A GLOBAL LEADER IN EPIGENETICS

INVESTOR PRESENTATION

MADX: ORY

1Q 2019

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ORYZON

Company Highlights

- MADX: ORY A **publicly traded** company on the Spanish Stock Exchange
- Integrated in the **IBEX Small Cap Index**
- A **clinical stage** biopharmaceutical company developing innovative therapies in the field of Epigenetics
- A competitive **EPIGENETIC PLATFORM** validated scientifically and clinically
- Three therapeutic programs in LSD1 in development with multiple indication opportunities
- Large IP portfolio with technology fully developed in-house
- **Raised €40M** (in 2015-2017). Additional **€13M** raised from investors in the US and Europe **in October 2018**
- **Cash runway** expected till **4Q2020**
- Loss/Earnings from Operations 2018: **-3.3M€**
- One of the **MOST LIQUID** companies in the MicroCap group in the Spanish Stock Market
  - 39.1 M Shares outstanding. Fully diluted
  - 350,000 daily volume (Avg Traded Volume in 2018)
  - +88M shares negotiated in 2018 / ≈5 months for share full turnover

IBEX Small Cap

BOLSA DE MADRID

ORYZON GENOMICS SA
BALANCE SHEET DATA (AUDITED)
(Amounts in thousands US $)

	December 31st, 2018	December 31st, 2017
Cash and cash equivalents	39.296 (1)	41.916
Marketable securities	162	256
Total Assets	77.231	73.210
Deferred revenue	0	0
Total Stockholders' equity	51.668	41.294

(1) *34,5 M€*

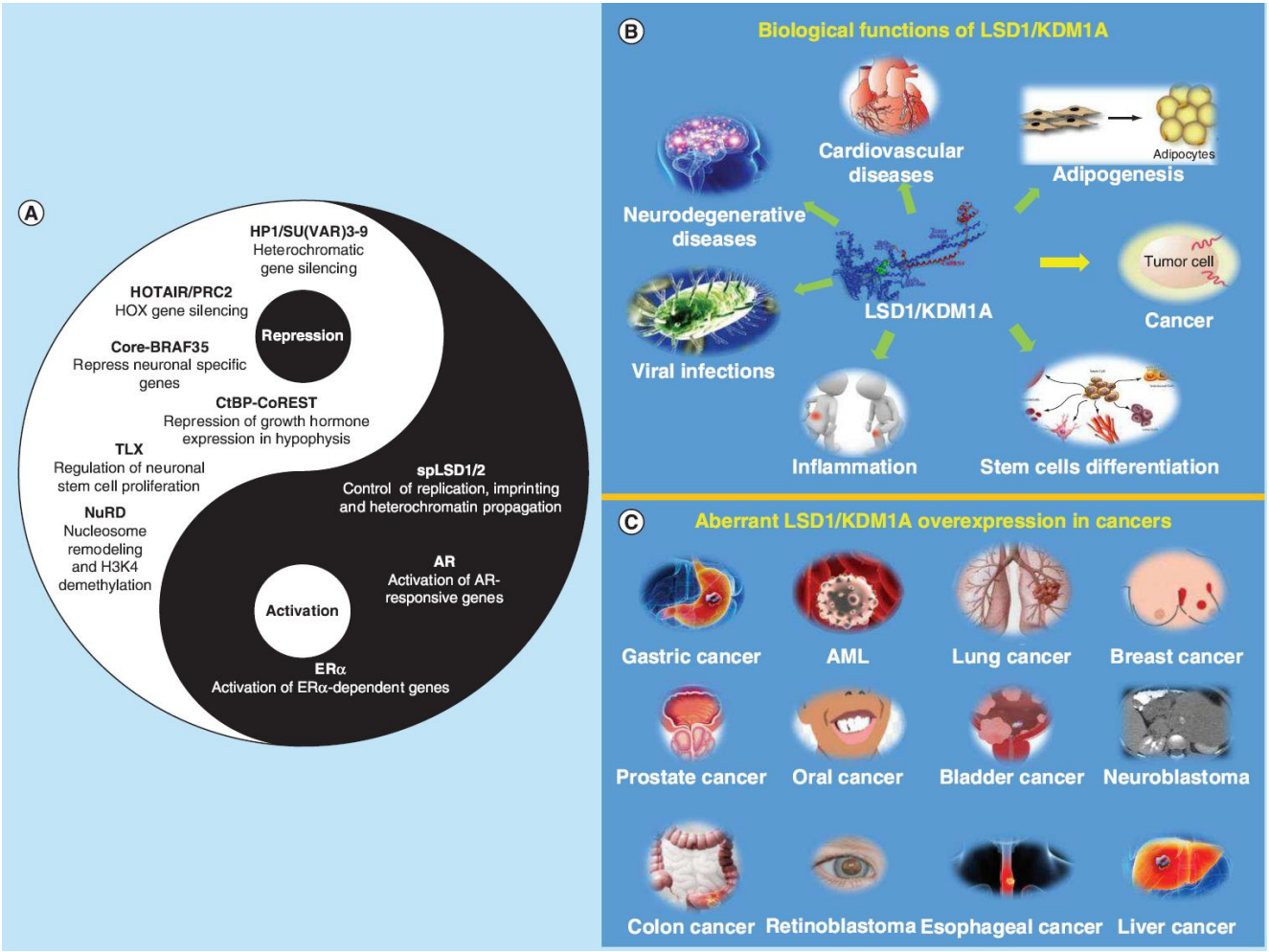
ORYZON

LSD1 in human diseases

Lysine specific histone demethylase 1 (LSD1), aka KDM1A, removes methyl marks at mono- and dimethyl-H3K4 (histone H3 lysine 4) and H3K9 (histone H3 lysine 9)

LSD1 is involved in different pathologies:

- ✓ Solid tumors
- ✓ HemOnc
- ✓ Hematol. disorders
- ✓ Inflammation
- ✓ Neurodegeneration
- ✓ Psychiatric disorders
- ✓ Viral Infections
- ✓ Others…



Fu et al., Future Med. Chem. 2017 9(11)

Extensive pipeline : 2 programs in clinic with multiple indications each

- A Productive Epigenetic Platform
- A strong focus on LSD1
- 3 Different LSD1 inhibitors in development
- Additional programs on other targets

Solid evidence of an epigenetics axis in CNS diseases

In Neurodegenerative disorders

- Historic results with HDACi's
  - HDACi improves HD symptoms in animal models
  - HDAC2 inhibition recovers memory on the AD bi-tg CK-p25 Tg mouse model
  - HDAC inhibition improves FTD
  - HDAC inhibition improves MS in EAE models
- See "The emerging field of epigenetics in neurodegeneration and neuroprotection" by Jee-Yeon Hwang, et al., Nature Reviews Neuroscience vol18, p 347–361 (2017)
- See "Epigenetic Alterations in Alzheimer's Disease" by JV. Sanchez-Mut & J. Gräff. Front Behav Neurosci. 2015; 9: 347.

- Identical twins (monozygotic)
- Same DNA with GBA risk mutation
- Discordant Parkinson's symptoms
- Onset differs up to 20 years.
- Patient derived iPSCs: difference in MAO-B levels

In Psychiatric disorders

- HDAC inhibition appears to play a role in major depression
- Histone methylation is also implicated in depression
- More than 40 years of clinical use of valproate in human clinics in CNS disorders: epilepsy, bipolar disorder and others
- See "Epigenetic Signaling in Psychiatric Disorders" by Peña et al., J Mol Biol. 2014 Oct 9; 426(20): 3389–3412.

