Aeglea BioTherapeutics (AGLE)

Nature Publication on Aeglea’s AEB3103 Highlights the Potential for L-Cyst(e)ine Depleting Treatments in Cancer

On November 21st, Aeglea BioTherapeutics (NasdaqGM: AGLE) announced the publication of a paper demonstrating cancer suppression in preclinical models with AEB3103 in *Nature Medicine*, a top-tier medical journal. Results showed that AEB3103 had a robust effect in suppressing tumor growth in prostate and breast cancer mouse models, while extending survival in a chronic lymphocytic leukemia (CLL) model. Additional data on this compound will be presented on December 3rd at the American Society of Hematology (ASH) annual meeting. AEB3103 is similar to Aeglea’s lead asset AEB1102 in that it is a pegylated, engineered human enzyme, but is specific for L-Cyst(e)ine dependent cancers instead of arginine. We also summarize preclinical data presented at the Society for Immunotherapy of Cancer (SITC) meeting earlier in November showing that treatment with AEB1102 could increase the sensitivity of cancers to anti-PD-1/L1 immunotherapies.

**L-Cysteine Uptake Plays a Key Role in Cancer Cell Survival and Proliferation.** Glutathione (GSH) is an antioxidant that is important for cancer cell survival and proliferation. It protects cancer cells from oxidative stress caused by high levels of reactive oxygen species (ROS) in tumors. In order to produce GSH, cellular uptake of L-cysteine (L-Cys) is necessary, and usually comes through its disulfide form, called L-cystine (CSSC). Aeglea indicated that several forms of cancer rely on extracellular L-Cys for survival, including myeloma, AML, CLL, solid tumors, GBM, triple-negative breast cancer, esophageal squamous cell carcinoma, small cell lung cancer, and prostate cancer.

Notably, L-Cys is a non-essential amino acid, meaning that the depletion of it in the body should impact tumors, while causing minimal effects on normal physiology. Aeglea's AEB3103 is a pegylated engineered human enzyme that degrades serum L-Cys and its more common dimeric form CSSC. The lack of L-Cys increases the amount of oxidative stress in tumors and can ultimately lead to cancer cell death. AEB3103 is highly efficient compared to wild-type glutamate-cysteine ligase, and has a 25 and 50 fold higher $k_{cat}/K_M$ for L-Cys and CSSC, respectively. $k_{cat}/K_M$ is a measure of catalytic efficiency that indicates how quickly an enzyme is working, and the affinity of the enzyme for its substrates. Aeglea is planning to study the combination of AEB3103 with other ROS inducing drugs due to the potential synergies.

**Expected Upcoming Milestones**

- **Q4 2016** – Complete enrollment of Phase I US trial with AEB1102 for Arginase I deficiency.
- **Q4 2016** – Complete enrollment of Phase I trial with AEB1102 for patients with solid tumors.
- **H1 2017** – Topline data from Phase I US trial with AEB1102 for Arginase I deficiency.
- **H1 2017** – Initiate Phase I expansion arms for several tumor types.
- **2017** – Complete enrollment of Phase I North American trial in AML and MDS.
- **2017** – Enroll patients in Phase II European trial with AEB1102 for Arginase I deficiency.
- **2017** – Topline data from Phase I trial with AEB1102 for patients with solid tumors.

Analysts

Jerry Isaacson, Ph.D. (AC)
(646) 597-6991
jisaacson@lifescicapital.com

Market Data

<table>
<thead>
<tr>
<th></th>
<th>Price</th>
<th>Market Cap (M)</th>
<th>EV (M)</th>
<th>Shares Outstanding (M)</th>
<th>Fully Diluted Shares (M)</th>
<th>Avg Daily Vol</th>
<th>52-week Range</th>
<th>Cash (M)</th>
<th>Net Cash/Share</th>
<th>Annualized Cash Burn (M)</th>
<th>Years of Cash Left</th>
<th>Short Interest (M)</th>
<th>Short Interest (% of Float)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$5.09</td>
<td>$68</td>
<td>$0</td>
<td>13.4</td>
<td>13.4</td>
<td>38,350</td>
<td>$3.89 - $12.75</td>
<td>$68.0</td>
<td>$5.07</td>
<td>$23.2</td>
<td>~2.9</td>
<td>0.01</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Financials

