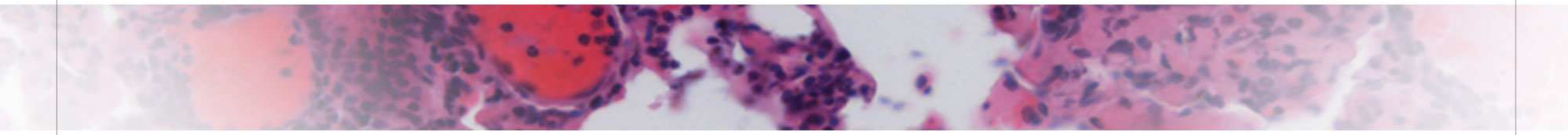
American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Iadademstat Combination with Azacitidine is a Safe and Effective Treatment in First Line Acute Myeloid Leukemia. Final Results of the ALICE Trial.

Olga Salamero[1], Tim Somervaille[2], Antonieta Molero[1], Evelyn Acuña-Cruz[3], Jose Antonio Perez-Simon[4], Rosa Coll[5], Montserrat Arnan[6], Brayan Merchan[7], Ana Perez[1], Isabel Cano[3], Rebeca Rodriguez-Veiga[3], Mabel Arevalo[8], Sonia Gutierrez[8], Claudia Fernandez[8], Carlos Buesa[8], Douglas V. Faller[9], Francesc Bosch[1], Pau Montesinos[3]

[1]Departament d'Hematología, Hospital Universitari Vall d'Hebron, Unitat de Hematología Experimental, Vall d'Hebron Institut d'Oncología (VHIO), Barcelona, Spain; [2]Haematology Department, The Christie Hospital NHS Foundation Trust, Manchester, UK; [3]Hospital Universitari i Politècnic La Fe, Institut d' Investigació Sanitaria La Fe (IISLAFE), Valencia, Spain ; [4]Hospital Universitario Virgen del Rocío; Instituto de Biomedicina (IBIS)/CSIC) Universidad de Sevilla, Sevilla, Spain; [5]Departament d'Hematología, Institut Català d'Oncología, Hospital Dr. Josep Trueta, Institut d'Investigacio Biomedica de Girona (IDIBGI), Universitat de Girona, Girona, Spain; [6]Departament d'Hematología, Institut Català d'Oncología, Hospital Duran i Reynals (ICO-IDIBELL), L'Hospitalet de Llobregat, Spain; [7]Departament d'Hematología, Hospital del Mar, Barcelona, Spain; [8]Oryzon Genomics SA, Cornella de Llobregat, Spain; [9]Oryzon Genomics SA, Boston, MA.

Disclosures

O. Salamero: *Abbvie, Celgene/BMS, Novartis:, Astellas, Jazz Phamaceuticals* Consultancy or Honoraria.

T. Somervaille: *Oryzon Genomics, Bristol Myers Squibb, Abbvie, Novartis:* Consultancy; *Imago Biosciences, CellCentric Ltd:* Research Funding.

A. Molero: *Oryzon Genomics:* Consultancy.

JA. Perez-Simon: Alexion, Jazz *Phamaceuticals,*, Gilead, Janssen, Novartis: Consultancy, Honoraria; Abbvie, Pfizer: Research Funding

M. Arnan: *MNS,* Jazz *Phamaceuticals Novartis, Abbvie:* Consultancy, Speakers Bureau.

C. Fernandez: *Oryzon Genomics:* Current Employment.

M. Arevalo: *Oryzon Genomics:* Current Employment.

S. Gutierrez: *Oryzon Genomics:* Current Employment.

C. Buesa: *Oryzon Genomics SA:* Current Employment, Current equity in publicly-traded company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties; *Mendelion, Palo Biopharma:* Current equity holder in private company. *Viracta Therapeutics:* Current equity holder in publicly-traded company.

D. Faller: *Oryzon Genomics:* Current Employment, Current equity holder in publicly-traded company; *Phoenicia Biosciences, Viracta,:* Current Employment, Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees, Patents & Royalties; Briacell: Consultancy, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Cytea:* Consultancy, Current equity holder in private company; *Takeda pharmaceuticals:* Current equity holder in publicly-traded company; *Faller Williams LLC:* Current equity holder in private company, Patents & Royalties; *Molecular Partners, Wuxi Inc:* Consultancy.

F.Bosch: *Celgene/BMS, Roche, Takeda, Astra-Zeneca, Novartis, Mundipharma, Gilead, Abbvie, Lilly, Beigene: Consultancy, Honoraria.*

P. Montesinos: *Pfizer, Jazz Phamaceuticals, Bristol Myers Squibb, Abbvie: :* Consultancy, Research Funding, Speakers Bureau; *Astellas, Gilead:* Consultancy, Speakers Bureau; *Takeda, Novartis, Menarini/Stemline:* Consultancy, Research Funding; *Incyte, Otsuka, Ryvu, Nerviano, Beigene, Kura Oncology:* Consultancy