ORYZON

Vafidemstat (ORY-2001)

A Phase II stage clinical compound

Vafidemstat (ORY-2001): a “Neuron-fixer”

- A small molecule that selectively inhibits LSD1 and MAO-B (IC50 s of 100nM in LSD1 / 75 nM in MAOB)
- Covalent binder. Excellent Pharmacology. High oral bioavailability
- Demonstrated target engagement
- Characterized in 6 and 9 months PC regulatory toxicological studies
- Positive results in 7 different animal models and in i*n-vitro* models
- Superior performance than other LSD1 inhibitors. Produces positive results in:
  - Cognition
  - Neuroprotection
  - Neuroinflammation
  - Social Withdrawal / Apathy
  - Aggression/Agitation
  - Others
- Biomarkers identified in animals that show promise for use in humans
- Capable of acting in all the processes that manifest in neurodegenerative disease patients
- Safe in humans in a Phase I trial with 106 healthy volunteers
- Crosses the BBB and human target engagement

In Phase IIa in three different clinical studies

ORYZON

Vafidemstat (ORY-2001) restores cognition measured by NORT in SAMP8 AD model

MILD

MODERATE

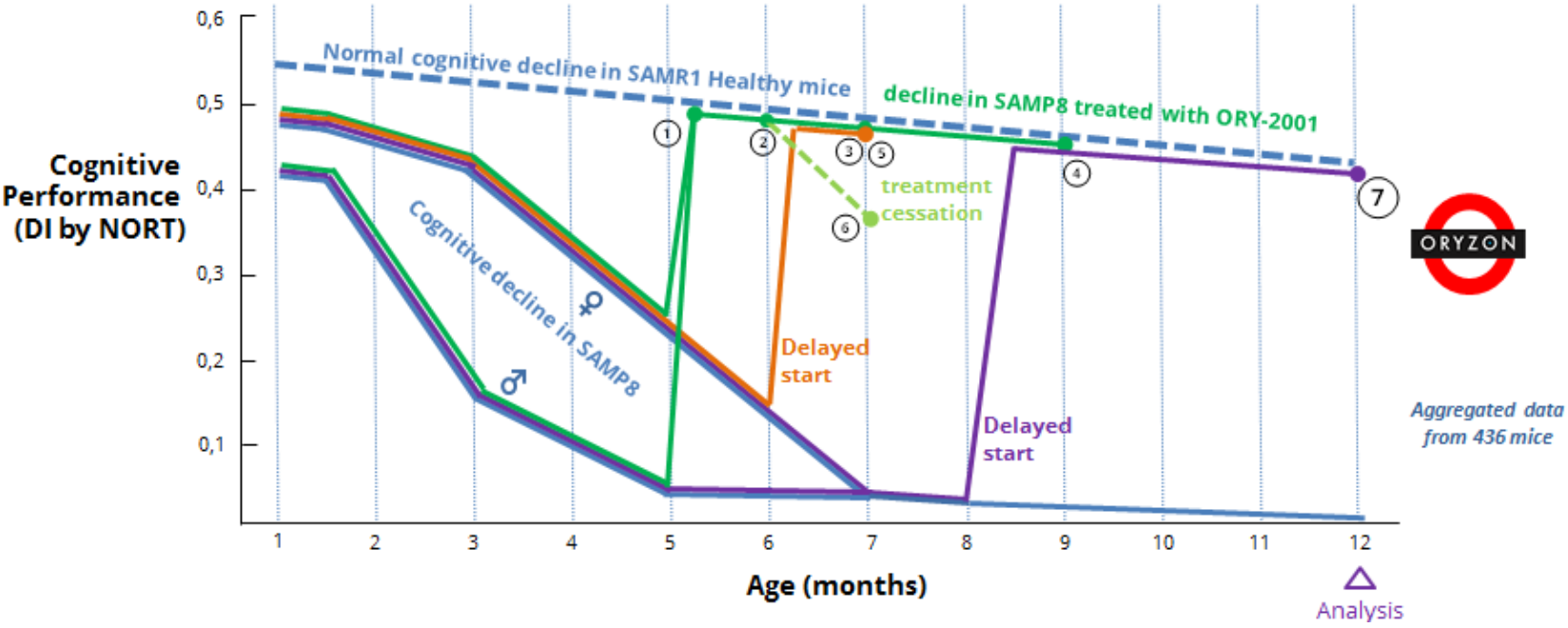
SEVERE

Treatment from month 5 during 1 week (1) , 1 month (2) , 2 months (3) , 4 months (4)

Treated from month 6 during 1 month (Delayed start-1) (5)

Treatment from month 5 during 1 month, tested at month 7 (1 month after treatment cessation) (6)

Treatment from month 8 during 4 months (Delayed start-2) (7)



Preclinical results suggestive of Disease modifying potential

(Similar memory restoration results observed with Vafidemstat in the R6/1 HD model. Positive effects in memory also described recently in the NMDA receptor-hypofunction mice with T-448, a selective LSD1 inhibitor from Takeda)

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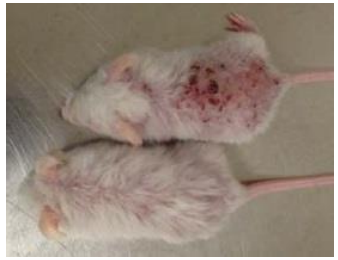
Vafidemstat (ORY-2001) reduces aggression in mice Alzheimer's Disease model



In the cognition tests we noticed that SAMP8 male mice treated with vehicle aggressed cage mates while ORY-2001-treated animals did not. Later we confirmed this in proper *Resident-intruder* aggression tests.

SAMP8 MICE treated with Vehicle
Resident Intruder test

SAMP8 MICE treated with ORY-2001 0,32mg
Resident Intruder test

SAMP8 animals treated with ORY-2001 are not **aggressive and have normal levels of basal activity (no sedation)**

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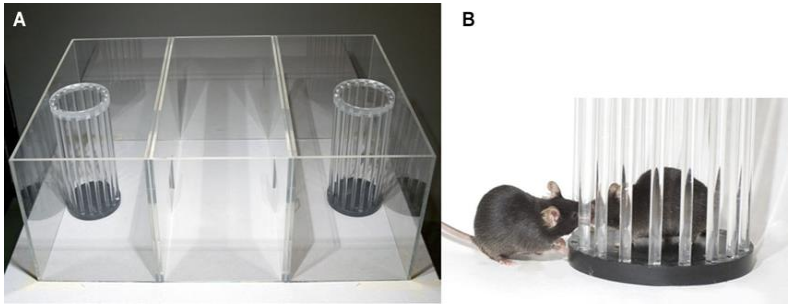
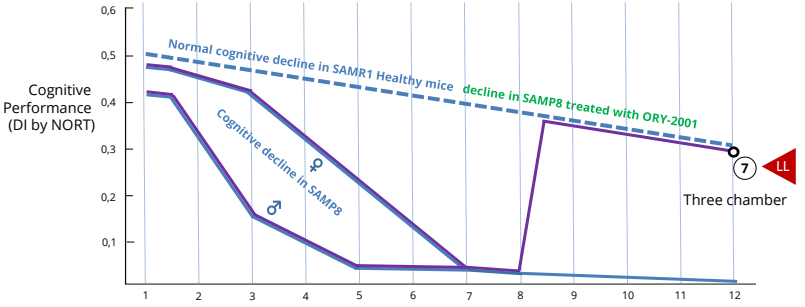
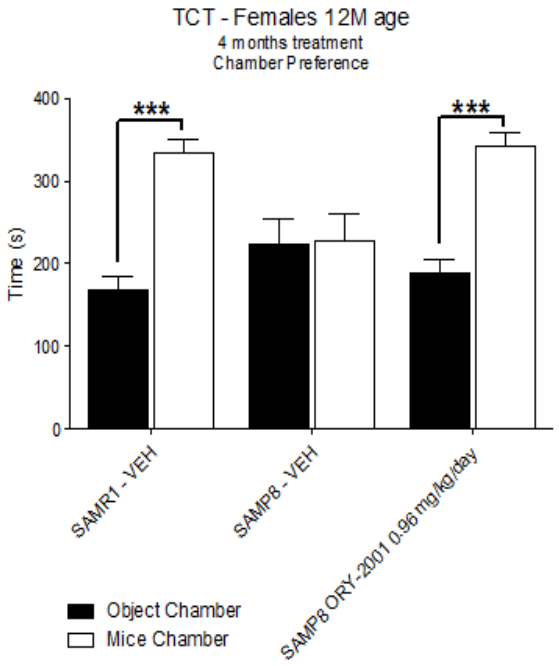
Vafidemstat (ORY-2001) also corrects the lack of sociability of aged SAMP8 mice

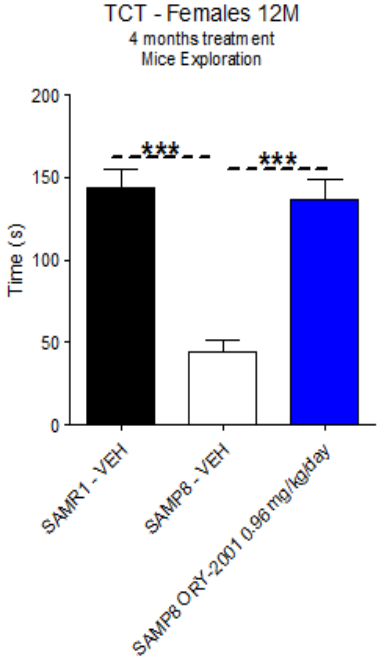
In the delayed start experiment, where treatment was initiated in **8 month** old SAMP8 mice and behavior was evaluated at **12 months** of age, treatment with ORY-2001 restored not only memory but also social interaction /sociability measured on the **Three chamber test Paradigm (TCT)**

