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Healthcare

Epigenetics: LSD1 & Precision Medicine

Here we highlight a Nature paper published last week, which in our view not only frames LSD1 as an important target in oncology, but also stirs up some nuanced themes which we believe are essential to understanding and executing epigenetic drug development correctly. Call us to discuss the wider epigenetic landscape, including all the targets and programs mentioned below.

What did we learn from this paper? (a) In medulloblastoma (MB), there is a tight interplay between the tumor-driver transcription factor Gfi1 and the histone demethylase LSD1; (b) The two proteins LSD1 and Gfi1 physically associate and together inhibit genes involved in neuronal commitment and differentiation; (c) LSD1 is essential for Gfi1-mediated transformation; and (d) Importantly, since direct targeting of Gfi1 is not possible, two LSD1 inhibitors tested (from GSK and ORY) potently inhibit growth of Gfi1-driven tumors.

Why is this all important? (a) It continues to validate LSD1 as key player in transformation, and as an important target in oncology. Although recently this target has extended in neurodegeneration, neuroinflammation, and neuropsychiatry, we continue to like its overlooked potential in wider oncology (we note that Oryzon (ORY.SM-Buy) currently has programs in both neuro and oncology); (b) It highlights a provocative conceptual bridge between LSD1 targeting in neurodegeneration and neuro-oncology, where the desired therapeutic outcomes are synaptogenesis and differentiation, respectively. As a reminder, these two neuronal phenomena do go hand in hand in development; and (c) It continues to support our long-standing thesis that the most productive use of targeted epigenetic agents is either outside of oncology in chronic conditions (for example, the bromodomain inhibitor apabetalone in Phase 3 in T2DM/CVD from Resverlogix (RVX.TO-Buy), or in molecularly-defined oncology carve-outs. In our view, the latter may include either: (a) genomically-defined subsets of a more prevalent cancer (for example, tazemetostat in EZH2-mutant follicular lymphoma, although recently Epizyme (EPZM-Buy) announced its intent to pursue the wider indication, nonetheless); or (b) a rare or orphan cancer whose monogenic pathology has a direct link to the epigenetic target (for example, the pending NDA in epithelioid sarcoma from tazemetostat, or the Phase 1 studies in Ewing sarcoma with the LSD1 inhibitors seclidemstat from Salarius and INCB059872 from Incyte).

What can we deduce about the two LSD1 agents used concurrently in this paper? Of note, the authors used both a GSK and an ORY compound in their preclinical assays, and then only the GSK compound in their mouse experiments. While we have no insight into their reason for these choices, we speculate that the *in vivo* advance of the GSK compound alone may have likely been due to a professional relationship between the publishing lab and GSK. We highlight that one of the paper's 17 authors is a member of the GSK Cancer Epigenetics group. Our review of public LinkedIn profiles reveals that this author has been at GSK for 8+ years, first as Scientific Leader and currently as Director, while our review of PubMed publication records reveals that this author has likely been a senior in the development of GSK's compound. Overall, then, we believe that: (a) in this paper, the two compounds look similar in cell assays, within experimental margin: they have approximate IC50s in tumor cells where LSD1 is indispensable, and they drive approximate post-mitotic cell viability; (b) in this paper, the GSK compound shows very good anti tumor graft action in mice, in our view, and so extrapolating from the assay comparison we expect the ORY compound to look similar if used in the same mouse experiment.

What will we watch for in the future? While the paper frames LSD1 as a key target for a precision medicine approach to MB, the compounds tested do not appear sufficiently MB tumor penetrant (though they may be brain penetrant): intracranial MBs are not susceptible, but flank MB grafts are (and here we highlight the innovative method used by the authors: treating the flank grafts post-resection, which approximates how clinical MB is treated). In our view, while this suggests that more work is required on the drug delivery / tumor exposure front in MB, it highlights new optionality for LSD1 targeting in molecular carve-outs of other tumors with aberrant Gfi1, such as colorectal cancer, and lymphoid and myeloid malignancies.

Reason for Report:
Industry Update

Roth Covered Companies Mentioned in this Report:

EPZM	$9.66	Buy
ORY.SM	$2.83	Buy
RVX.TO	$3.20	Buy

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

Epizyme, Inc. (EPZM - Buy - $18PT)

Valuation. Our 12-month price target of $18/share ($15 for tazemetostat in mutant follicular lymphoma + $3 in cash) is based on a DCF-NPV-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) 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 2020 for epithelioid sarcoma and 2021 for follicular lymphoma. 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.

Resverlogix Corp. (RVX.TO - Buy – C$10PT)

Valuation. Our 12-month price target of C$10/share is driven exclusively by the value of apabetalone in T2DM, weighted using a 60% probability of success, and is based on a DCF-NPV 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 apabetalone in clinical studies; (2) failure of apabetalone to gain regulatory approval; and (3) smaller than projected commercial opportunity for apabetalone 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. 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 data from the planned clinical program. Positive clinical data could yield a potential accelerated path toward approval, however we currently project that the drug candidate apabetalone may only reach the market around 2021. Investors may choose to delay investment in the company, despite potential excitement, until meaningful clinical data is generated.