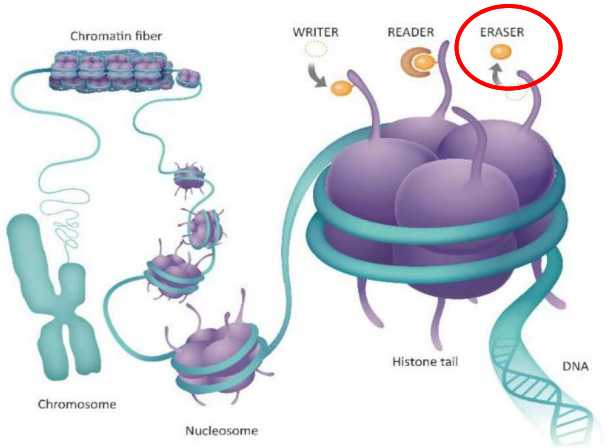
LSD1/KDM1A, an epigenetic enzyme with key roles in oncology

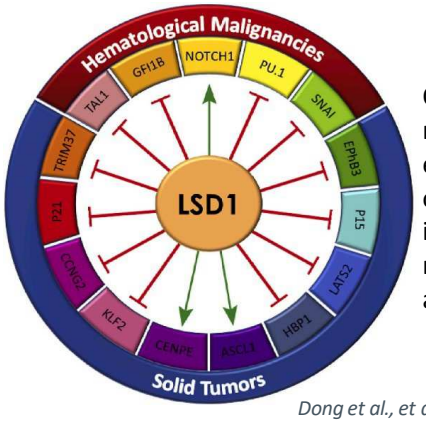
LSD1 (Lysine demethylase 1) is an epigenetic enzyme (eraser) with **catalytic histone demethylase activity** that regulates gene expression by altering chromatin structure, acting both as a **transcriptional corepressor (on H3K4me1/2) and as a transcriptional coactivator (on H3K9me1/2**). LSD1 also demethylates non-histone substrates including DNMT1, TP53, STAT3 and E2F1

LSD1 has also **scaffolding activity to form multiprotein complexes** (CoREST, NuRD) with HDACs, RCORs and other transcription factors to regulate gene expression with key implications in oncogenesis

LSD1 is required for stem cell pluripotency and lineage commitment during embryonic development and adult homeostasis

Elevated LSD1 expression has been correlated with **poor prognosis** in prostate cancer, NSCLC, SCLC, neuroblastoma, breast cancer, and leukemias





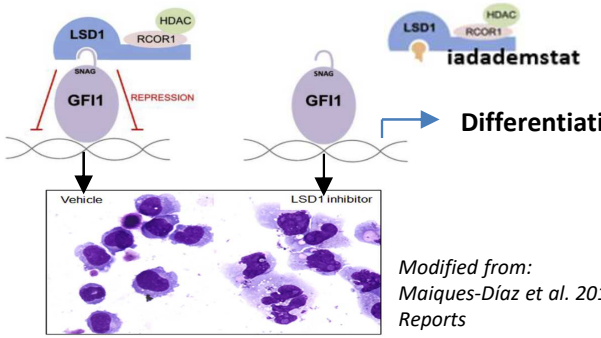
Overview of regulatory effects of LSD1 on target genes in hematological malignancies and solid tumors

Dong et al., et al Eur J Med Chem 2022

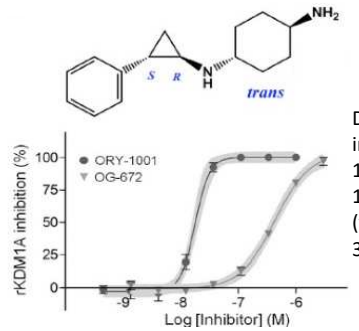
H3K4 me1/2: mono and dimethyl lysine 4 of histone 3; H3K9 me1/2: mono and dimethyl lysine 9 of histone3; DNMT1: DNA Methyltransferase 1; TP53: Tumor Protein p53; STAT3:Signal Transducer and Activator of Transcription 3; E2F1:2F Transcription Factor 1; CoREST: RCOR1 transcription repressor complex; NuRD: Nucleosome Remodeling and Deacetylase; HDAC: Histone Deacetylase; NSCLC: Non-Small Cell Lung Carcinoma; SCLC: Small Cell Lung Carcinoma

Iadademstat (ORY-1001) is a potent, selective, oral LSD1 inhibitor

- Iadademstat is an **irreversible**, highly **selective**, **potent**, small molecule LSD1 inhibitor
- Covalently binds to FAD-cofactor of LSD1 and **inhibits its catalytic and scaffolding activity** by preventing interaction with several transcription factors
- **Iadademstat inhibits LSD1:GFI1 interaction resulting in the activation of genes involved in differentiation of AML cells**
- **Orally bioavailable**, with excellent pharmacologic properties, predictable PK and **no DDI**
- Clinical activity demonstrated in R/R AML and R/R SCLC as single agent and in combinations
- Safe and **well tolerated** in monotherapy. **No off-target toxicities**



Modified from:
Maiques-Díaz et al. 2018, Cell Reports



Dose-response curves of rKDM1A inhibition by ORY-1001 (circles, IC50 = 18 nM, 95% confidence interval [CI] = 15–21 nM) and its enantiomer OG-672 (triangles, IC50 = 430 nM, 95% CI = 357–517 nM).