TCT is widely used to evaluate drugs as a model for **Autism Spectrum Disorder**









Vafidemstat (ORY-2001) enhances sociability

Vafidemstat (ORY-2001) induced expression changes in Inflammatory genes

Several inflammatory biomarkers were reduced in the model

S100A9 as a biomarker for treatment with ORY-2001

- S100A9 is an alarmin, amplifier of inflammation, innate immune system, activates TLR4
- Amyloidogenic
- Up-regulated in the hippocampus of SAMP8 mice
- Modulated by ORY-2001 treatment
- S100A9 KO or KD is beneficial in Tg2576 and APP/PS1 transgenic models for AD → functional implication
- **Upregulated in the human AD brain,** and may contribute to plaque formation
- Involved in neuroinflammatory processes, not limited to AD but also found in:
  - Traumatic Brain Injury
  - Post-Operative Cognitive Decline
  - Multiple Sclerosis

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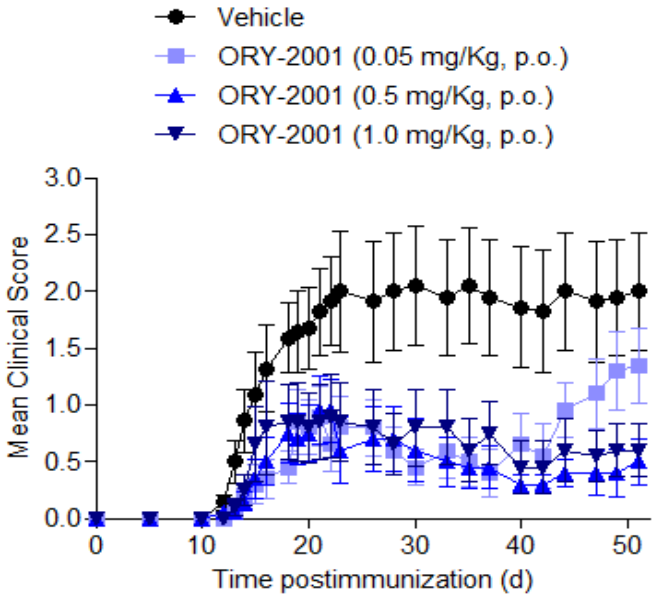
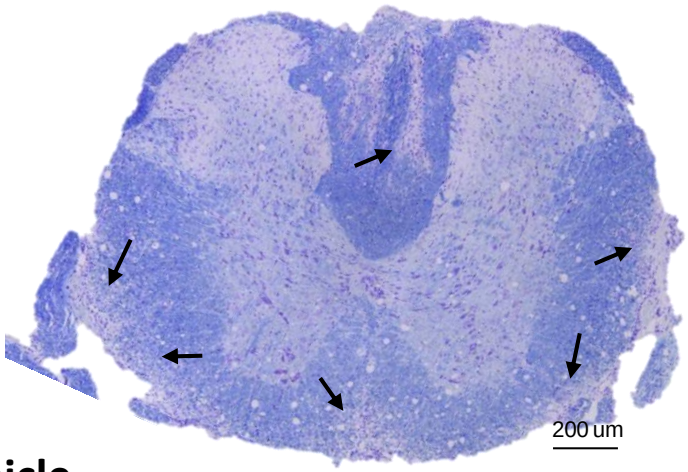
Vafidemstat (ORY-2001) is effective in the EAE and Thyler's models and reduces neuroinflammation

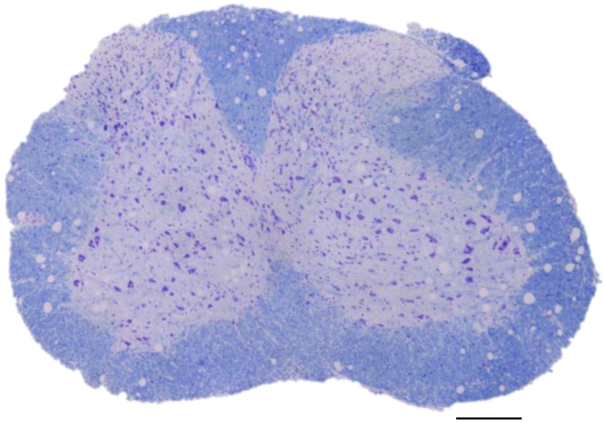
- In specific models of inflammation, ORY-2001 protects the brain and CNS from acute inflammatory stress, as shown in the EAE model where immune infiltration in the spinal cord is significantly reduced, demyelination is avoided and the clinical score is greatly reduced
- ORY-2001 also provides protection in other murine models with induced demyelinating disease
- ORY-2001 reduces microglial activation in Theiler's MS model
- ORY-2001 is neuroprotective, restoring axonal integrity in TMEV model and also in a glutamate excitotoxicity in vitro model



therapeutic treatment (p.o.)



Vehicle



ORY-2001

ORYZON

Vafidemstat (ORY-2001), a “Neuron fixer”: Preclinical Summary

- ✓ Positive results in 7 different animal models/test paradigms and in *in-vitro* models
- ✓ Anti LSD1 activity is the driving effector
- ✓ Does not reduce basal activity nor provokes sedation
- ✓ Capable of acting in most of the processes that manifest in patients with different neurodegenerative and psychiatric diseases
- ✓ Biomarkers identified in animals that show promise for use in human

		Relevance in some CNS disorders							
		Neurodegenerative space				Psychiatric space			
ORY-2001 Results in PC models		AD	MS	PD	HD	ADHD	BPD	ASD	Depression
+	Cognition / Memory	+	+	+	+			+	
+	Neuroprotection	+	+	+	+	+	+	+	+
+	Neuroinflammation	+	+	+	+	+	+	+	+
+	Social Withdrawal / Apathy	+	+	+	+	+	+	+	+
+	Sociability					+	+	+	+
+	Aggression/Agitation	+		+	+	+	+	+	+

These data may substantially broaden the potential clinical development of ORY-2001 beyond the current indications of AD and MS that the company is initially advancing in clinical trials

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Vafidemstat (ORY-2001)

CLINICAL DEVELOPMENT

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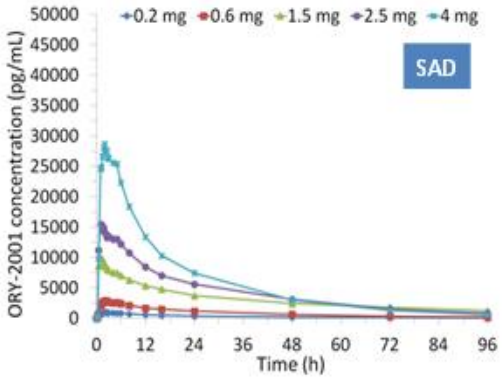
Vafidemstat (ORY-2001) Phase I: Safety and hematology

- ✓ **Safe and well tolerated in a +100 healthy volunteers Phase I study**
- ✓ **No hematological impact at the planned doses**
- ✓ **Efficiently crossed the BBB:**
  - ✓ ORY-2001 concentrations measured in CSF at 2, 6 and 12 h after a single oral 2 mg or 4 mg dose
  - ✓ CSF levels comparable to corresponding unbound plasma concentrations (CSF/plasma$_u$ ratio ≈ 0.7-0.9)

- ✓ **ORY-2001 efficiently inhibits the brain human LSD1**
- ✓ **PK Oral PK T1/2 ≈ 22h allowing once daily oral**
- ✓ **PK/PD data allow to select Phase II doses**



- ✓ **ORY-2001 has been already administered to many patients in the ongoing Phase IIs with no safety issues so far**

Vafidemstat (ORY-2001) is in Phase II in humans in AD and MS where we expect to have the first read outs in 2H2019

ORYZON

ETHERAL: **E**pigenetic **THER**apy in **AL**zheimer's Disease

An ambitious Phase IIa study to provide useful information to design future Phase II/III studies

