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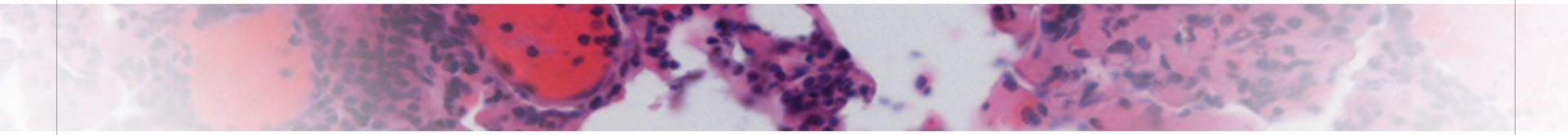

Robust Efficacy Signals in elderly AML Patients treated with Iadademstat in Combination with Azacitidine (ALICE Phase IIa Trial)

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Disclosure

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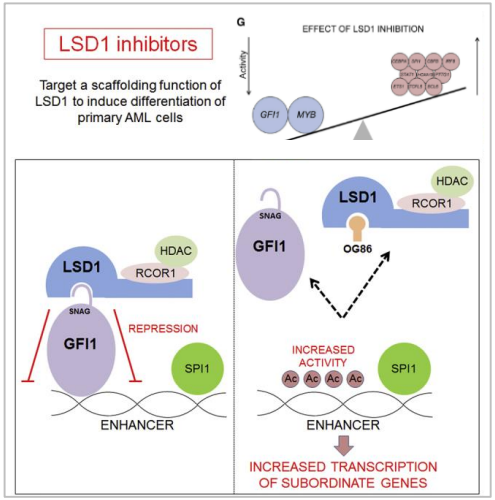
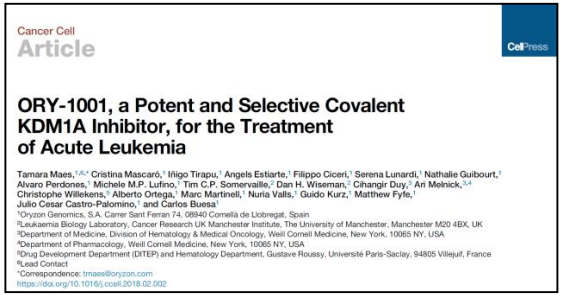
Iadademstat in AML

- LSD1 is a key effector of the differentiation block in MLL leukemia
- LSD1i disrupt the interaction of LSD1 and transcription repressor GFI1, which is bound to a discrete set of enhancers located close to transcription factor genes that regulate myeloid differentiation




Cancer Cell
Article

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

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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

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Iadademstat has demonstrated

- ✓ Highly active and selective LSD1 inhibition
- ✓ Safe and well tolerated in monotherapy
- ✓ Side effects mostly confined to the hematological compartment as predicted by the MoA
- ✓ Strong differentiating activity, especially in MLLr
- ✓ Signs of clinical activity as single agent in patient population (R/R all-in)

ALICE Design and Demographics

A Phase IIa study to evaluate the safety, tolerability, dose finding and efficacy of iadademstat (ORY-1001) in combination with azacitidine in elder*ly* unfit patients with previously untreated AML

- Single arm & Open label. Up to 36 patients to be enrolled.
- 5 active sites in Spain.
- **Primary endpoint**: Safety and tolerability of the combination with hypomethylating agent, azacitidine.
- **Secondary endpoints:** Responses; time to response; duration of response and overall survival.
- **Main Inclusion criteria:**
  - Subjects with AML according to WHO classification, considered ineligible for intensive chemotherapy or who have refused it.
  - Subjects may not have received azacitidine or prior treatment for AML other than hydroxyurea.

Demographic data		
nº of patients		19
Sex	Male	9 (47.4 %)
	Female	10 (54.6 %)
Age	Mean	76
	(Min/Max)	(70/83)
Race	Caucasian	14 (100%)
Weight	Mean (kg)	71.5
	(Min/Max)	(54.5/104)
Height	Mean (cm)	160.3
	(Min/Max)	(150/175)
BMI	Mean	27.9
	(Min/Max)	(20/36.1)

AML Diagnose	
WHO (n=19)	
AML not otherwise categorized	11 (57.9 %)
AML and MDS, therapy-related	6 (31.6 %)
AML with recurrent genetic abnormalities	2 (10.5 %)
FAB (n=15)	
M0 (myeloblastic, minimally differentiated)	3 (20 %)
M1 (myeloblastic, minimal maturation)	3 (20 %)
M2 (myeloblastic, with granulocytic maturation)	5 (33.3 %)
M4 (acutemyelomonocytic leukemia)	3 (20 %)
M5a (monoblastic)	1 (6.7 %)