Maes et al., Cancer Cell; 2018

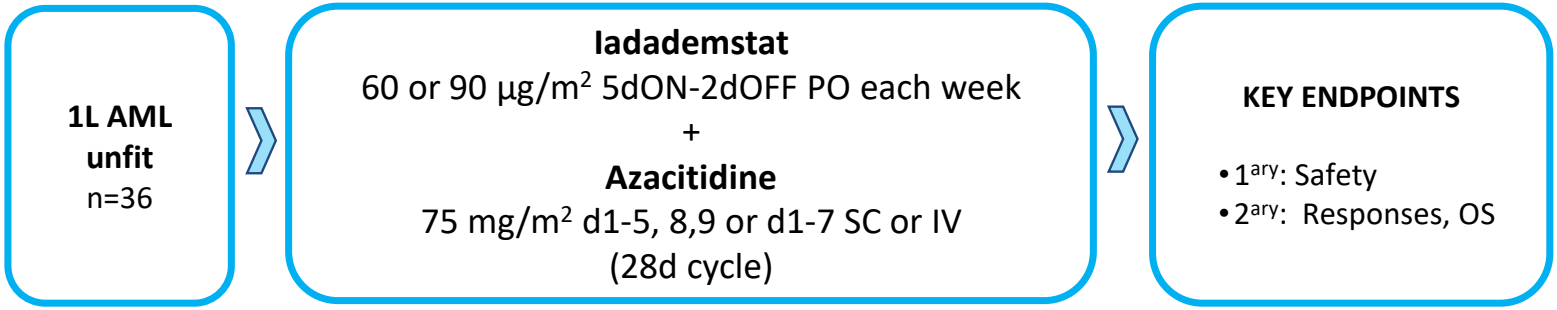
J Clin Oncol. 2020 Dec 20; 38(36): 4260–4273. PMCID: PMC7768337
Published online 2020 Oct 14. doi: 10.1200/JCO.19.03250 PMID: 33052756

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

FAD: Flavin Adenine Dinucleotide; DDI: Drug-Drug Interaction; PK: Pharmacokinetics; R/R AML: Relapsed/Refractory Acute Myelogenous Leukemia; R/R SCLC: Relapsed/Refractory Small Cell Lung Carcinoma; SNAG: Snail/Gfi-1; GF1: Growth Factor Independent 1 transcriptional repressor.

ALICE: iadademstat+azacitidine in first line, unfit, AML patients

"A Phase IIa study to assess the safety, tolerability, dose finding and efficacy of ORY-1001 in combination with azacitidine in adult patients with AML in first line therapy"



- Single arm & Open label. 36 patients enrolled from Jan-2019 to Oct-2021
- 6 active enrolling sites in Spain. EUDRACT NUMBER: 2018-000482-36
- Primary endpoint: Safety and tolerability of the combination of iada with hypomethylating agent, azacitidine
- Secondary endpoints: PK/PD, ORR (CR/CRi/PR), TTR, DoR, EFS, OS
- Main Inclusion criteria:
  - Subjects with AML according to WHO classification, considered ineligible for intensive chemotherapy or who had refused it
  - Subjects may not have received azacitidine or prior treatment for AML other than hydroxyurea

PO:oral; SC: Subcutaneous; IV: Intravenous; ORR: Overall Response Rate; TTR: Time To Response; DoR: Duration of Response; OS: Overall Survival; CR: Complete Remission; CRi: Complete Remission with incomplete hematologic recovery; PR: Partial Response; EFS: Event-Free Survival; PD: Pharmacodynamics; WHO: World Health Organization.

Demographics

Demographics	n=36	
Age	Median (range)	75.5 (70-83)
AML type	De novo	79%
	Secondary	21%
ECOG	0-1	91%
	2-3	9%
WBC (10^9/L)	Median (range)	2.3 (0.7-13.2)
Bone Marrow Blast count	<30%	24%
	30 to 50%	44%
	>50%	32%
Cytogenetic risk	Intermediate	47%
	Adverse	53%
Cytopenias at baseline (Grade ≥ 3)	Anemia	15%
	Neutropenia	53%
	Thrombocytopenia	53%
Transfusion Dependence		41%

Demographics	n=36	
Somatic mutations (n≥3)	RAS/MAPK pathway (RAS, RAF, NF1, PTPN11)	n=11
	TP53	n=10
	TET2	n=10
	DNMT3A	n=8
	ASXL1	n=7
	SRSF2	n=6
	NPM1	n=5
	FLT3 ITD/TKD	n=5
	IDH1/2	n=4
	RUNX1	n=4
	CEBPA	n=4
	EZH2	n=4
	ETV6	n=3
	BCOR	n=3

ECOG: Eastern Cooperative Oncology Group; TET2: Tet Methylcytosine Dioxygenase 2' coding gene; RAS: Rat Sarcoma virus gene family coding gene; RAF: MAP kinase kinase kinase (MAP3K) coding gene; MAPK: Mitogen-activated protein kinases; NF1: Neurofibromatosis type 1 gene; PTPN11: non-receptor protein tyrosine phosphatase SHP2 coding gene; DNMT3A: DNA Methyltransferase 3A coding gene; ASXL1: Additional Sex Combs Like-1 gene; NPM1: Nucleophosmin 1 coding gene; FLT3 ITD/TKD: Fms Related Receptor Tyrosine Kinase 3 coding gene (Internal Tandem Duplication/Tyrosine Kinase Domain mutations); SRSF2: Serine/arginine-rich splicing factor 2 coding gene; IDH 1-2: Isocitrate Dehydrogenase 1-2 coding gene; RUNX1: runt-related transcription factor 1 coding gene; CEBPA: CCAAT Enhancer Binding Protein Alpha coding gene; EZH2:Enhancer of Zeste 2 Polycomb repressive complex 2 coding gene; BCOR:BCL6 Corepressor ding gene.