<table>
<thead>
<tr>
<th></th>
<th>FY Dec</th>
<th>2014A</th>
<th>2015A</th>
<th>2016A</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS</td>
<td>Q1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Q2</td>
<td>NA</td>
<td>NA</td>
<td>(0.46)A</td>
</tr>
<tr>
<td></td>
<td>Q3</td>
<td>NA</td>
<td>NA</td>
<td>(0.47)A</td>
</tr>
<tr>
<td></td>
<td>Q4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>FY</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

For analyst certification and disclosures please see page 5
**AEB3103 Prolongs Survival in Mice with CLL.** CLL cells rely on the uptake of CSSC to be converted into L-Cys from surrounding bone marrow stromal cells. L-Cys in turn released into the CLL microenvironment and taken up by CLL cells. The efficacy of single agent AEB3103 was compared to fludarabine and a combination of the two in mice with leukemic cells that were isolated from TCL1-Tg; p53 -/- mice. This mouse model has a TCL1 transgenic and p53 deletion genotype. It has a drug-resistance phenotype that mimics CLL in humans who have a chromosomal 17p deletion, which is a more aggressive form of CLL that often leads to resistance to treatments like fludarabine. Treated mice were roughly 2 months old, which is approximately when they began developing CLL-like disease. As shown in **Figure 1**, mice had a median overall survival of 7.4 months when treated with the combination of AEB3103 and fludarabine (n= 10), 7 months when treated with AEB3103 alone (n= 10), 5.3 months when treated with fludarabine monotherapy (n= 10), and 3.5 months when not treated with any therapy (n= 47). These data in addition to those discussed below indicate that AEB3103 may have an effect in both hematological malignancies and solid tumors.

![Figure 1. Overall Survival of Mice Treated with AEB3103](image)

**Antitumor Activity with AEB3103 Seen in Prostate and Breast Cancer Mouse Models.** In the published preclinical results, the antitumor activity of AEB3103 was evaluated in syngenic male FVB/N mice with different palpable prostate cancer cell lines called HMVP2, DU145, and PC3. Mice were implanted with the PC3 and HMVP2 cancer cells, and administered either a saline control, 100 mg/kg heat-inactivated AEB3103, 50 mg/kg AEB3103, or 100 mg/kg AEB3103 starting 10 and 15 days after implantation. Heat inactivated AEB3103 was used as another control to determine the presence of residual impurities and endotoxin in the active protein. Mice implanted with DU145 cells were only treated with saline control or 100 mg/kg of AEB3103 9 days after implantation. Treatment occurred every 4 days for a 4-week period.

As shown in **Figure 2**, treatment with AEB3103 led to a statistically significant decrease in tumor volume growth rate in all three cell lines compared to both saline control and heat-inactivated AEB3103. The HMVP2 model is labeled c, the DU145 model is labeled e, and the PC3 model is labeled f. This effect was dose dependent in the PC3 cell line, whereas similar efficacy was observed with both AEB3103 doses in the HMVP2 cell line. Notably, comparable efficacy results were observed in a MDA-MB-361 breast cancer xenograft model.
Figure 2. Antitumor Activity with AEB3103 in Prostate Cancer Mouse Models

AEB3103 has Long Lasting Effect in Mice. The pharmacodynamics and pharmacokinetics of AEB3103 were measured in non-tumor bearing FVB/N mice using a single 50 mg/kg dose. FVB/N mice are often used for genetic studies and transgenic experiments due to their ability to produce large litters. The clearance half-life of AEB3103 was 25 ± 2 hours, and as shown in the left panel of Figure 3, serum CSSC in 5 mice was almost completely eliminated for 4 days with levels recovering to the pre-dosing concentration at day 6. The right panel of Figure 3 shows that free L-Cys levels in 5 mice were reduced by over four-fold for roughly 2 days prior to slowly recovering back to normal levels. It is worth noting that the compound used in this preclinical model may not be the one taken forward into the clinic, and so enhancements to the pharmacokinetic/pharmacodynamics profile may occur. As a comparison, the half-life of AEB1102 is 37 ± 3 hours, and is dosed at a frequency of once weekly in its ongoing Phase I solid tumor trial. Measurements in this analysis were based on serum metabolomics. Notably, there were no organ abnormalities, weight loss, or adverse events were observed in the mice.

