Pioneering personalized medicine in epigenetics

ORYZON

CORPORATE PRESENTATION

1Q-2021

ORY:SM / ORY.MC

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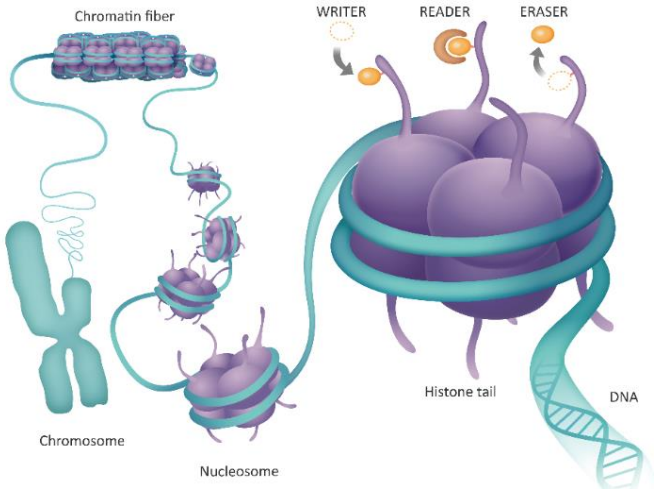
An Epigenetic champion determined to bring new therapies to the patients



Epigenetics expertise applied to Oncology and CNS indications

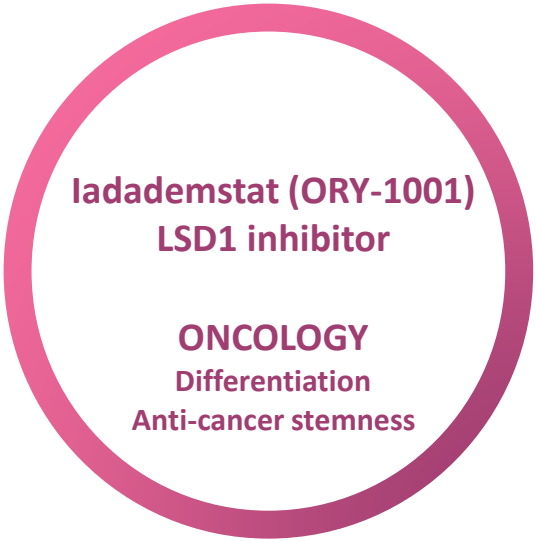
Two molecules with positive clinical data in humans. Programs in Phase II

A leading & growing epigenetic platform with an expanding pipeline

One of the most liquid biotech stocks in Europe: +90 M shares negotiated in 2020

+25% stock performance in 2020. Cash runway expected until 1Q2023

Oryzon's pipeline: Multiple shots on goal to address significant unmet medical needs



- AML / SCLC
- 4 Phase I/II clinical trials: ≈100 patients treated
- Safe & well tolerated
- Phase II in AML ongoing (+80% ORRs on evaluable pts)
- Phase II w ICIs in prep

- BPD / SCZ / PMS / AD
- 6 Phase I/II clinical trials: +250 subjects treated
- Safe & well tolerated
- Efficacious in Phase IIa in aggression
- Phase IIb in BPD (ongoing) and SCZ (in prep)
- Deploying a precision medicine approach

- Ready for candidate nomination

Oryzon is pioneering LSD1 epigenetics in CNS and Oncology

- A rich pipeline
- The LSD1 specialist: (+350 subjects treated)
- PoC of clinical efficacy in both programs (Onco and CNS)

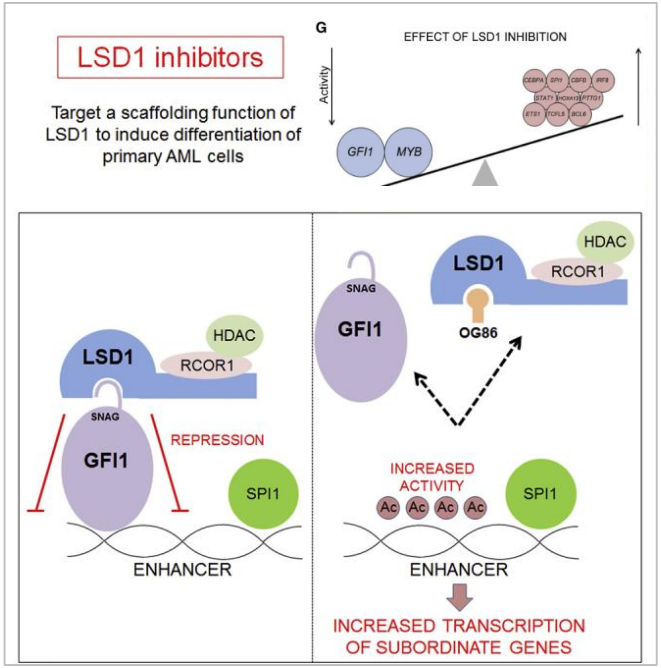
ORYZON

IADADEMSTAT

A Phase II clinical stage agent in Oncology

LSD1 and cancer

- LSD1 is involved in different cancers and **in cancer stemness**
- **High levels of LSD1 often correlate with more aggressive forms of cancer and/or bad prognosis**
- **Iadademstat** is a highly potent and selective, orally active, small molecule LSD1i. Best in class. Positive preclinical *in-vivo* results in different xenograft models. Full characterization published in top-ranked journal



Modified from Maiques-Diaz et al. 2018, Cell Reports 22, 3641–3659

Cancer Cell
Article

CellPress

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

Tamara Maes,[1,6,*] Cristina Mascaró,[1] Iñigo Tirapu,[1] Angels Estiarte,[1] Filippo Ciceri,[1] Serena Lunardi,[1] Nathalie Guibourt,[1] Alvaro Perdones,[1] Michele M.P. Lufino,[1] Tim C.P. Somervaille,[2] Dan H. Wiseman,[2] Cihangir Duy,[3] Ari Melnick,[3,4] Christophe Willekens,[5] Alberto Ortega,[1] Marc Martinell,[1] Nuria Valls,[1] Guido Kurz,[1] Matthew Fyfe,[1] Julio Cesar Castro-Palomino,[1] and Carlos Buesa[1]

