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Healthcare

Epigenetics: Welcoming LSD1 to the I-O Revolution

In our coverage of epigenetics, two months ago we were the first to bring to the attention of U.S. investors Oryzon Genomics (ORY.SM-Buy), a Spanish epigenetic biotech with clinical programs in both oncology and neuro (read our initiation chapter on AML & NSCLC and our quicktake on Alzheimer's). Herein we discuss the latest independent research on LSD1, the epigenetic target being pursued by Oryzon alongside larger players like GSK (GSK-NC) and Incyte (INCY-NC).

The topline. Last week, an article published in Cell from the epigenetics veteran Yang Shi (Harvard) shows that: (a) LSD1 loss in tumor cells stimulates anti-tumor T cell immunity; (b) LSD1 ablation enhances tumor immunogenicity and T cell infiltration; and (c) LSD1 inhibition overcomes resistance to anti-PD-1 therapy in a mouse melanoma model.

The nitty gritty. More specifically, the research article shows that loss of LSD1 in tumor cells increases expression of endogenous retroviral elements (ERVs) and decreases expression of components of the RNA-induced silencing complex (RISC). This leads to double-stranded RNA (dsRNA) stress and activation of type 1 interferon (IFN), which enhances tumor immunogenicity and anti-tumor T cell immunity, and limits tumor growth even in poorly immunogenic tumors. In line with these findings, the paper also highlights a nice inverse correlation between LSD1 expression and CD8+ T cell infiltration across human cancers.

What it means. In our view, this paper just made all LSD1 inhibitors out there more valuable, especially those such as Oryzon's which we believe are not getting sufficient value or attention for their primary positioning in the first place. In the larger picture, while in the last two years combining any random drug "X" with checkpoint inhibitors has become a routine fast-track to an ASCO abstract or a valuation step up, rarely in all those cases do we see a priori mechanistic or preclinical evidence for the I-O synergy such as the one described above.

As a reminder, we have already seen some combinations of epigenetic agents with I-O therapy go into testing, suggesting potential class utility. For example, we point to a study of the EZH2 inhibitor tazemetostat with atezolizumab in R/R DLBCL and NSCLC from Epizyme (EPZM-Buy), and a study of the EZH2 inhibitor CPI-1205 with ipilimumab or pembrolizumab in solid tumors from Constellation Pharma (private). Interestingly, we have also seen combos of HDAC inhibitors with I-O therapy from Mirati (MRTX-NC) and Syndax (SNDX-NC). However, historically HDAC inhibitors have struggled with target selectivity/specificity and thus with their therapeutic window (it is hard to selectively inhibit particular HDAC isoforms), and we generally remain skeptical about how targeted their combo can really get.

Overall, we expect oncology to remain a growing framework for LSD1 development, as existing LSD1 drug candidates, clinical and preclinical, now also pick up an extra I-O identity (and extra derivative value). Read our Oryzon initiation for short summaries of the several other LSD1 inhibitors in development, their respective indications, and potential points of differentiation.

Reason for Report:
Industry Update

Roth Covered Companies Mentioned in this Report:

EPZM	$13.60	Buy
ORY.SM	$4.15	Buy

Stock prices are as of previous day's close, if not otherwise specified

Epizyme, Inc. (EPZM - Buy - $26PT)

Valuation. Our 12-month price target of $26/share ($18 for tazemetostat in mutant follicular lymphoma + $4 for tazemetostat in genetically-defined solid tumors + $4 in cash) is based on a DCF-NPV-SOP analysis using a 12% discount rate and 2% growth rate. Factors which could impede the achievement of our target price include, but are not limited to: (1) success or failure and/or setbacks of tazemetostat and/or other future pipeline candidates in clinical studies; (2) success or failure of tazemetostat and/or other future pipeline candidates to gain regulatory approval; and (3) larger or smaller than projected commercial opportunity due to changes in market size, competitive landscape, and drug pricing and reimbursement.

Experimental therapeutic product risk. The company's risk profile is based primarily, in our belief, on the clinical prospects of tazemetostat. Current funding at the company is being directed toward its multiple clinical programs and should there be any missteps, negative trial data or delays, this could impact the stock negatively.

Development timeline risk. The company's shares could be subject to increased volatility, in our belief, based on the time frame required to obtain registrational data and clarity on the regulatory path for the current clinical programs of tazemetostat. Positive clinical data may yield a potential accelerated path toward approval, and we currently project that tazemetostat could reach the market in 2019 for genetically-defined solid tumors and 2020 for subsets of NHL. Investors may choose to delay investment in the company, despite potential excitement, until further clarity on the regulatory and commercial prospects and timetable.

Competitive risk. The development, regulatory, and commercial prospects of tazemetostat could be affected by the clinical milestones achieved by competitor programs in the same or related indications, which include competitor agents specifically targeting EZH2, agents targeting related epigenetic functionalities, and agents that are mechanistically unrelated but that may outperform tazemetostat clinically in liquid and solid tumors.

Financing risk. As with a majority of development-stage biotechnology companies, the ability to maintain sufficient funding is critical to the progress of pipeline candidates. Should the company experience problems raising sufficient capital, its development programs' progress could be significantly impeded, leading to both delays in development timelines as well as potential negative effects on investor confidence. Each of these could have a negative impact on share price.

Oryzon Genomics SA (ORY.SM - Buy - €15PT)

Valuation. Our 12-month price target of €15/share (€4/share for ORY-1001 in AML + €10/share for ORY-2001 in AD + €1/share in cash) is based on a DCF-SoP analysis using a 12% discount rate and 1% growth rate. Factors which could impede the achievement of our target price include, but are not limited to: (1) failure and/ or setbacks of the drugs in clinical studies; (2) failure of the drugs to gain regulatory approval; and (3) smaller than projected commercial opportunity due to changes in market size, competitive landscape, and drug pricing and reimbursement.