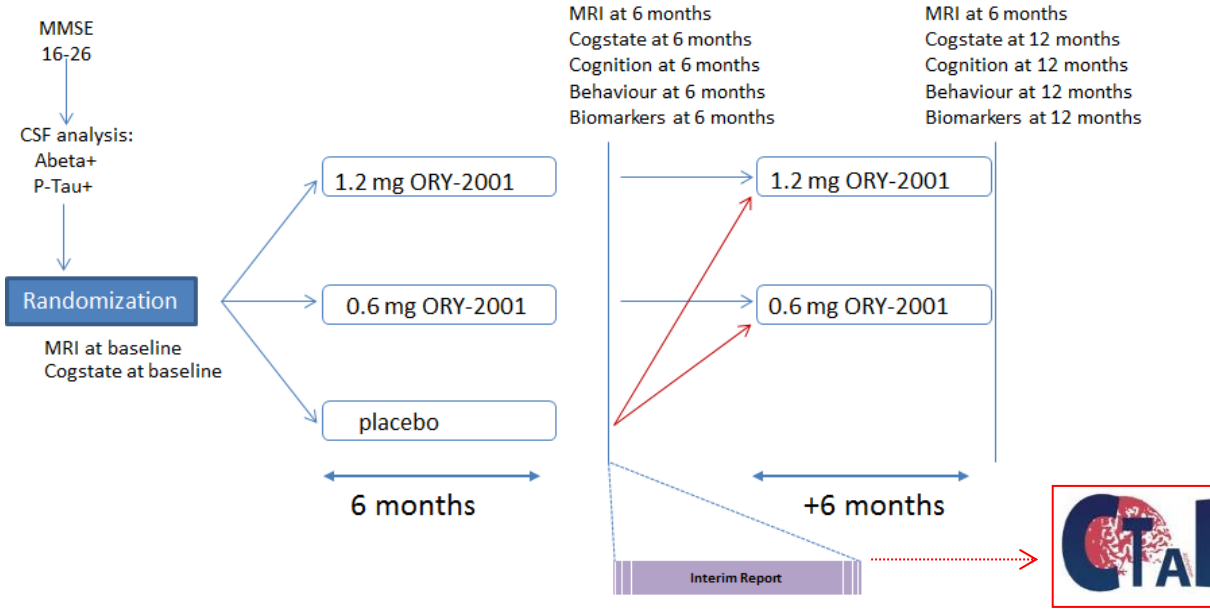
CLINICAL STUDY PROTOCOL

A multicentre, multinational, randomised, double-blind, placebo-controlled, 3-arm, 24-week parallel-group study to evaluate the safety, tolerability and preliminary efficacy of ORY-2001 in patients with mild-moderate Alzheimer's Disease. ETHERAL Study

- **Mild to Moderate AD** patients
- Nº of patients: **150**
- Primary Objective: Safety & Tolerability
- Secondary Objectives :
  - Cognition/Agitation/Apathy/QoL
  - Volumetric MRI
- **Biomarker guided study** with several CSF inflammatory Biomarkers

- 125 in EU. 17 sites
- Spain, France & UK actively recruiting
- **68 randomized** as per mid February

- A Twin study in US: around 25 patients
- IND 1Q2019
- FPI expected 1Q2019

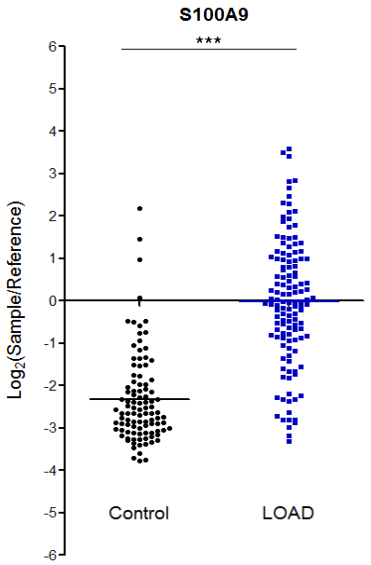


Vafidemstat (ORY-2001) ETHERAL Phase IIa: Biomarker strategy

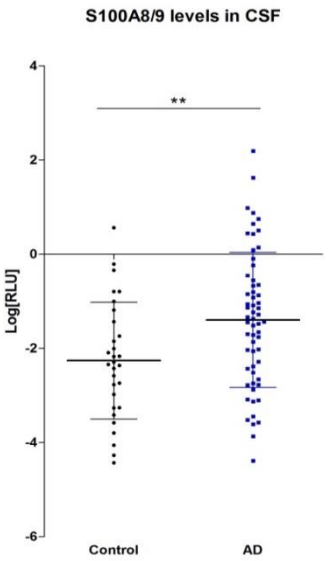
S100A9 has been characterized as one of the TOP10 up-regulated genes in LOAD dataset

- ✓ S100A9 PROTEIN levels are significantly increased in CSF from AD patients compared to age-matched controls
- ✓ S100A9 CSF PROTEIN levels will be monitored in ETHERAL AD trial
  - ✓ S100A9 and inflammation have a correlation with the disease
  - ✓ Inflammation plays a mechanistic role in the progression of the disease
  - ✓ ORY-2001 reduces S100A9 in animals

Human PFC (RNA)



Human CSF (protein)



S100A9 CSF levels will be monitored in Phase II studies
S100A9 has the potential to be a surrogate biomarker for drug activity
S100A9 data might be part of a rationale for a fast track

Changes in S100A9 in patient's CSF may have important clinical development implications

ORYZON

SATEEN A pilot study in MS to see a proof of biological activity

SAfety, **T**olerability and **E**fficacy in an **E**PIGE**N**ETIC approach to treat Multiple Sclerosis

Randomised, double-blind, placebo-controlled, 3-arm, 36 weeks parallel-group study to evaluate the safety and tolerability of ORY-2001 in patients with Relapsing-Remitting Multiple Sclerosis (RRMS) and Secondary Progressive Multiple Sclerosis (SPMS)

Spain only; 9 sites; 24 patients (RR & SP)

Active recruitment ongoing

Excellent safety. One patient is +1year on treatment

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Vafidemstat (ORY-2001): REIMAGINE: A Basket trial in aggression

ORY-2001 REIMAGINE Study

Vall d'Hebron Institut de Recerca VHIR

- A single center open label exploratory basket trial to assess the effect of ORY-2001 in reducing aggression in patients with two neurodegenerative and three neuropsychiatric indications
- N=30, with 6 participants per condition
- Single arm of ORY-2001 (1.2 mg)
- 8 weeks treatment duration
  - AD
  - DLB
  - BPD
  - ADHD
  - ASD
- Approved September 2018
- FPI 4Q 2018
- Expected LPO 1Q 2019

Top Line Data 2-4Q2019

Conferences where preliminary data are expected to be presented

ORYZON

Iadademstat (ORY-1001)

A Phase II stage clinical compound

Iadademstat (ORY-1001): the most advanced LSD1 inhibitor in clinic

- A small molecule that selectively inhibits LSD1
- Covalent binder. Active in cells at subnanomolar levels
- Preclinical in-vivo positive results in xenografts of AML, SCLC and in PDX of SCLC
- Characterized in PC regulatory toxicological studies
- First LSD1 drug to enter into clinical trials
- Best in Class
- MoA identified in Leukemia, SCLC and medulloblatoma
- Produces positive results in a Acute Leukemia Phase I/IIa trial (manuscript submitted):
  - Safe and well tolerated and therefore a meaningful candidate for combination with other agents
  - PD Biomarkers identified in different subsets of leukemia
  - Antileukemic activity observed in 29% of patients (12/41), including one CRi as Proof of Biological concept
- Identified Biomarkers to stratify SCLC patients
- Phase IIa ongoing in SCLC (CLEPSIDRA)
- Phase IIa ongoing in AML (ALICE)
- Preclinical / Biomarkers and new combos under constant investigation

In Phase IIa in two different clinical studies

ORYZON

Iadademstat (ORY-1001) is a clean and safe LSD1 inhibitor

- ✓ Iadademstat is a First & Best in Class selective LSD1 inhibitor in oncology
- ✓ The most advanced LSD1 inhibitor in clinical development in solid and hematological tumors

Cancer Cell
Article

CellPress

ORY-1001, a Potent and Selective Covalent KDM1A Inhibitor, for the Treatment of Acute Leukemia

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RESEARCH ARTICLE CANCER EPIGENETICS

Targeting NOTCH activation in small cell lung cancer through LSD1 inhibition

Arnaud Augert[1,*], Emily Eastwood[1,*], Ali H. Ibrahim[1], Nan Wu[1], Eli Grunblatt[1], Ryan Basom[2], Denny Liggitt[3], Keith D. Eaton[4], ..
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Sci. Signal. 05 Feb 2019:
Vol. 12, Issue 567, eaau2922
DOI: 10.1126/scisignal.aau2922