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https://doi.org/10.1016/j.ccell.2018.02.002

Iadademstat produces differentiation in acute leukemia patients

Encouraging results in monotherapy in a FiM Acute Leukemia Phase I/IIa trial

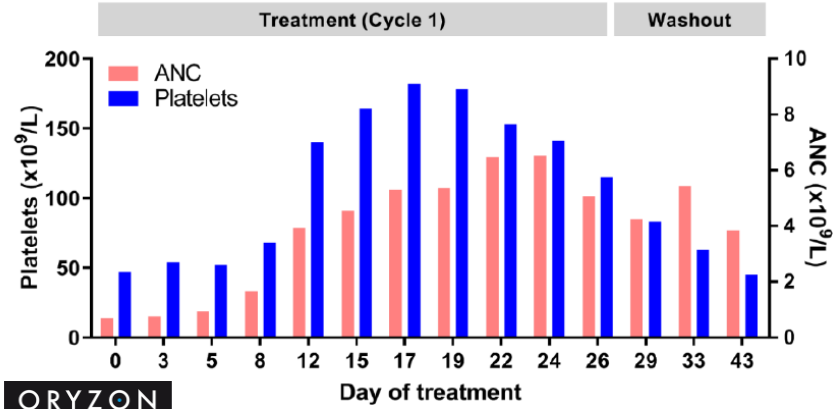
- Dose Finding (5-220 ug/sqm) in 27 patients all-in
- Extension Cohort of 14 patients (MLL / erythroleukemia)
- Good safety profile
- Dose-dependent PK
- Strong differentiation, in particular in patients with MLL translocations: 80% of evaluable patients
- Antileukemic activity observed in 29% of patients (12/41), including one CRi as Proof of Biological concept

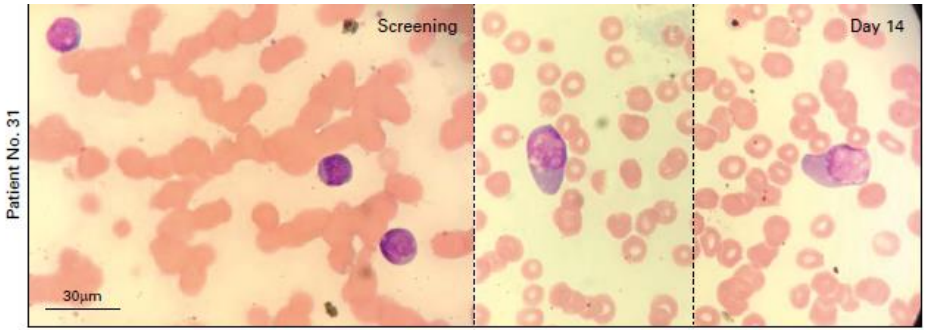
Journal of Clinical Oncology

original reports

First-in-Human Phase I Study of Iadademstat (ORY-1001): A First-in-Class Lysine-Specific Histone Demethylase 1A Inhibitor, in Relapsed or Refractory Acute Myeloid Leukemia

https://ascopubs.org/doi/full/10.1200/JCO.19.03250





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Phase II ALICE: An AML trial with LSD1i in Combination with azacitidine in the Elderly or unfit

A Phase IIa study investigating iadademstat in combination with azacitidine in elderly or unfit 1L AML patients

- Multicenter, single arm & open label study
- Up to 36 patients to be enrolled
- **Primary endpoint:** Safety and tolerability of the combo with hypomethylating agent azacitidine
- **Secondary endpoints:** Response; time to response; duration of response; overall survival

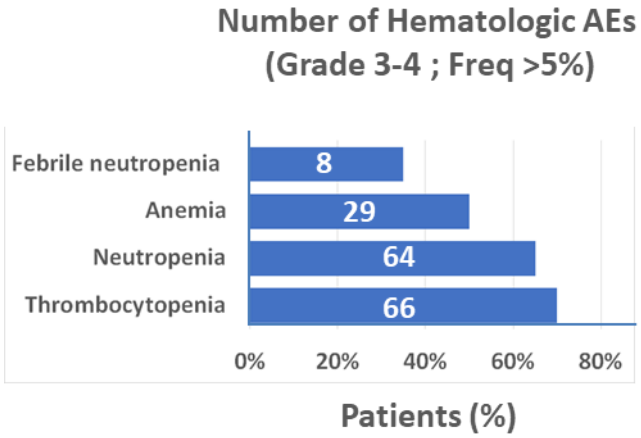
- Current Accrual status as per Dec 31, 2020

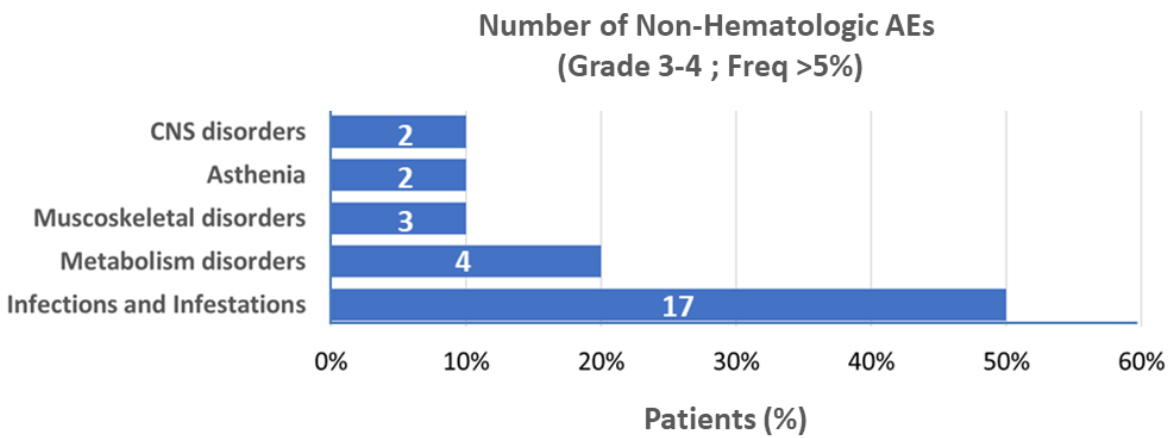
  21 patients enrolled, of which:
  - 20 patients enrolled as per protocol
  - 14 evaluable patients (bone marrow aspirate available after C1)
  - 5 patients not evaluable (no available bone marrow aspirate)
  - 1 patient still in C1 (BMA programmed by mid January)