Experimental therapeutic product risk. The company's risk profile is based primarily, in our belief, on the company's thesis being based on the clinical and commercial prospects of pipeline candidates. Current funding at the company is being directed toward these programs and should there be any missteps, negative trial data or delays, this could impact the stock negatively. Adding additional risk to both programs is their early stage nature. Drug development is fraught with failures and this risk is increased significantly during the earlier stages of development.

Development timeline risk. The company's shares could be subject to increased volatility, in our belief, based on the time frame required to get meaningful proof of concept data from the planned clinical program. Positive clinical data could yield a potential accelerated path toward approval, however we currently project that our modeled drug candidates ORY-1001 and ORY-2001 may only reach the market in 2023 and 2024, respectively. Investors may choose to delay investment in the company, despite potential excitement, until meaningful clinical data is generated.

Financing risk. As with a majority of development-stage biotechnology companies, the ability to maintain sufficient funding is critical to the progress of pipeline candidates. Should the company experience problems raising sufficient capital, its development programs' progress could be significantly impeded, leading to both delays in development timelines as well as potential negative effects on investor confidence. Each of these could have a negative impact on share price.

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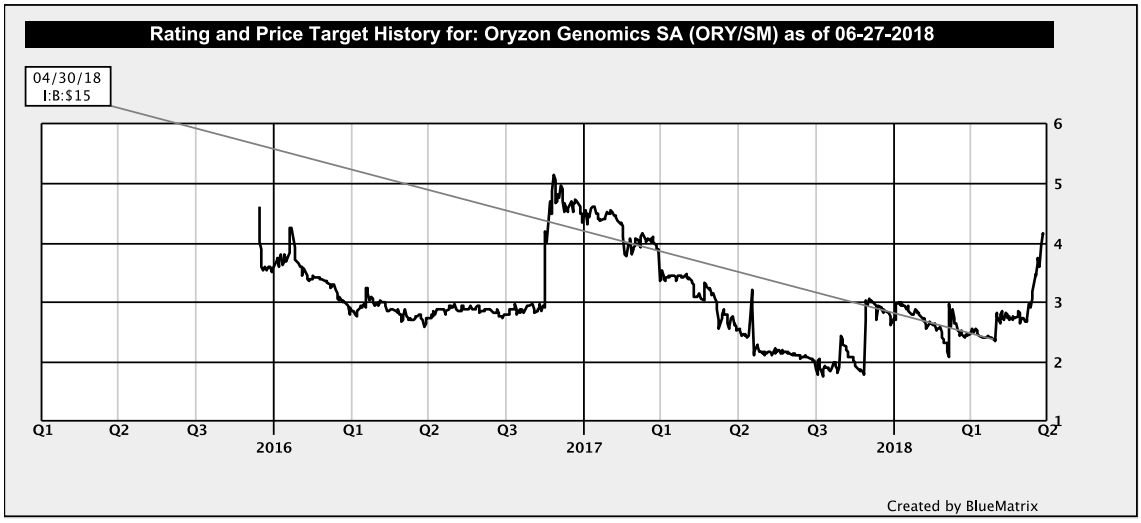
For important disclosure information regarding the companies in this summary report, please contact: The Director of Research at (800) 678-9147 or write to: ROTH Capital Partners, LLC, Attention: Director of Research, 888 San Clemente Drive, Newport Beach, CA 92660

Disclosures:

ROTH makes a market in shares of Epizyme, Inc. and as such, buys and sells from customers on a principal basis.

Shares of Oryzon Genomics SA may be subject to the Securities and Exchange Commission's Penny Stock Rules, which may set forth sales practice requirements for certain low-priced securities.



Each box on the Rating and Price Target History chart above represents a date on which an analyst made a change to a rating or price target, except for the first box, which may only represent the first note written during the past three years. **Distribution Ratings/IB Services** shows the number of companies in each rating category from which Roth or an affiliate received compensation for investment banking services in the past 12 month.

Distribution of IB Services Firmwide

	IB Serv./Past 12 Mos.

			as of 06/28/18	
Rating	**Count**	**Percent**	**Count**	**Percent**
Buy [B]	**260**	**71.43**	**141**	**54.23**
Neutral [N]	**52**	**14.29**	**25**	**48.08**
Sell [S]	**6**	**1.65**	**2**	**33.33**
Under Review [UR]	**45**	**12.36**	**23**	**51.11**

Our rating system attempts to incorporate industry, company and/or overall market risk and volatility. Consequently, at any given point in time, our investment rating on a stock and its implied price movement may not correspond to the stated 12-month price target.

Ratings System Definitions - ROTH employs a rating system based on the following:

Buy: A rating, which at the time it is instituted and or reiterated, that indicates an expectation of a total return of at least 10% over the next 12 months.

Neutral: A rating, which at the time it is instituted and or reiterated, that indicates an expectation of a total return between negative 10% and 10% over the next 12 months.

Sell: A rating, which at the time it is instituted and or reiterated, that indicates an expectation that the price will depreciate by more than 10% over the next 12 months.

Under Review [UR]: A rating, which at the time it is instituted and or reiterated, indicates the temporary removal of the prior rating, price target and estimates for the security. Prior rating, price target and estimates should no longer be relied upon for UR-rated securities.

Not Covered [NC]: ROTH does not publish research or have an opinion about this security.

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