Article Figures & Data Info & Metrics eLetters PDF

Targeted epigenetic therapy for SCLC

Small cell lung cancer (SCLC) is an aggressive neuroendocrine tumor with no targeted therapeutic options and in which chemotherapy is only partially effective. Previous studies indicated that SCLC growth is suppressed by drugs that inhibit the histone lysine demethylase LSD1. Augert *et al.* found that LSD1 epigenetically suppressed the expression of the gene encoding NOTCH1, enabling the activity of the neuroendocrine cell lineage–associated transcription factor ASCL1. Blocking LSD1 with iadademstat (ORY-1001), a drug that has just been approved for phase 2 clinical trials in leukemia, reactivated NOTCH signaling and

ORY-1001: Overcoming the Differentiation Block in AML

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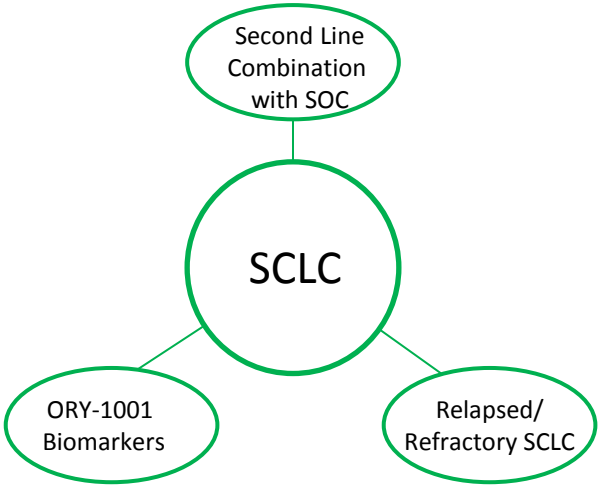
https://doi.org/10.1016/j.ccell.2018.02.014

In this issue of *Cancer Cell*, Maes and colleagues report *in vitro* and *in vivo* findings with ORY-1001—an oral, highly potent and selective covalent small-molecule inhibitor of lysine-specific demethylase 1 (LSD1)—in development for acute myeloid leukemia (AML), as well as correlative data from two AML patients receiving ORY-1001.

ORYZON

Iadademstat a flexible CDP for a Large Market Opportunity

MoA well characterized in SCLC, AML and Medulloblastoma



Small Cell Lung Cancer is the main indication under exploration

POTENTIAL IADADEMSTAT ONCOLOGICAL INDICATIONS:

Solid Tumors

Small Cell Lung Cancer
Prostate cancer
Colorectal cancer
Bladder cancer
Some breast cancers

HemONC

AML
MDS
Myelofibrosis
Non Hodgkin Lymphoma

Brain Tumors

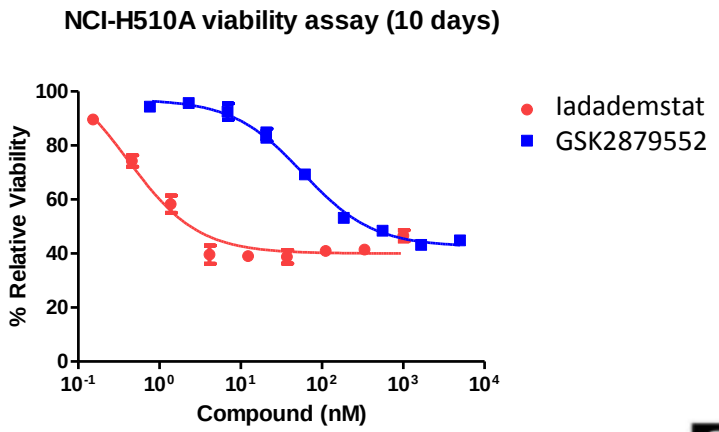
Medulloblastoma
Glioblastoma

ORYZON

Iadademstat opportunity in SCLC

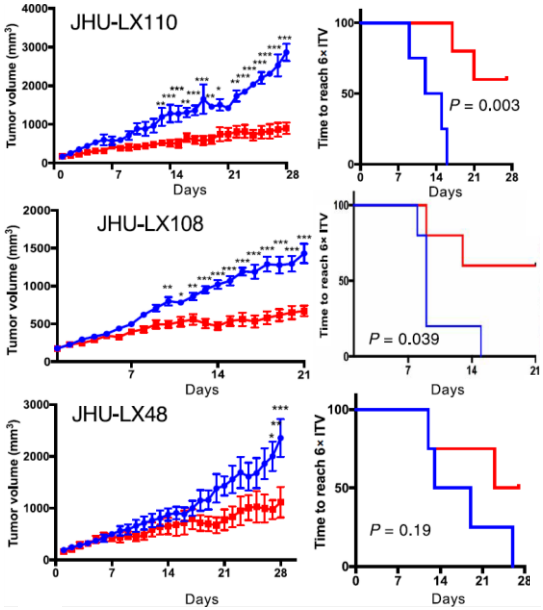
- LSD1 is a target well characterized in SCLC and validated in preclinical models. LSD1 inhibitors are effective in vitro and in-vivo xenograft models of SCLC
- Iadademstat is the best and first in class LSD1 inhibitor in clinic development
- Iadademstat produces complete and durable tumor regression in different chemoresistant PDX models
- Characterized MoA (induction of Notch and repression of ASCL1)
- Identified and patented Biomarkers that are differential in sensitive cell lines
- Characterization of Biomarkers in tumors and plasma from patients
- Phase II Clinical trial ongoing in second line SCLC patients using these biomarkers to stratify patients and identify super-responders

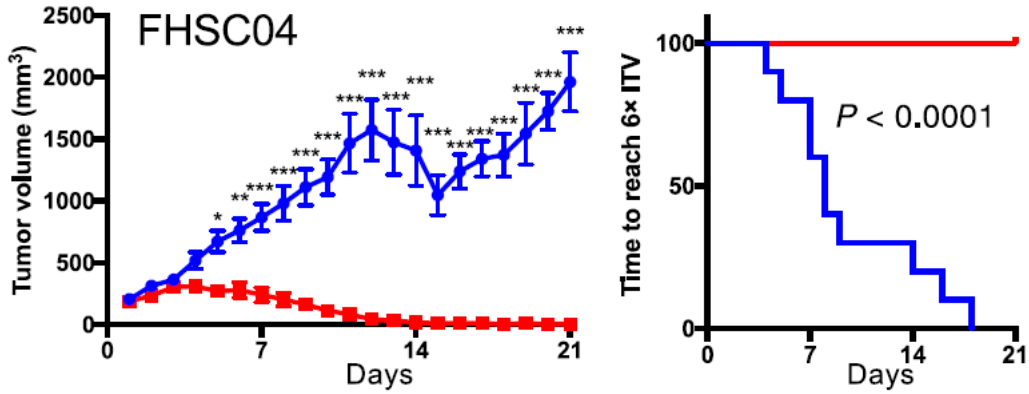
Iadademstat is ~2 orders of magnitude more potent in sensitive cell lines than **GSK's clinical LSD1 inh. GSK2879552** (side by side comparison)



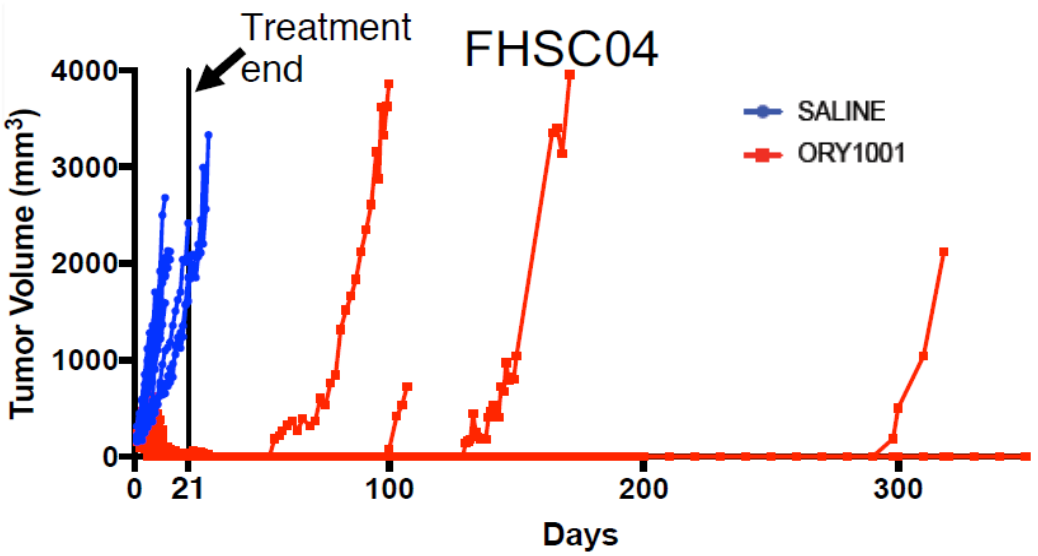
Iadademstat (ORY-1001) is efficient in PDX- SCLC