Patients disposition

36 Patients treated

2 protocol major deviations

34 enrolled per protocol
16 at 60 µg/m²/d cohort
18 at 90 µg/m²/d cohort

7 died before 1st assessment:
3 at 60 µg/m²/d cohort
4 at 90 µg/m²/d cohort

27 evaluable for efficacy
13 at 60 µg/m²/d cohort
14 at 90 µg/m²/d cohort

10 censored at the last visit
5 at 60 µg/m²/d cohort
5 at 90 µg/m²/d cohort

17 reported dead
8 at 60 µg/m²/d cohort
9 at 90 µg/m²/d cohort

At End of study:
6 alive [3 on compassionate use (CU) iada]
2 in 60 µg/m²/d cohort (1 in CU)
4 in 90 µg/m²/d cohort (2 in CU)
4 UNK survival (alive at the time of last visit)
4 in 60 µg/m²/d cohort

Disposition	n=36 pts accrued and treated		
Reason for treatment discontinuation			
n (%)	60 µg/m²/d n=17	90 µg/m²/d n=19	Overall n=36
Disease progression	8 (41.7)	4 (21.1)	12 (33.3)
Treatment toxicity	0	1 (5.3)	1 (2.8)
Patient decision	2 (11.8)	2 (10.5)	4 (11.1)
Investigator decision	2 (11.8)	2 (15.8)	5 (13.9)
Death	4 (25.3)	7 (36.8)	11 (30.6)
Compassionate use (CU)	1 (5.9)	2 (10.5)	3 (8.3)

Data base lock Sep 30, 2022

Safety

Overview of AEs[#4]	AEs (n)					
Subjects with	60 µg/m2/d n=17	90 µg/m2/d n=19	Overall n=36	60 µg/m2/d n=17	90 µg/m2/d n=19	Overall n=36
AEs	17 (100.0)	19 (100.0)	36 (100)	16 (94.1)	17 (89.5)	33 (91.7)
SAEs	16 (94.1)	18 (94.7)	34 (94.4)	1 (5.9)	2 (0.5)	**3 (8.3)****
AEs ≥G3	17 (100)	19 (100)	**36 (100)**	15 (88.2)	16 (84.2)	**31 (86.1)**
AEs leading to treatment **reduction**	2 (11.8)	7 (36.8)	9 (25.0)	2 (11.8)	5 (26.3)	**7 (19.4)**
AEs leading to treatment **delay**	10 (58.8)	11 (57.9)	21 (58.3)	7 (41.2)	8 (42.1)	**15 (41.7)**
AEs leading to treatment **hold**	9 (52.9)	13 (68.4)	22 (61.1)	6 (35.3)	4 (21.1)	**10 (27.8)**
AEs leading to treatment discontinuation	5 (29.4)	7 (36.8)	12 (33.3)	0	2 (10.5)	2 (5.6)
Fatal AEs	3 (17.6)	8 (42.1)	**11**(30.6)*	0	1 (5.3)	**1 (2.8)**

