound with improved ADME profile
- File IND and start new phase 1 study and refine patient selection
ESSA 9/2017: Focus on Next Generation NTD Inhibitors

• Decisions:
  o Board decision to focus company and resources on the development of next generation aniten compounds
  o The company will not proceed to Phase 2 trial with EPI-506
  o Today ESSA announced a company restructuring to focus on retaining staff for activities involved in Aniten compound selection and characterization for IND preparation, with goal of initiation of Phase 1 by 1Q 2019
    » Restructuring annual savings of $7M
  o The company is actively exploring the potential for advancing these compounds in collaboration or partnership
ESSA Value Proposition and Near-term Milestones

- Initial proof-on-concept established showing NTD inhibition can be done safely and provide a clinical benefit in mCRPC
- Numerous lessons learned on how to select patients and measure patient responses in a refractory mCPRC population
- Un-partnered Aniten franchise with high potency compounds rapidly advancing to IND
  - Aniten compounds exhibit similar potency of AR-inhibition as ENZ
- Numerous near-term clinical and corporate milestones:

<table>
<thead>
<tr>
<th>Milestone Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>Designate a lead Aniten compound for IND-enabling studies</td>
<td>1H18</td>
</tr>
<tr>
<td>Advance discussions with strategic partners regarding a collaboration</td>
<td>2018</td>
</tr>
<tr>
<td>File and IND on the lead Aniten in mCRPC</td>
<td>1H2019</td>
</tr>
<tr>
<td>Description</td>
<td>Value</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Cash (as reported 6/30/17)</td>
<td>$7.2M</td>
</tr>
<tr>
<td>Shares Outstanding</td>
<td>29.1M</td>
</tr>
<tr>
<td>Share price (7/08/17)</td>
<td>$0.44</td>
</tr>
<tr>
<td>Market Capitalization (7/08/17)</td>
<td>$12.5M</td>
</tr>
<tr>
<td>Ticker (NASDAQ)</td>
<td>EPIX</td>
</tr>
<tr>
<td>Ticker (TSX)</td>
<td>EPI</td>
</tr>
</tbody>
</table>
For further information, please contact:

**Investor Relations**

ir@essapharma.com
Back-Ups
Biological Complexity of Late Stage mCRPC

- The Phase 3 clinical trials of abiraterone and enzalutamide were conducted in a biologically different patient population
  - Patients progressing after initial ADT (e.g. Lupron and Casodex)

- Patients in the ESSA EPI-506 trial were later stage, having failed at least 1 second generation anti-androgen, and often both

- These patients are more biologically complex than previously realized (see Robinson Cell 161 1215, 2015)

- NTD inhibitors may form part, but not all of a therapeutic strategy for these advanced patients
Aberrations in AR Pathway Found in mCRPC (Robinson et al Cell 161,1215 2015)
Aberrations in the AR Pathway Found in mCRPC

- Cohort of 150 mCRPC affected individuals

- 107/150 harbored AR pathway aberrations
  - Majority were AR amplification or mutations
  - Other pathway genes affected: FOXA1, NCOR1/2, SPOP ZBTB16 (PLZF)

- Evidence for intra-tumoral heterogeneity

- Splice variants present in majority of pre-abiraterone/enzalutamide cases but at very low ratios

  - Robinson et al Cell161:1215, 2015