Figure 3. Reduction in CSSC and L-Cys Following Single Dose of AEB3103

Source: Cramer, S.L. et al., 2016
SITC Data Showed Treatment with AEB1102 Could Sensitize Cancers to Anti-PD-1/L1 Therapies. Aeglea presented preclinical data at SITC showing that treatment with AEB1102 could increase the sensitivity of cancers to anti-PD-1/L1 therapies. AEB1102 was evaluated in a CT26 colon carcinoma xenograft model and a Lewis lung xenograft model. Mice were treated with control, 3 mg/kg of single-agent AEB1102, single agent anti-PD-1/L1 or combination treatments. Efficacy was evaluated in non-staged mice, which were treated 3 days following implantation, and in staged mice, which had established palpable tumors.

As shown in Figure 4, treatment with AEB1102 plus anti-PD-L1 in the CT26 colon carcinoma model led to a decreased rate of tumor volume growth in the recently transplanted mice, and an increased overall survival in the mice with established tumors at the start of treatment in the colon carcinoma model. The combination treatment showed a statistically significant advantage over both single agent PD-L1, and single agent AEB1102. In the Lewis Lung Model, the combination of AEB1102 and an anti-PD-L1 agent also led to the greatest inhibition of tumor growth, while providing the longest survival advantage.

Figure 4. Tumor Growth Inhibition with AEB1102 Plus anti-PD-1/L1 in CT26 Colon Carcinoma Model

Risk to Investment

We consider an investment in Aeglea Biotherapeutics to be a high-risk investment. Aeglea Biotherapeutics is a development stage company with no history of taking a treatment to market and currently has no FDA approved drugs in its portfolio. The Company’s clinical programs have not yet entered Phase III trials and have generated limited data to date. Furthermore, early indications of efficacy do not necessarily translate into positive late-stage results. Phase III clinical trials will result in significant additional expenses to the Company and may require additional rounds of dilutive financing. As with any company, Aeglea Biotherapeutics may be unable to obtain sufficient capital to fund planned development programs. There are regulatory risks associated with the development of any drug and Aeglea Biotherapeutics may not receive FDA approval for its candidates despite significant time and financial investments. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet expectations.
Analyst Certification

The research analyst denoted by an “AC” on the cover of this report certifies (or, where multiple research analysts are primarily responsible for this report, the research analyst denoted by an “AC” on the cover or within the document individually certifies), with respect to each security or subject company that the research analyst covers in this research, that: (1) all of the views expressed in this report accurately reflect his or her personal views about any and all of the subject securities or subject companies, and (2) no part of any of the research analyst’s compensation was, is, or will be directly or indirectly related to the specific recommendations or views expressed by the research analyst(s) in this report.

DISCLOSURES

This research contains the views, opinions and recommendations of LifeSci Capital, LLC (“LSC”) research analysts. LSC (or an affiliate) has received compensation from the subject company for producing this research report. Additionally, LSC expects to receive or intends to seek compensation for investment banking services from the subject company in the next three months. LSC (or an affiliate) has also provided non-investment banking securities-related services, non-securities services, and other products or services other than investment banking services to the subject company and received compensation for such services within the past 12 months. LSC does not make a market in the securities of the subject company.

Neither the research analyst(s), a member of the research analyst’s household, nor any individual directly involved in the preparation of this report, has a financial interest in the securities of the subject company. Neither LSC nor any of its affiliates beneficially own 1% or more of any class of common equity securities of the subject company.

LSC is a member of FINRA and SIPC. Information has been obtained from sources believed to be reliable but LSC or its affiliates (LifeSci Advisors, LLC) do not warrant its completeness or accuracy except with respect to any disclosures relative to LSC and/or its affiliates and the analyst's involvement with the company that is the subject of the research. Any pricing is as of the close of market for the securities discussed, unless otherwise stated. Opinions and estimates constitute LSC’s judgment as of the date of this report and are subject to change without notice. Past performance is not indicative of future results. This material is not intended as an offer or solicitation for the purchase or sale of any financial instrument. The opinions and recommendations herein do not take into account individual client circumstances, objectives, or needs and are not intended as recommendations of particular securities, companies, financial instruments or strategies to particular clients. The recipient of this report must make his/her/its own independent decisions regarding any securities or financial instruments mentioned herein. Periodic updates may be provided on companies/industries based on company specific developments or announcements, market conditions or any other publicly available information. Additional information is available upon request.

No part of this report may be reproduced in any form without the express written permission of LSC. Copyright 2016.