Competitive risk. The future commercial profile of apabetalone (including but not limited to pricing, commercial uptake ramp, and peak penetration), may be affected by the competitive dynamics in the diabetes and cardiovascular space, dependent on other approved and/or experimental agents.

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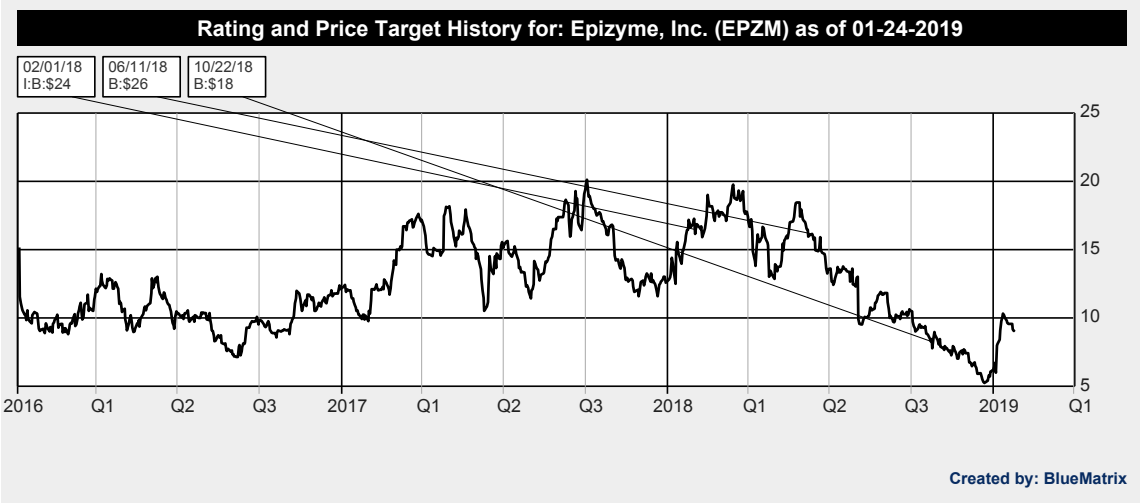
For important disclosure information regarding the companies in this summary report, please contact: The Director of Research at (800) 678-9147 or write to: ROTH Capital Partners, LLC, Attention: Director of Research, 888 San Clemente Drive, Newport Beach, CA 92660

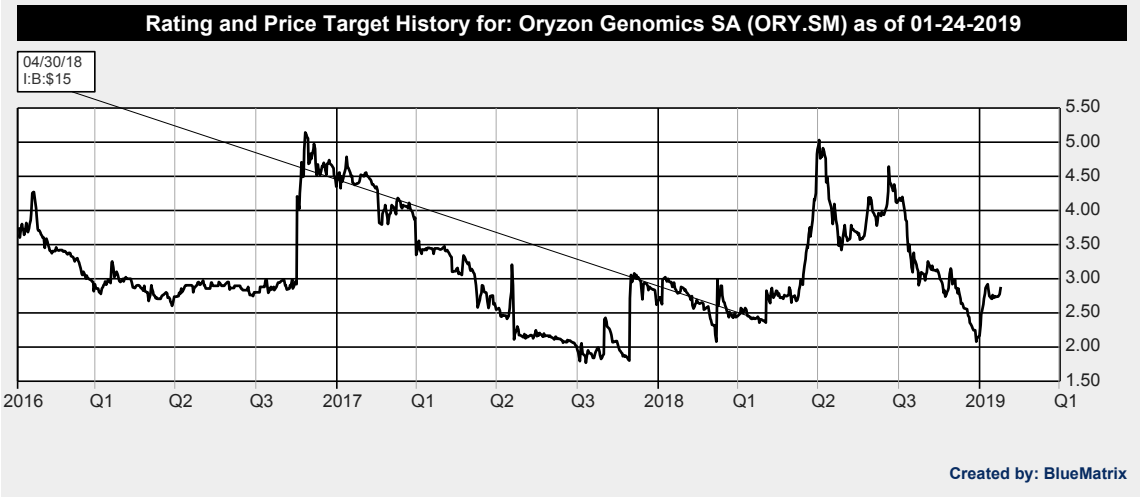
Disclosures:

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

Within the last twelve months, ROTH has received compensation for investment banking services from Oryzon Genomics SA.

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 01/27/19	
Rating	**Count**	**Percent**	**Count**	**Percent**
Buy [B]	**270**	**78.49**	**148**	**54.81**
Neutral [N]	**46**	**13.37**	**26**	**56.52**
Sell [S]	**3**	**0.87**	**2**	**66.67**
Under Review [UR]	**25**	**7.27**	**11**	**44.00**

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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