Last report presented at

Phase II ALICE: good safety and tolerability profile of the iadademstat + azacitidine combo

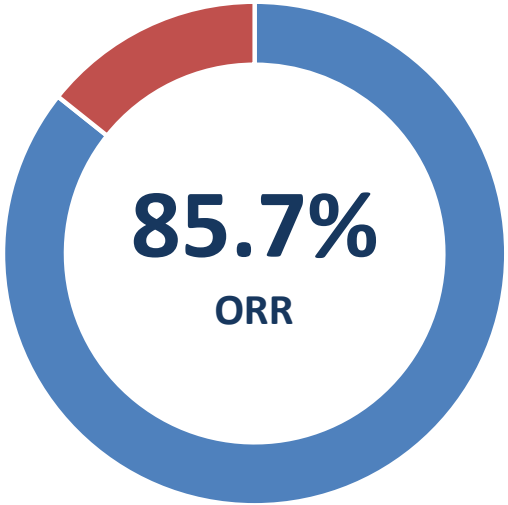
Besides the expected hematological impact, the combo appears to be **safe and well tolerated** (data as per October, 30 2020, N=20 patients)



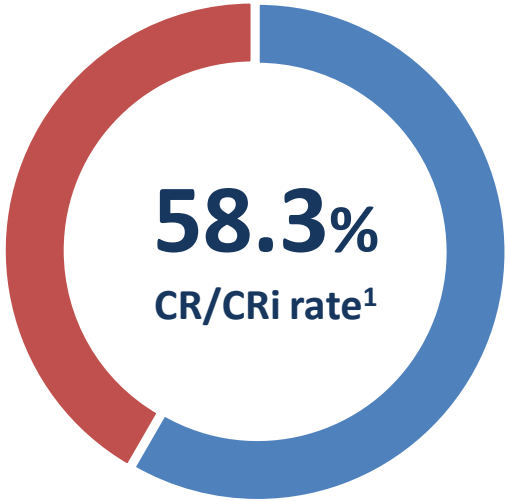


- From the 41 SAEs, only 2 have been considered to be probably related to iadademstat (1 ICH and 1 DS)
- From the 21 patients enrolled, four fatalities occurred in the first month. Only one was considered probably/possibly related to treatment (iada/aza) (1 fatal ICH)
- No QTc prolongation; no neuronal, hepatic, renal or any other organ toxicity

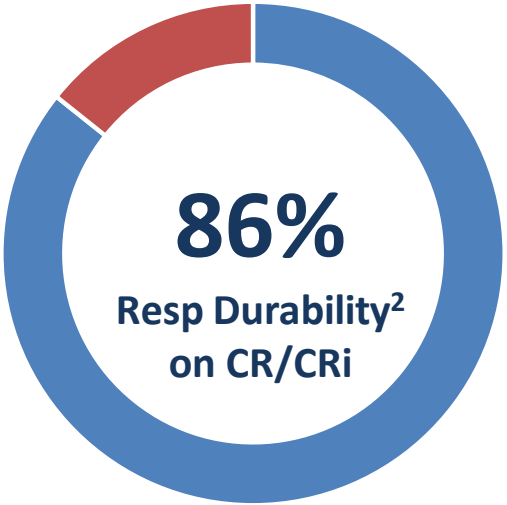
Phase II ALICE: High ORR rates, rapid onset of action, and clinically meaningful durability



34 days
Time to response



11.2 months
Current mOS in CR/CRi



9.7 months
Current mDoR

- Longer responses maturing: 4 Patients already +1y, longest EFS response (ongoing) 715 days
- 40% Transfusion independent patients from those with +120d on treatment

Data from ASH2020 updated as per Dec 31 and corresponding to 14 evaluable patients
(1) % over the ORR population (2) Durability >6 months

https://www.oryzon.com/sites/default/files/events/20201207_ASH2020_poster.pdf

62nd ASH® Annual Meeting and Exposition
DECEMBER 5-8, 2020

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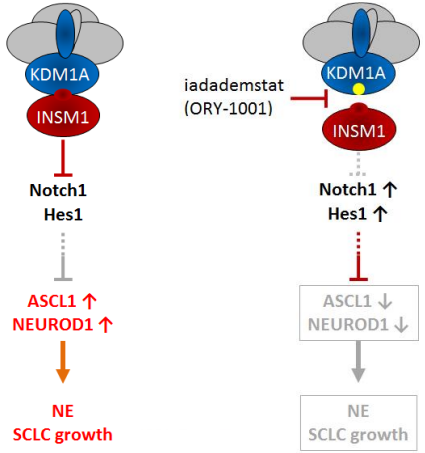
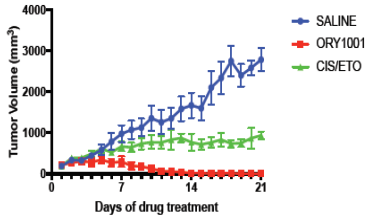
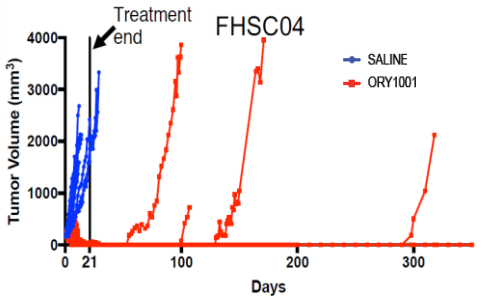
Iadademstat a therapeutic approach for SCLC with a well-defined MoA