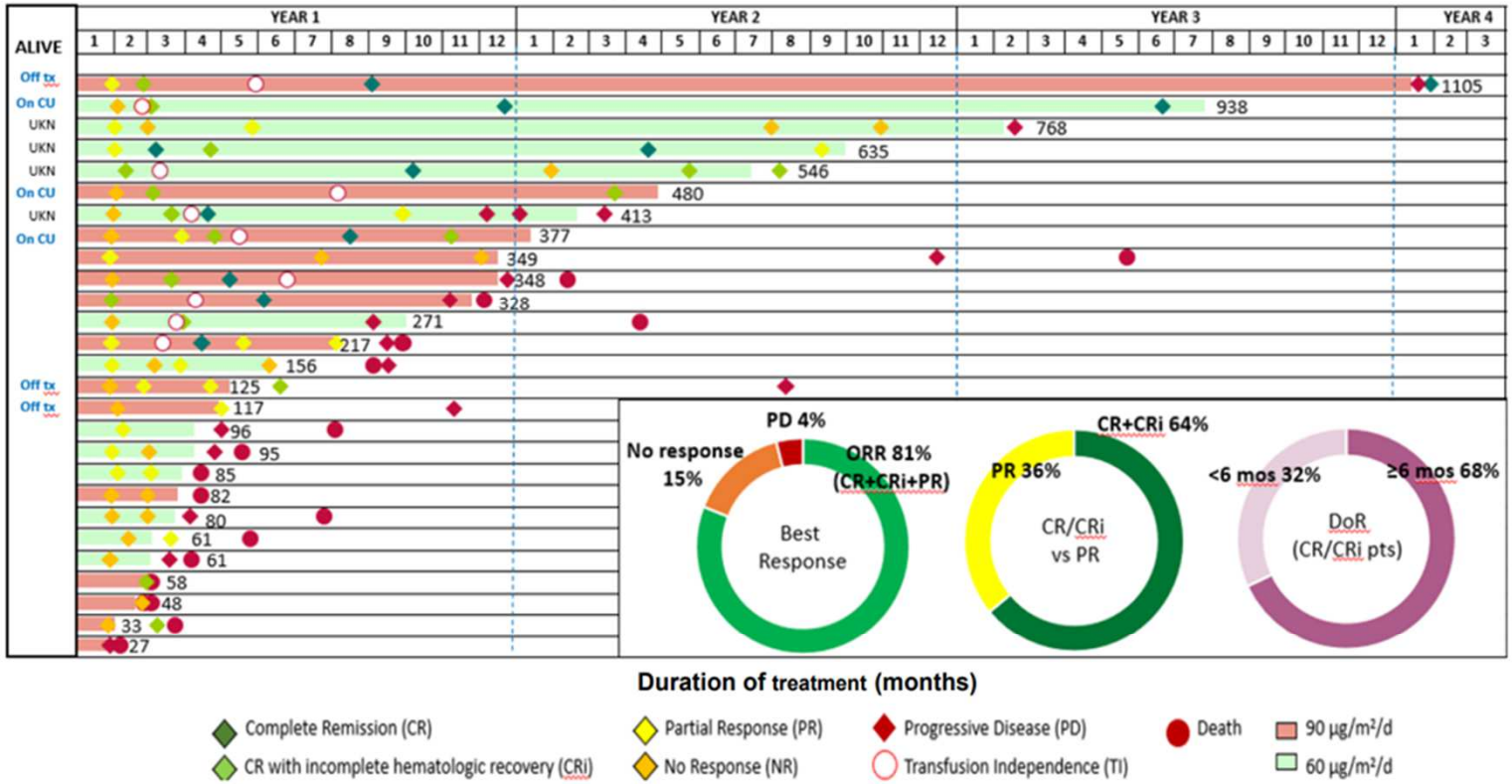
AEs include all reported AEs, including both Treatment Emergent and non-Treatment Emergent.
*Deaths due to Infections (8), bleeding (3). Additionally, there were 2 other reported study deaths (PD and death)
Treatment related SAEs occurred in 3 patients, one with febrile neutropenia (G3) one with differentiation syndrome (G3) and one with intracranial hemorrhage (G5)

Hb: Haemoglobin; Lympho: Lymphocyte; WBC: White Blood Cell

n=36 Safety Analysis Population	n (%)		
Preferred Term	**SAEs (in >1 pt)**	**AEs G3-4 (in >2 pt)**	**Related AEs (>10%)**
Investigations			
Platelet ct decreased	0	32 (88.9)	**23 (63.9)**
Neutrophil ct decreased	0	23 (63.9)	**20 (55.6)**
Hb abnormal/decreased	0	5 (13.9)	0
Lympho abnormal/decreased	0	4 (11.2)	0
WBC abnormal/decreased	0	4 (11.2)	0
All Others			
Febrile neutropenia	14 (38.9)	17(47.2)	1 (2.8)
Pneumonia	5 (13.9)	3 (8.3)	0
Pyrexia	4 (11.1)	1 (2.8)	0
Cellulitis	3 (8.3)	4 (11.1)	0
Sepsis	3 (8.3)	3 (8.3)	0
COVID-19 pneumonia	3 (8.3)	0	0
Respiratory tract infection	2 (5.6)	2 (5.6)	0
Skin infection	2 (5.6)	2 (5.6)	0
Urinary tract infection	2 (5.6)	2 (5.6)	0
Septic shock	2 (5.6)	1 (2.8)	0
Haemorrhage intracranial	2 (5.6)	0	1 (2.8)
Constipation	1 (2.8)	3 (8.3)	9 (25.0)
Hypotension	1 (2.8)	3 (8.3)	0
Anaemia	0	24(66.7)	15 (41.7)
Asthenia	0	5 (13.9)	9 (25.0)
Hypokalaemia	0	3 (8.3)	0
Dysgeusia	0	1 (2.8)	15 (41.7)
Nausea	0	0	6 (16.7)
Decreased appetite	0	0	4 (11.1)

Efficacy: Responses

Responses as recorded in eCRF by investigators for the efficacy population. First, last and changes in assessments indicated.