- Response to ORY-1001 in PDX models of SCLC is variable, but some are very strong





- FHSC04 model: derived from a SCLC patient who relapsed after fist line therapy
- **6/10 FHSC04 mice treated with ORY-1001 did not show relapse after 300 days**



Data from David MacPherson Lab

FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

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Iadademstat (ORY-1001): SCLC Current Clinical Development Plan

CLEPSIDRA: A **C**ombination trial of **L**SD1 and **E**top-**P**latinum in **S**mall Cell Lung Cancer in **biomarker-ID** **R**elapsed p**A**tients

A Phase IIa study to assess the safety, tolerability, dose finding and efficacy of Iadademstat (ORY-1001) in combination with platinum-etoposide chemotherapy in patients with relapsed, extensive-stage disease small cell lung cancer who are positive to candidate predictive biomarkers

- ✓ Single arm
- ✓ Open label; 4 sites in Spain
- ✓ Up to 36 patients to be enrolled
- ✓ **Primary end point**: Safety and tolerability of the combo with platinum-etoposide therapy
- ✓ **Secondary endpoints:** RECIST responses; time to responses; duration of response; and overall survival

Preliminary Results

- ✓ Patient 1 already completed the first cycle of combo iada+SoC and has started cycle 2.
- ✓ Satisfactory and dynamic recruitment pace: 3 more patients enrolled 2nd week of February

→ 2019 ASCO ANNUAL MEETING

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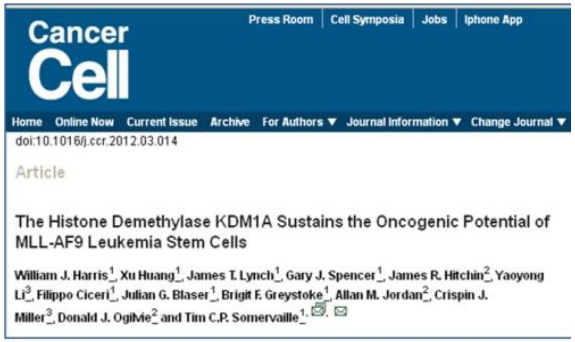
Iadademstat (ORY-1001) MoA: a potent differentiating agent to treat Acute Leukemias

LSD1 is a target for HEMATOLOGICAL CANCERS, and in particular, for a subset of acute myeloid leukemia: *mixed lineage leukemia* MLL-AML

- ✓ Oryzon's LSD1 inhibitors block progression of leukemia into the circulation in mice with experimentally initiated MLL-AF9 AML
- ✓ Oryzon's LSD1 inhibitors target Leukemia Stem Cells but spare normal HSPCs


Cancer Cell

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doi:10.1016/j.ccr.2012.03.014

Article

The Histone Demethylase KDM1A Sustains the Oncogenic Potential of MLL-AF9 Leukemia Stem Cells

William J. Harris[1], Xu Huang[1], James T. Lynch[1], Gary J. Spencer[1], James R. Hitchin[2], Yaoyong Li[3], Filippo Ciceri[1], Julian G. Blaser[1], Brigit F. Greystoke[1], Allan M. Jordan[2], Crispin J. Miller[3], Donald J. Ogilvie[2] and Tim C.P. Somervaille[1],


nature medicine

nature.com > journal home > advance online publication > letter > abstract

NATURE MEDICINE | LETTER

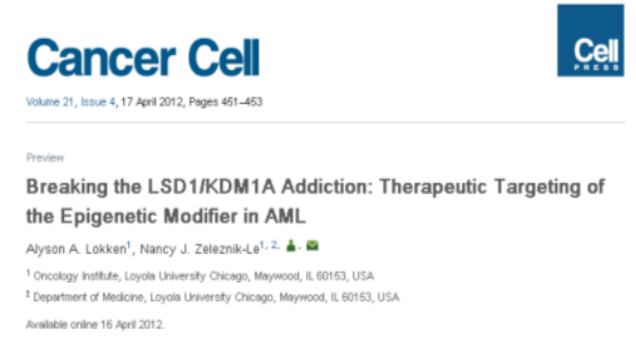
Inhibition of the LSD1 (KDM1A) demethylase reactivates the all-*trans*-retinoic acid differentiation pathway in acute myeloid leukemia

Tino Schenk, Weihsu Claire Chen, Stefanie Göllner, Louise Howell, Liqing Jin, Katja Hebestreit, Hans-Ulrich Klein, Andreea C Popescu, Alan Burnett, Ken Mills, Robert A Casero Jr, Laurence Marton, Patrick Woster, Mark D Minden, Martin Dugas, Jean C Y Wang, John E Dick, Carsten Müller-Tidow, Kevin Petrie & Arthur Zelent

Affiliations | Contributions | Corresponding author

Nature Medicine (2012) | doi:10.1038/nm.2661

Received 19 April 2011 | Accepted 03 January 2012 | Published online 11 March 2012


Cancer Cell

Cell

Volume 21, Issue 4, 17 April 2012, Pages 451–453

Preview

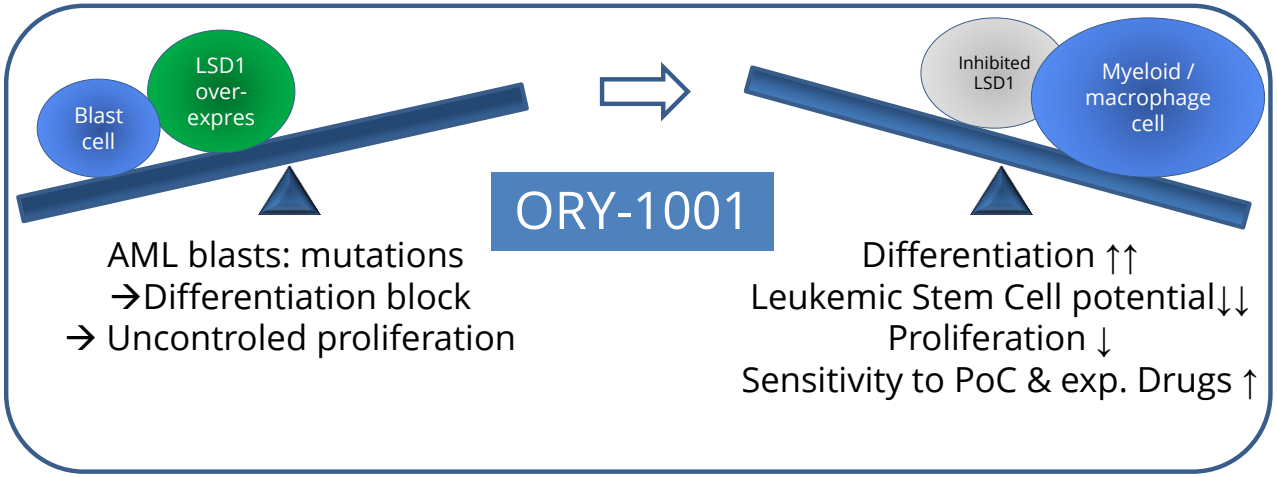
Breaking the LSD1/KDM1A Addiction: Therapeutic Targeting of the Epigenetic Modifier in AML

Alyson A. Lokken[1], Nancy J. Zeleznik-Le[1, 2],

[1] Oncology Institute, Loyola University Chicago, Maywood, IL 60153, USA

[2] Department of Medicine, Loyola University Chicago, Maywood, IL 60153, USA

Available online 16 April 2012.