- LSD1 is a **well characterized target in SCLC**
- Iadademstat produces **complete and durable tumor regression** in different **chemoresistant SCLC PDX models**
- Iadademstat is **efficacious in combos with platinum/etoposide and other agents as ICIs**
- Identified and patented **biomarkers** that differentiate SCLC tumors by their sensitiveness to LSD1i

- Two clinical studies done with iadademstat in SCLC:
  - Phase I study (NCT02913443) (18 patients) → RP2D in mono
  - Phase IIa (CLEPSIDRA) (14 patients) Safety in mono & Signs of clinical efficacy





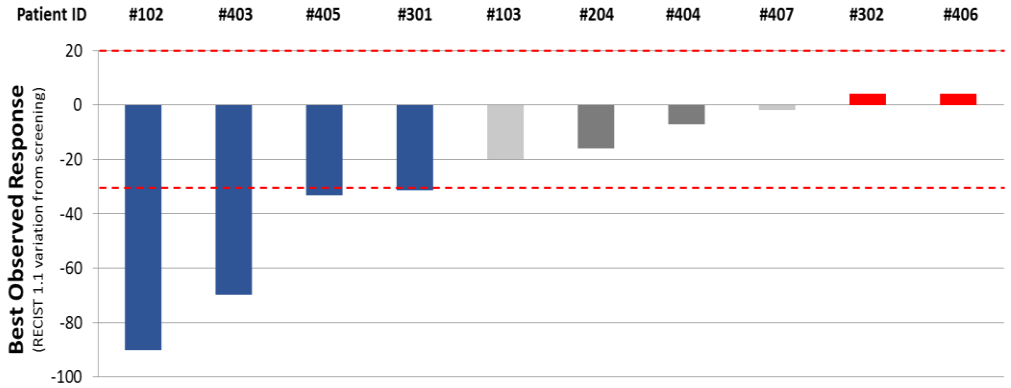


FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

Iadademstat: SCLC - Phase II CLEPSIDRA - encouraging efficacy signals

- Open label, multicenter, Phase IIa study
- Biomarker selected, sensitive platinum relapsed SCLC patients with extended disease
- iada in combination with 4-6 cycles carboplatin/etoposide (21 d/cycle). After chemo, iada could be administered alone

- Platinum/etoposide in combination with iadademstat displayed strong hematotox
- Yet, efficacy signals were encouraging with **40% OR** and **mean DoR of 4.5 months**
- **60 % clinical benefit rate** (6/10 evaluable patients): 4PRs + 2 long-term SD
- Current level of observed responses suggests that **patient selection by biomarkers** may be effective to increase ratio of ORs



Efficacy	
N	14
Biomarker positive (+/+)	12 (ITT)
Evaluable patients (EP)	10 (EP)
OR on EP	4 (40%)
CR	*0 (0%)*
PR	*4 (40%)*
LT-SD on EP	2 (20%)
Clinical benefit on EP (OR and LT-SD)	60%
mean DoR (months) (min, max)	4.5 (0.2-14.0)
ORR on ITT	33%

VIRTUAL 2020 ESMO congress
SCIENCE: 19-21 SEPTEMBER 2020
EDUCATION: 16-18 OCTOBER 2020

2020 THE LATEST ADVANCES IN ONCOLOGY now in a virtual format

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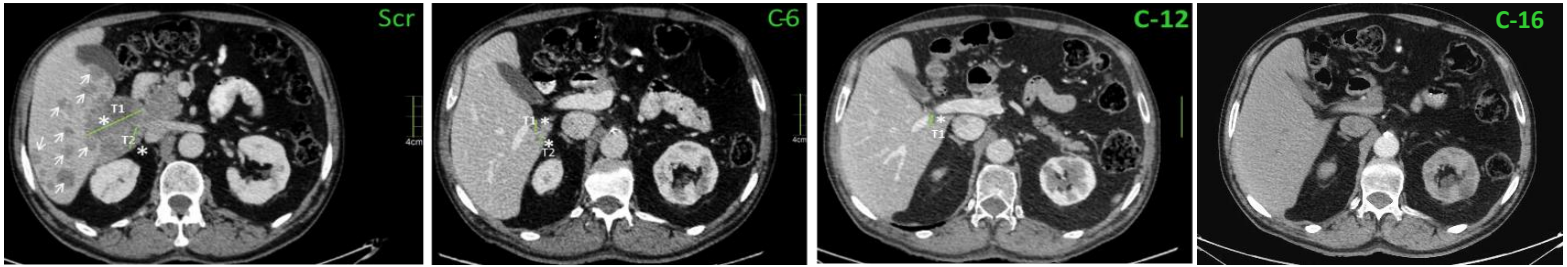
Iadademstat: SCLC - Phase II CLEPSIDRA - results warranting further studies

- A suitable dosing regimen for the iada/CE combo not identified
- Yet, in the four patients dosed with **iadademstat alone for at least 1C** it was **safe** and **showed no hematological, general or neuronal toxicity**, suggesting potential for monotherapy and for other combos with less hematotoxic partners
- Patient #102 showed initially 78.7% of tumor reduction after 6 cycles of triplet. Since then, and on iadademstat alone for 16 additional cycles, **all hematotox disappeared. Patient experienced additional therapeutic benefit** with 90.3% of tumor reduction by RECIST



Patient #102	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6	cycle 7	cycle 8	cycle 9	cycle 10	cycle 11	cycle 12	cycle 13	cycle 14	cycle 15	cycle 16	cycle 17	cycle 18	cycle 19	cycle 20	cycle 21	cycle 22
PE																						
iadademstat	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Best response		PR -43.3%		PR -71.2%		PR -78.7%		PR -86.3%			PR -86.3%		PR -86.3%			PR -90 %				PR -90 %		DP *Brain Mets*