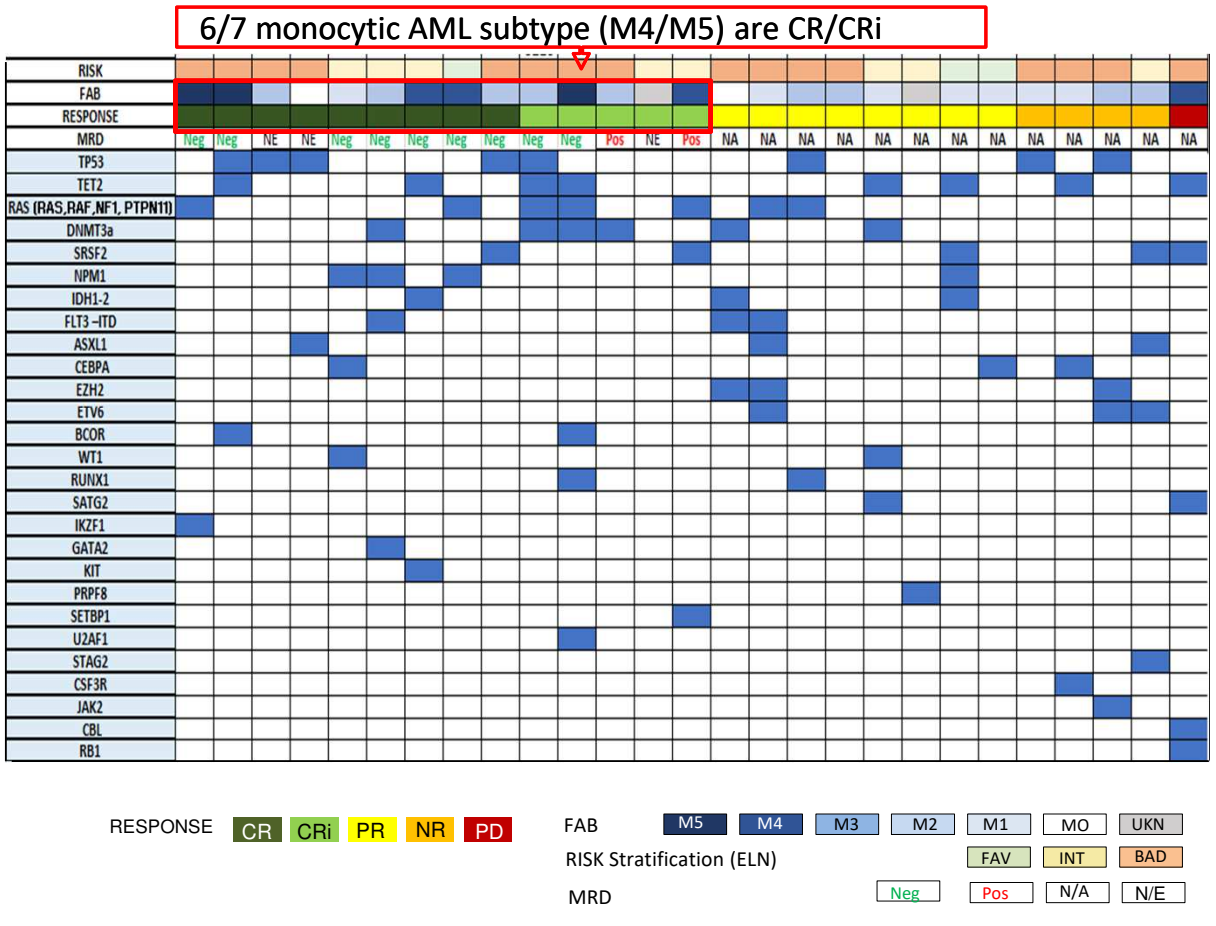


Summary of Responses n=27	n	%
CR	9	33%
CRi	5	19%
PR	8	30%
NR	4	15%
PD	1	4%
CR/CRi	14	52%
ORR (CR/CRi/PR)	22	81%
TTR	n=22 Median [95% CI]	2.1 mos [1.1,2.6]
DoR	n=22 Median [95% CI]	8.8 mos [2.8,17.4]

CR/CRi pts n=14	n	%
MRD neg	9 out of 11 evaluable	82% 9/11
Achieved TI (RBC & Plt)	10	71% 10/14

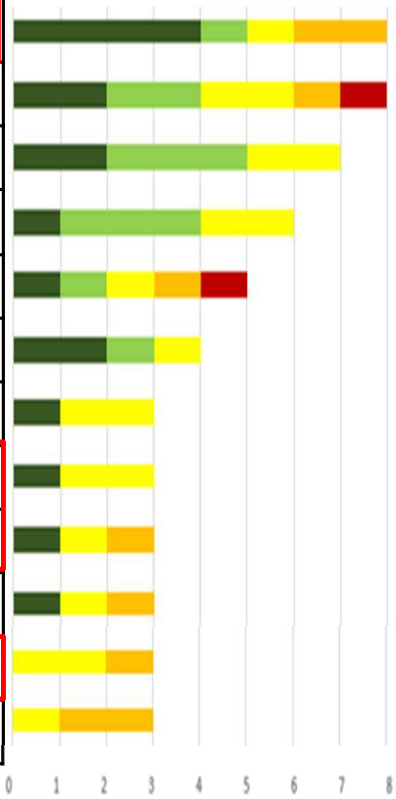
CU: Compassionate use; tx: treatment; UKN: Unknown; eCRF: electronic clinical record file; CR: Complete Remission; CRi: Complete Remission with incomplete hematologic recovery; PR: Partial Response; NR: No response; PD: Progressive Disease; ORR: Overall Response Rate; MRD: Measurable Residual Disease; TTR: Time To Response; DoR: Duration of Response; TI: Transfusion Independence; RBC: Red blood cells; Plt: Platelets