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ALICE: An **A**ML trial with **L**SD1**i** in **C**ombination with azacitidine in the **E**lderly

A Phase IIa study to evaluate the safety, tolerability, dose finding and efficacy of Iadademstat (ORY-1001) in combination with azacitidine in older patients with AML in first line therapy

- ✓ Single arm
- ✓ Open label
- ✓ Up to 36 patients to be enrolled
- ✓ **Primary end point**: Safety and tolerability of the combo with hypomethylating agent Azacitidine
- ✓ **Secondary endpoints:** Responses; time to responses; duration of response; and overall survival

Preliminary Results

- ✓ 3 patients have already gone through the first cycle; Good tolerability
- ✓ Satisfactory and dynamic recruitment pace: 2nd cohort started by February

EHA EUROPEAN HEMATOLOGY ASSOCIATION

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Iadademstat a flexible CDP for a Large Market Opportunity

POTENTIAL ADDITIONAL ONCOLOGICAL INDICATIONS AND NEW COMBO APPROACHES:

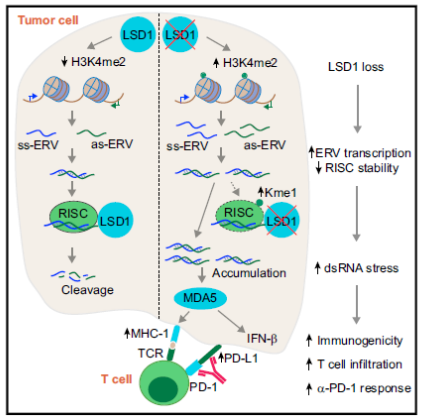
Possible combinations with I-O check point inhibitors

Article

Cell

LSD1 Ablation Stimulates Anti-tumor Immunity and Enables Checkpoint Blockade

Graphical Abstract



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Wanqiang Sheng, Martin W. LaFleur, Thao H. Nguyen, ..., Housheng Hansen He, Arlene H. Sharpe, Yang Shi

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In Brief

Ablating the histone demethylase LSD1 genetically or pharmacologically enhances tumor immunogenicity by stimulating endogenous retrovirus expression and downregulating RNA-induced silencing complex, supporting the promise of LSD1 inhibition in overcoming resistance to checkpoint blockade in cancer treatment.

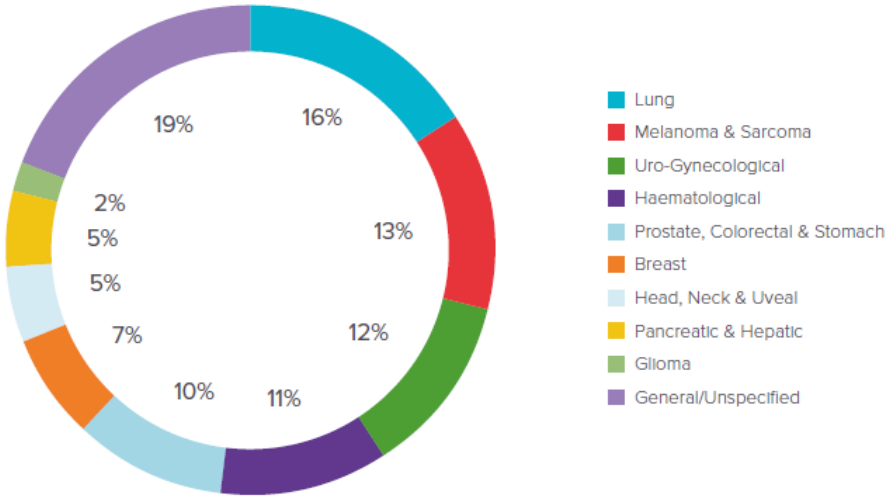
Highlights

- ERV induction and RISC reduction activate dsRNA-IFN pathway upon LSD1 inhibition
- LSD1 loss in tumor cells stimulates anti-tumor T cell immunity
- LSD1 ablation enhances tumor immunogenicity and T cell infiltration
- LSD1 inhibition overcomes resistance to anti-PD-1 therapy in a mouse melanoma model

Data resources

GSE112230

Anti-PD-1/PD-L1 MAb combination studies by (broad) indication (grouping)



Studies listed on clinicaltrials.gov involving combinations of PD-1 or PD-L1 agents
Source:"PD-1/PD-L1 Combination Therapies" report, 2017, Evaluate Ltd

Iadademstat a flexible CDP for a Large Market Opportunity

POTENTIAL ADDITIONAL ONCOLOGICAL INDICATIONS AND NEW COMBO APPROACHES:

Brain Tumors

Medulloblastoma
Glioblastoma

ARTICLE

https://doi.org/10.1038/s41467-018-08269-5 OPEN

Lsd1 as a therapeutic target in Gfi1-activated medulloblastoma

Catherine Lee[1,2], Vasilisa A. Rudneva[3], Serap Erkek[4,5,6], Marc Zapatka[7], Lianne Q. Chau[1], Silvia K. Tacheva-Grigorova[1], Alexandra Garancher[1], Jessica M. Rusert[1], Ozlem Aksoy[8], Robin Lea[8], Helai P. Mohammad[9], Jianxun Wang[10], William A. Weiss[8], H. Leighton Grimes[11], Stefan M. Pfister[4,12], Paul A. Northcott[3] & Robert J. Wechsler-Reya[1,2]

Drugs that modify the epigenome are powerful tools for treating cancer, but these drugs often have pleiotropic effects, and identifying patients who will benefit from them remains a major clinical challenge. Here we show that medulloblastomas driven by the transcription factor Gfi1 are exquisitely dependent on the enzyme lysine demethylase 1 (Kdm1a/Lsd1). We demonstrate that Lsd1 physically associates with Gfi1, and that these proteins cooperate to inhibit genes involved in neuronal commitment and differentiation. We also show that Lsd1 is essential for Gfi1-mediated transformation: Gfi1 proteins that cannot recruit Lsd1 are unable to drive tumorigenesis, and genetic ablation of Lsd1 markedly impairs tumor growth in vivo. Finally, pharmacological inhibitors of Lsd1 potently inhibit growth of Gfi1-driven tumors. These studies provide important insight into the mechanisms by which Gfi1 contributes to tumorigenesis, and identify Lsd1 inhibitors as promising therapeutic agents for Gfi1-driven medulloblastoma.

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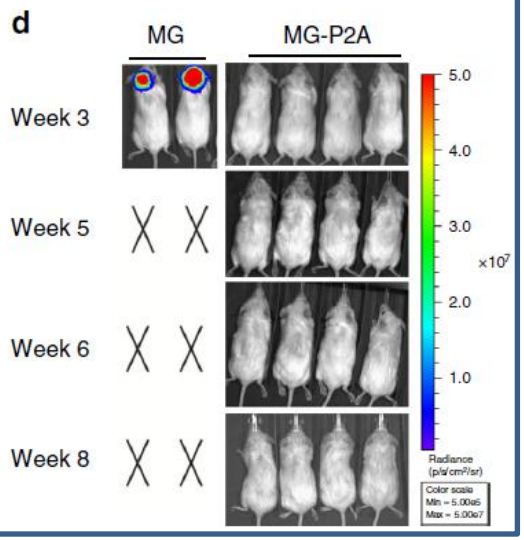
Other potential Solid Tumor indications for Iadademstat: Medulloblastoma

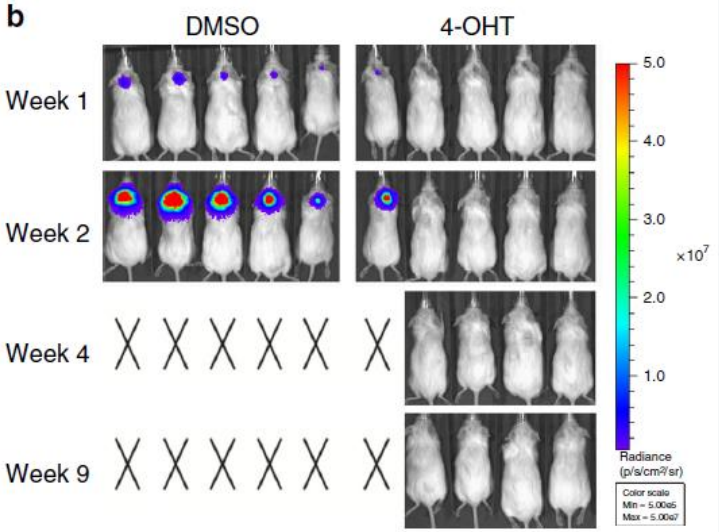
nature COMMUNICATIONS
ARTICLE
OPEN
Lsd1 as a therapeutic target in Gfi1-activated medulloblastoma