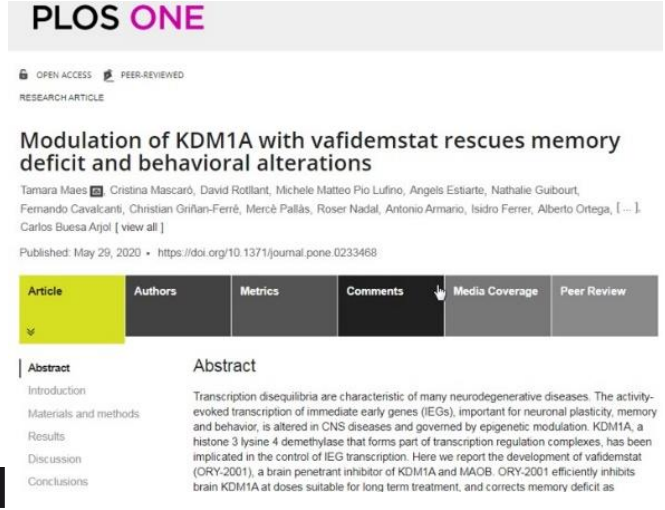
15 cycles in monotherapy, with a **total** tumor size **reduction of 90%** and a **relative** tumor size **reduction during iadademstat monotherapy of 53%**

VAFIDEMSTAT
A Phase II compound for CNS diseases

Vafidemstat (ORY-2001): a “Neuron-fixer” drug in Phase IIb

Preclinical characterization

- Vafidemstat is a **small molecule** LSD1i, optimized for CNS. Low nM activity & **strong pharmacology**.
- **Positive** results in **7 different animal model read-outs generated**
- Epigenetic **MoA** that reduces **neuroinflammation** and overexpresses key **plasticity neuronal genes**



PLOS ONE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Modulation of KDM1A with vafidemstat rescues memory deficit and behavioral alterations

Tamara Maes, Cristina Mascaró, David Rotllant, Michele Matteo Pio Lufino, Angels Estiarte, Nathalie Guibourt, Fernando Cavalcanti, Christian Griñan-Ferré, Mercè Pallàs, Roser Nadal, Antonio Armario, Isidro Ferrer, Alberto Ortega, [...], Carlos Buesa Arjol [view all]

Published: May 29, 2020 • https://doi.org/10.1371/journal.pone.0233468

Article | Authors | Metrics | Comments | Media Coverage | Peer Review

Abstract

Introduction

Materials and methods

Results

Discussion

Conclusions

Abstract

Transcription disequilibria are characteristic of many neurodegenerative diseases. The activity-evoked transcription of immediate early genes (IEGs), important for neuronal plasticity, memory and behavior, is altered in CNS diseases and governed by epigenetic modulation. KDM1A, a histone 3 lysine 4 demethylase that forms part of transcription regulation complexes, has been implicated in the control of IEG transcription. Here we report the development of vafidemstat (ORY-2001), a brain penetrant inhibitor of KDM1A and MAOB. ORY-2001 efficiently inhibits brain KDM1A at doses suitable for long term treatment, and corrects memory deficit as

Clinical characterization

- **Safe and well tolerated in Phase I and various Phase II studies**
  - Vafidemstat has been administered to + 250 volunteers and patients
  - Phase IIs (MS, AD, ADHD, BPD and ASD patients) with no safety signals
  - Longest exposure to date: 18 months
- **High BBB penetration (CSF levels)**
- **Human brain target engagement established in CSF**
- **Clinical efficacy observed in humans**

Vafidemstat reduces agitation and aggression: REIMAGINE and REIMAGINE-AD Phase IIa trials

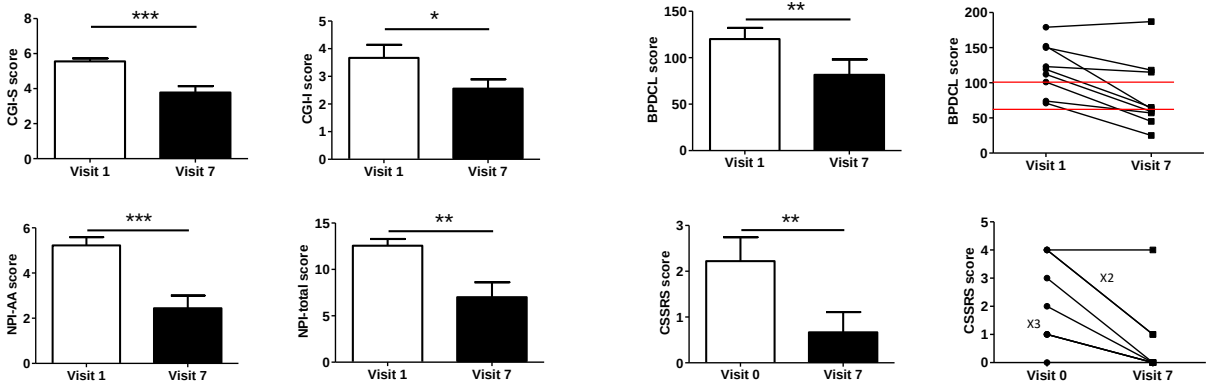
Open label trials: **REIMAGINE** (30 patients, PPAS: n=23 : 9 BPD, 6 ASD, 8 ADHD). **REIMAGINE-AD** (12 moderate/severe AD patients, PPAS: n=7)

Primary endpoint: Safety & Tolerability. Secondary endpoints: Reduction of aggression as measured by validated scales / Other significant measures

REIMAGINE basket trial

Vafidemstat reduces agitation-aggression and improves overall status in BPD patients and also in ADHD and ASD patients after 2 months of treatment

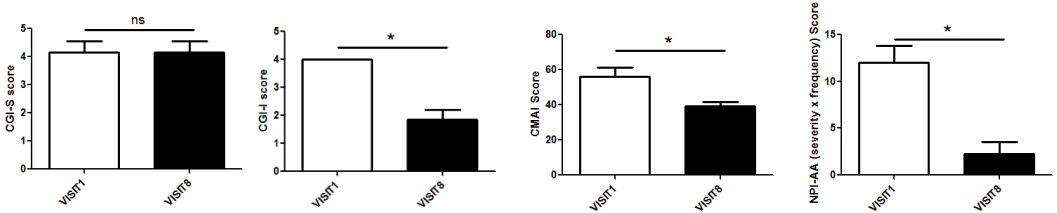
BPD patients



REIMAGINE-AD trial

Vafidemstat reduces agitation-aggression in moderate and severe AD patients after 6 months of treatment