Efficacy: Responses by AML subtype, risk and mutation profile



Responses for mutations found in 3 or more evaluable patients

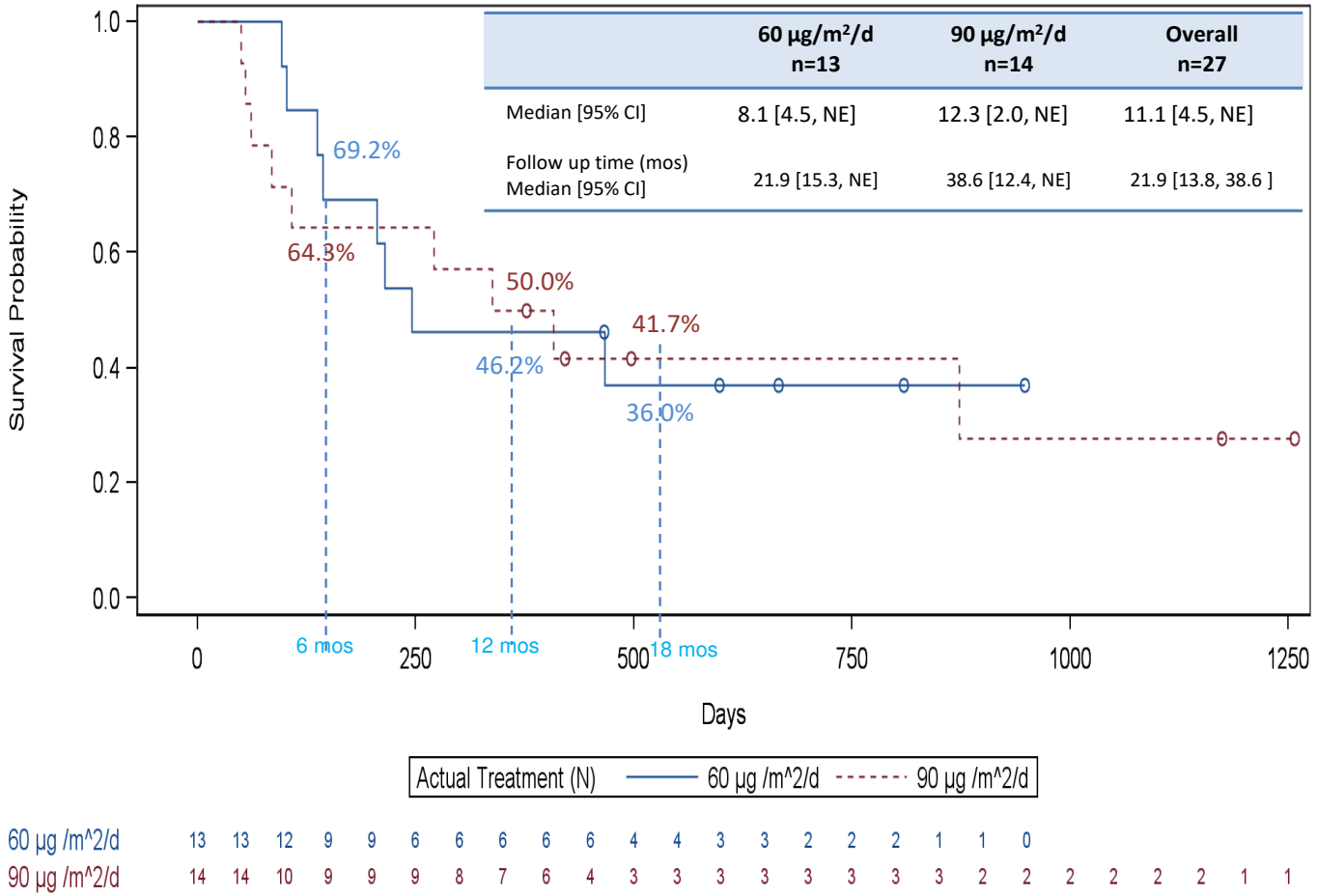
Mutation	% responders out of evaluable mutated patients
TP53	6/8 (75%)
TET2	6/8 (75%)
RAS pathway	7/7 (100%)
DNM3TA	6/6 (100%)
SRF2	3/5 (60%)
NPM1	4/4 (100%)
IDH1-2	3/3 (100%)
FLT3-ITD	3/3 (100%)
ASXL1	2/3 (67%)
CEBPA	2/3 (67%)
EZH2	2/3 (67%)
ETV6	1/3 (33%)



FAB: French-American-British classification system; ELN: European Leukemia Net; MRD: Measurable Residual Disease

Efficacy: OS

Efficacy analysis set (n=27)



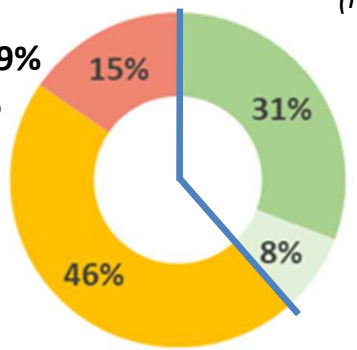
	60 µg/m²/d n=13	90 µg/m²/d n=14	Overall n=27
Median [95% CI]	8.1 [4.5, NE]	12.3 [2.0, NE]	11.1 [4.5, NE]
Follow up time (mos) Median [95% CI]	21.9 [15.3, NE]	38.6 [12.4, NE]	21.9 [13.8, 38.6]