LSD1 inhibition is key in medulloblastoma

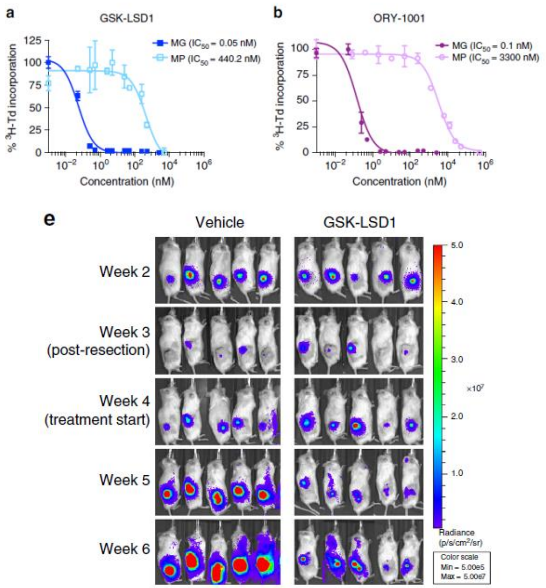
Gfi1 SNAG domain is required for transformation of NSCs



LSD1 is required for tumorigenic potential of Myc-Gfi1-transformed NSCs



LSD1i is effective *in vitro* and *in vivo* against Gfi1-driven MB



MoA:

Gfi1 is a key driver of medulloblastoma initiation and maintenance and Lsd1 is a critical mediator of its effects. Gfi1 and Lsd1 act by repressing genes important for neuronal fate commitment and differentiation. Pharmacological targeting of Lsd1 may be effective for treatment of Gfi1-activated medulloblastoma.

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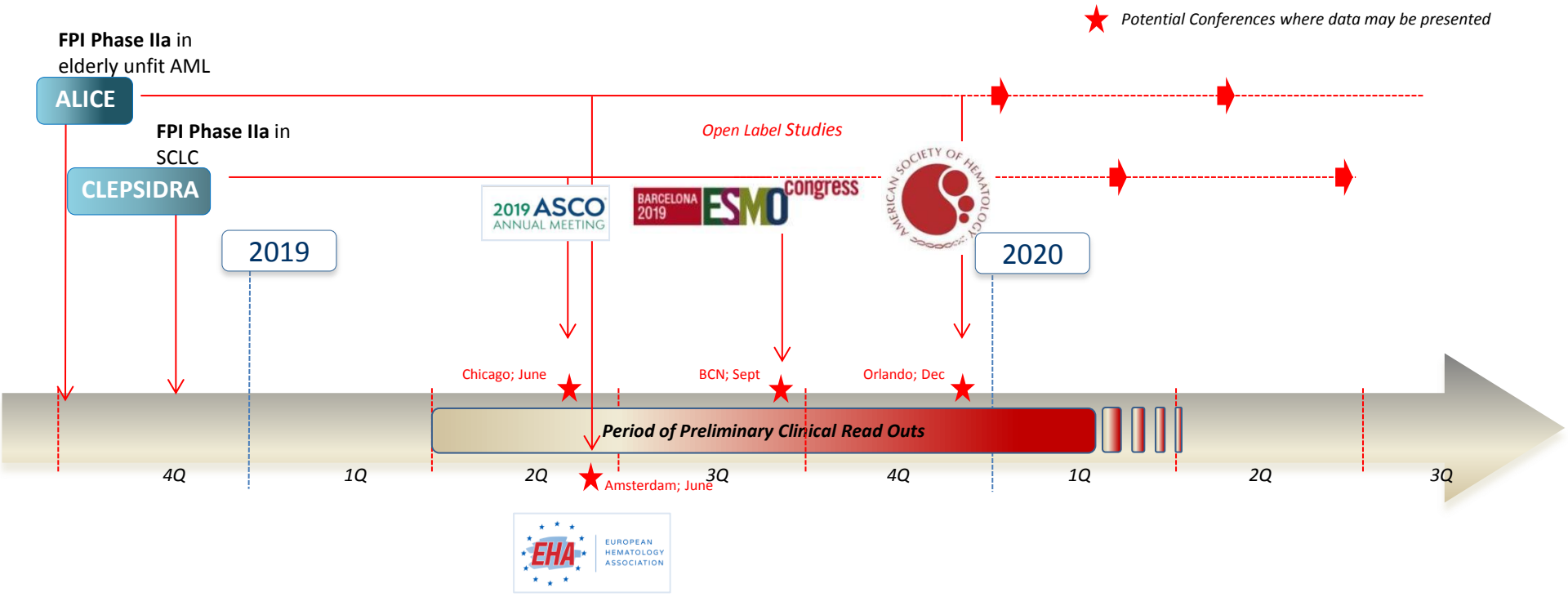
Recent & Anticipated Oryzon main catalysts

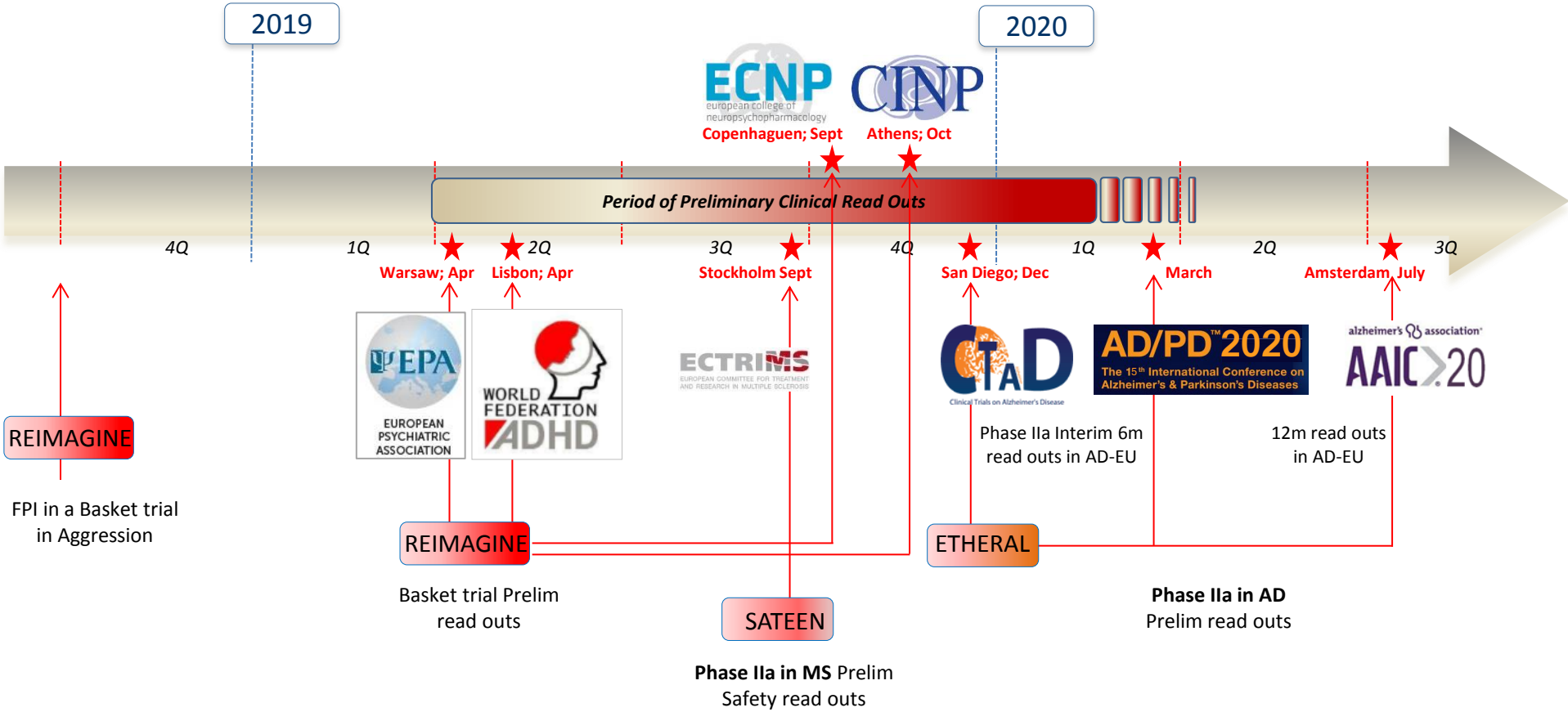
IADADEMSTAT (ORY-1001): lead CANCER asset



Recent & Anticipated Oryzon main catalysts

VAFIDEMSTAT (ORY-2001): lead CNS asset

★ *Conferences where preliminary data are expected to be presented*



ORYZON
A GLOBAL LEADER
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