AD patients



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Vafidemstat 2021 activities: 2 Phase IIb & preparing precision medicine studies

PORTICO: PhIIb in BPD

- Double blind, PCB controlled adaptive design w interim analysis to assess statistical power. 156 patients
- Two primary endpoints: overall clinical BPD improvement and improvement in aggression
- CTA approved in Spain. Identification of sites in US, DE, BG and SRB is ongoing
- Pre-IND meeting with FDA scheduled 10-Feb-2021
- FPI expected 1Q2021

Prevalence of borderline personality disorder around 1.6% in the general population [1]
1.4 million patients in US are being treated

EVOLUTION: PhIIb in SCZ

- Double blind, PCB controlled adaptive design w interim analysis to assess statistical power. 80 patients (40 vafi:40 placebo)
- To address SCZ Negative and Cognitive Symptoms: vafi as add-on to SoC
- Primary endpoint: efficacy
- 6-10 Spanish Hospitals
- Spanish Government funded
- CTA expected 1Q21 & FPI expected 1H2021

Prevalence of schizophrenia and related psychotic disorders in the U.S. range between 0.25% and 0.64% [2]

PRECISION MEDICINE

Preparative work for subsequent PhII trials with vafidemstat:

- **PMS observational study**
  - 20 patients to be characterized
  - Ongoing
- **SETD1A observational case-control study**
  - 60 subjects to be characterized (20+20+20)
  - Initiation expected in 1Q21
  - 6 months till conclusion

1% of people with autism have Phelan-McDermid syndrome. That means between 1/8,000-15,000[3]

1. https://www.ncbi.nlm.nih.gov/books/NBK430883/
2. https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml#:~:text=Across%20studies%20that%20use%20household,between%200.25%25%20and%200.64%25
3. https://www.pmsf.org/about_pms/ and https://www.cdc.gov/ncbddd/autism/data.html

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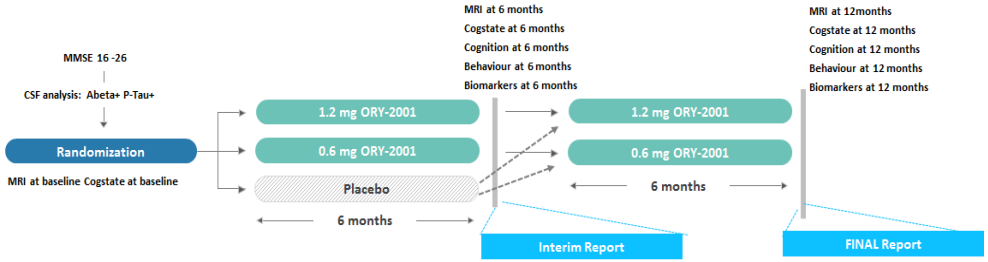
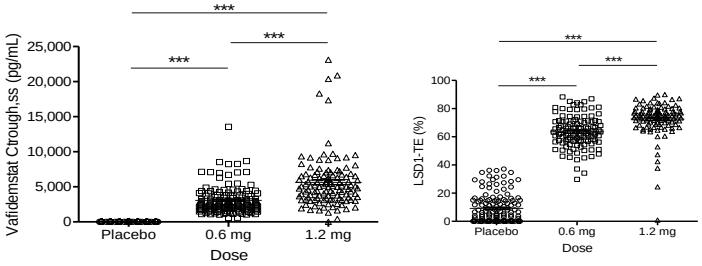
A Phase II trial in AD: ETHERAL, Epigenetic THERapy in ALzheimer's Disease

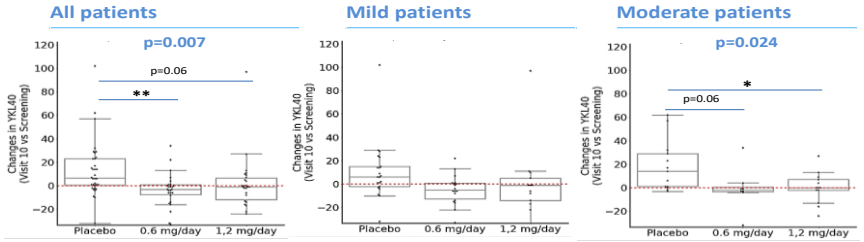
A double-blind Phase IIa study to provide useful information to design future studies

- **141 Mild to Moderate AD** patients (6+6 months)
- Primary Objective: Safety & Tolerability
- Secondary Objectives:
  - Cognition/Agitation/Apathy/Depression/QoL
  - Volumetric MRI
  - CSF BIOMARKERS





LSD1-TE: LSD1 Target Engagement



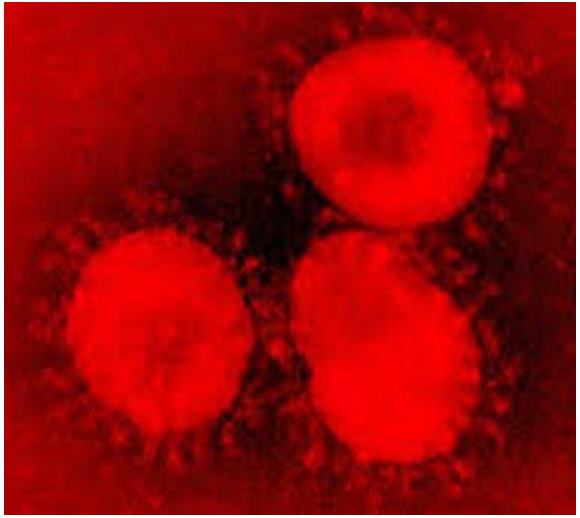
Safe and well tolerated at both doses after 12 month treatment
Good PK and Target engagement
Inflammatory CSF biomarker YKL40 reduced in keeping with PC results