CI: Confidence Interval; mos: months

Efficacy: Responses, exposure and TE by dose cohort

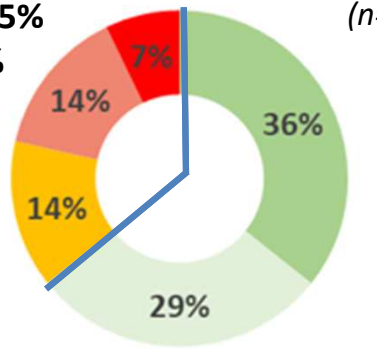
60 µg/m2/day *(n=13)*

- **CR/CRi 39%**
- **ORR 85%**



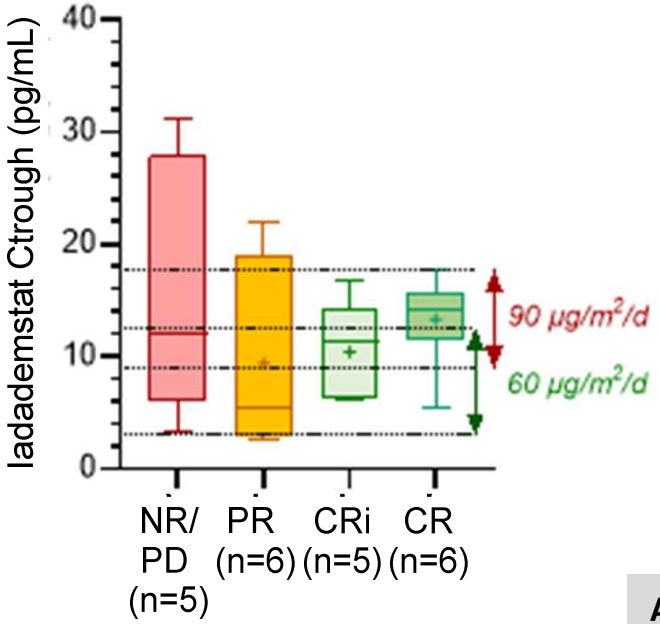
90 µg/m2/day *(n=14)*

- **CR/CRi 65%**
- **ORR 79%**

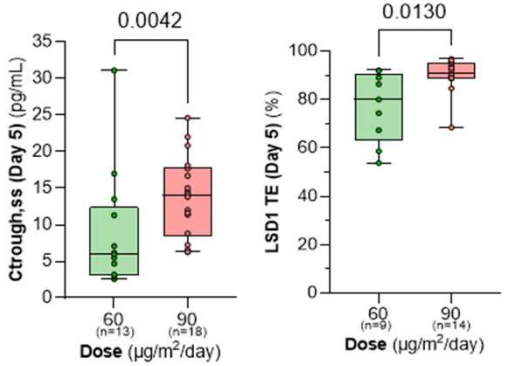


CR CRi PR NR PD

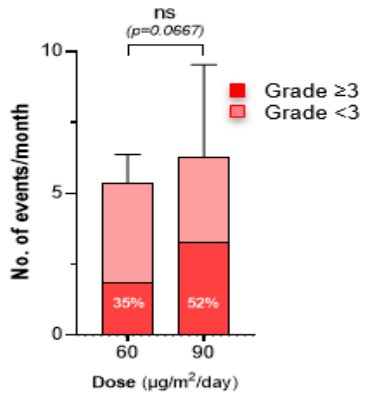
- **Patients with deeper responses show median iadademstat Ctrough levels achieved in the majority of patients in the 90 µg/m²/d cohort**



- **Higher C_{trough} and LSD1 TE are achieved in the 90 µg/m²/d dose cohort**



AEs per dose cohort are not statistically different



Conclusions

- **The combination of iadademstat with azacitidine appears to be safe and effective** for the treatment of newly diagnosed unfit AML patients. **Toxicity is manageable with no significant non-hematological toxicity observed**
- **81% of evaluable patients responded. Responses are rapid, deep and durable**
  - 64% of responses were CR/CRi; 71% of those achieved transfusion independence and 82% were MRD-neg
  - 86% responded by 2 cycles
  - 36% of patients responded for ≥12 months and 30% for ≥18 months
- **The RP2D is established at 90 µg/m2/d iadademstat in combination with SoC azacitidine**.
  - LSD1 target engagement consistently reaches >90%, translating in higher quality of response without compromising safety
  - Median OS is > 1 year (with 50% and 42% of patients surviving after 12 and 18 months respectively)
- **Responses were seen in patients with a diverse array of AML mutations, including those with FLT3 and TP53 mutations and with monocytic AML subtypes**, all known to confer poor prognosis to current SoC treatments
- **Further exploration of iadademstat, in combination with other therapies**, for the treatment of AML and specifically in populations with suboptimal outcomes, **is warranted**.
  - See TIP published abstract #5341 of new FRIDA study with iadademstat+gilteritinib in R/R AML

Acknowledgements

- To the patients and their families who made this trial possible
- To the clinical study teams for their excellent work, especially given the very difficult times during which the study was conducted
- The study is supported by Oryzon Genomics S.A.

Questions to: Olga Salamero, osalamero@vhio.net