Covid-19 trial: ESCAPE - vafidemstat to prevent ARDS

ESCAPE: Phase II study in adult severely diseased COVID-19 patients

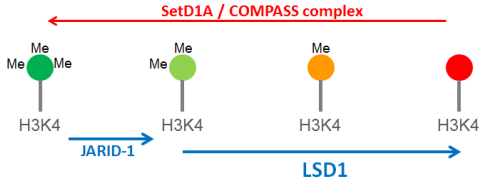
Multicenter, open label, two arms randomized study in combination with best supportive care (1:1)

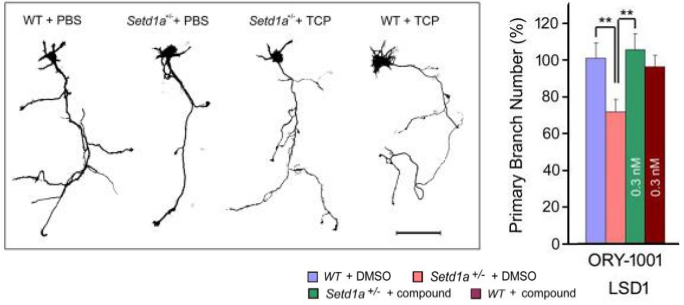
- N= 40
- Primary endpoint: efficacy of vafidemstat, in combination with standard of care to prevent Acute Respiratory Distress Syndrome (ARDS) in adult severely ill patients with CoVID-19
  - Reduction in the incidence of patients (%) requiring mechanical ventilation and referral to ICU from day 1 to day 14
  - Decrease in global mortality and mortality associated to CoVID-19 pneumonia within the period from Day 1 to Day 14
- Secondary endpoints
  - Reduction of systemic and pulmonary inflammatory biomarkers associated to CoVID-19 pneumonia: IL-6, IL1-beta, D-dimer-D, PCR, LDH, Ferritin, Total Lymphocytes
  - Other
- Six sites currently approved in Madrid and Barcelona areas
- Actively recruiting (FPI in April 2020)



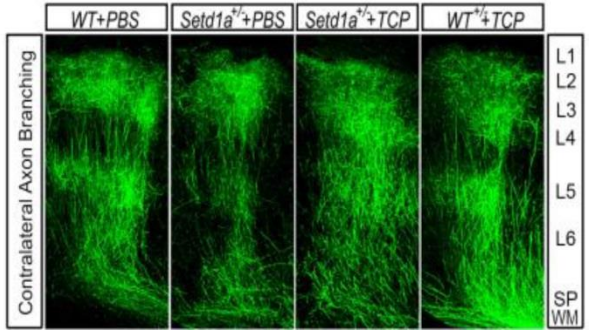
Methylation is involved in SCZ and ASD and LSD1 inhibition rescues phenotypes in genetic models

Cell Reports 32, 108126, September 15, 2020

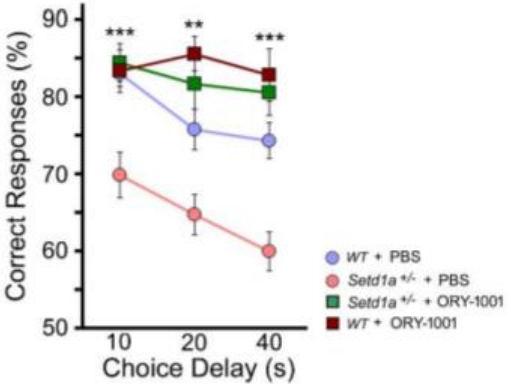




LSD1 inhibition rescues the contralateral axon branching deficits in-vivo in Setd1a $^{+/-}$mice

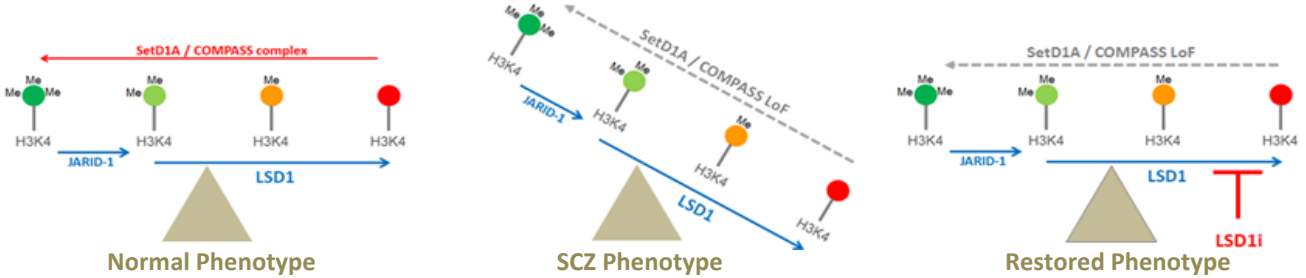


Rescue of WM performance in Setd1a+/- mice treated with ORY-1001



LSD1 inhibition paves the way for personalized medicine in psychiatry

- **A clear molecular mechanism of action**



- **SCZ patients carrying these mutations identified in several US and EU communities**

Pioneering **precision medicine collaboration** in **SCZ** initiated with **Columbia University**:

- Pilot observational study to characterize psychometrically l.o.f. patients
  - 60 individuals to be baselined
- Pilot study will inform a subsequent vafidemstat Phase II trial in SetD1A mutant patients
- Additional further characterization work in preclinical Setd1A models

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Project to start 1Q2021

LSD1 inhibition rescues different phenotypes in genetic models of Autistic Spectrum Disorder

nature neuroscience

Article | Published: 12 March 2018

Social deficits in *Shank3*-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition

Luye Qin, Kaijie Ma, Zi-Jun Wang, Zihua Hu, Emmanuel Matas, Jing Wei & Zhen Yan

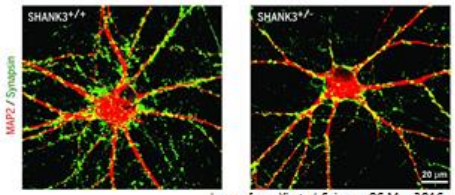


Image from Yi et al *Science* 06 May 2016

Mutation of SHANK3 gene is causally linked to ASD. HDAC & LSD1 inhib rescue the mice phenotype Qin et al Nat Neurosci. 2018. & Zhen Yan Oral Comm SF-2019

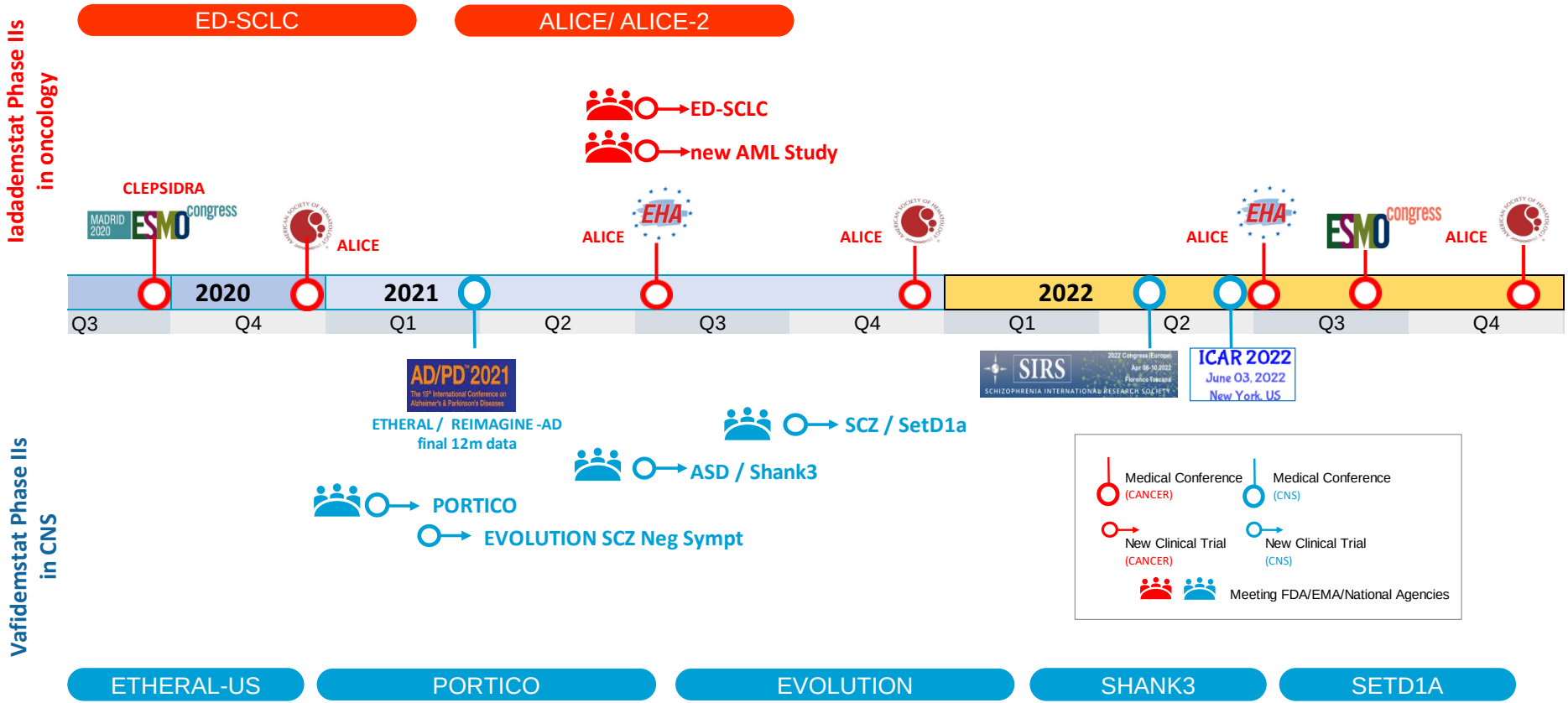
LSD1 inhibition also rescues the Shank3 ASD phenotype

Zhen Yan *Oral Comm* SFN-2019

- Pioneering **precision medicine collaboration** entered with **INGEMM-La Paz Hospital** in Madrid for **Phelan-McDermid Syndrome (PMS)**
- PMS is thought to be one of the causes of ASD
- INGEMM has identified the mutation in + 200 PMS patients
- Patient psychometric characterization is ongoing in preparation of future clinical study with vafidemstat

SaludMadrid Hospital Universitario La Paz Hospital Carlos III Hospital Cantoblanco

Anticipating a rich flow of clinical catalysts (non-comprehensive selection)



Potential Conferences where data may be presented & potential meetings with regulatory agencies

ORYZON – a unique investment opportunity in an epigenetic platform

- A differentiated proposition in **EPIGENETIC** drugs in **CNS and ONCOLOGY**
- **2 molecules** in **Phase II** with promising clinical signals of efficacy in patients
- **Pioneers in CNS epigenetics**
  - **Vafidemstat reduces agitation/aggression** in psychiatric disorders (BPD, ADHD, ASD) and in AD
  - **Two new Phase IIb studies in Borderline personality disorder and in SCZ** (negative symptoms and cognition) to start in 2021. Trial in agitation/aggression in AD under evaluation
  - Trials in genetically-defined patient subpopulations in SCZ and ASD under study → **Options to get accelerated approval**
- **Most advanced LSD1i** (iadademstat) **in Oncology**
  - **Robust and durable positive efficacy results** reported in the ongoing Phase II trial in AML (85% ORRs)
  - **A SCLC trial with ICI in preparation**
- **Rich pipeline** of clinical **news** expected in the next quarters. Clinical operations in US started and under expansion
- A **cash efficient** company with a seasoned international management team
- One of the most liquid stocks in its group on the Spanish Stock Exchange. **Potential dual listing on Nasdaq in the future**
- **Continuous presence in the US market**. Four successful PIPEs executed in 2017-20 led by US investment Banks and with participation of US-EU-Israeli investors

ORYZON

Pioneering Personalized Medicine in

EPIGENETICS