Preliminary Safety Results

Besides the expected hematological impact, the iadademstat-azacitidine combination appears to be safe and well tolerated

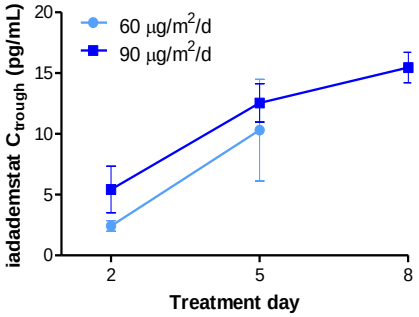
- ✓ 247 AEs affecting all patients were reported as related to the study drugs (ARs), azacitidine or iadademstat
  - Most of them were related to the hematological compartment, mainly neutropenia and thrombocytopenia
  - Only 3 Grade 3-4 adverse reactions were observed in two patients not related with the hematological compartment (asthenia, dysgeusia and weight reduction)
- ✓ Among the 41 serious adverse events reported, only 2 were considered as related to iadademstat (differentiation syndrome and a fatal ICH).
- ✓ Seven deaths have been reported, 5 of them before first bone marrow assessment.

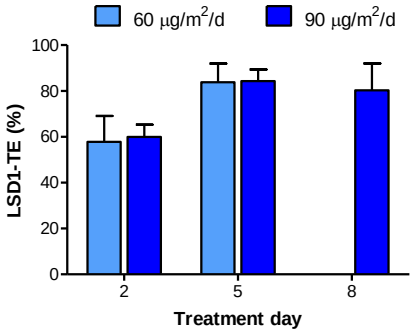
System Organ Class *Preferred Term*	Number of patients (%) Event count			
	Adverse events (AEs)	Adverse reactions (ARs)	Serious Adverse events (SAEs)	Serious Adverse reactions (SARs)
Investigations	**17 (89.5) 228**	**16 (84.2) 151**	**2 (10.5) 2**	**0 (0.0) 0**
Platelet count decreased	14 (73.7) 102	13 (68.4) 78	0 (0.0) 0	0 (0.0) 0
Neutrophil count decreased	13 (68.4) 95	12 (63.2) 70	0 (0.0) 0	0 (0.0) 0
Other	14 (73.7) 31	3 (15.8) 3	2 (10.5) 2	0 (0.0) 0
Gastrointestinal disorders	**17 (89.5) 61**	**10 (52.6) 19**	**1 (5.3) 1**	**0 (0.0) 0**
Constipation	12 (63.2) 27	6 (31.6) 10	0 (0.0) 0	0 (0.0) 0
Nausea	6 (31.6) 9	3 (15.8) 5	1 (5.3) 1	0 (0.0) 0
Other	10 (52.6) 25	3 (15.8) 4	0 (0.0) 0	0 (0.0) 0
General disorders and administration conditions	**16 (84.2) 47**	**6 (31.6) 11**	**5 (26.3) 5**	**0 (0.0) 0**
Asthenia	11 (57.9) 23	5 (26.3) 10	0 (0.0) 0	0 (0.0) 0
Pyrexia	8 (42.1) 11	1 (5.3) 1	3 (15.8) 3	0 (0.0) 0
Others	7 (36.8) 13	0 (0.0) 0	2 (10.5) 2	0 (0.0) 0
Blood and lymphatic system disorders	**16 (84.2) 117**	**7 (36.8) 41**	**6 (31.6) 7**	**0 (0.0) 0**
Anaemia	13 (68.4) 101	6 (31.6) 40	0 (0.0) 0	0 (0.0) 0
Febrile neutropenia	8 (42.1) 9	0 (0.0) 0	6 (31.6) 7	0 (0.0) 0
Other	5 (26.3) 7	1 (5.3) 1	0 (0.0) 0	0 (0.0) 0
Metabolism and nutrition disorders	**15 (78.9) 53**	**4 (21.1) 7**	**0 (0.0) 0**	**0 (0.0) 0**
Hypoalbuminaemia	7 (36.8) 7	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Hyperglycaemia	5 (26.3) 6	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Other	11 (57.9) 40	4 (21.1) 7	0 (0.0) 0	0 (0.0) 0
Infections and infestations	**13 (68.4) 29**	**0 (0.0) 0**	**12 (63.2) 17**	**0 (0.0) 0**
Respiratory tract infection	3 (15.8) 3	0 (0.0) 0	1 (5.3) 1	0 (0.0) 0
Pneumonia	3 (15.8) 3	0 (0.0) 0	3 (15.8) 3	0 (0.0) 0
Other	12 (63.2) 23	0 (0.0) 0	11 (57.9) 13	0 (0.0) 0
Nervous system disorders	**13 (68.4) 22**	**7 (36.8) 11**	**3 (15.8) 3**	**1 (5.3) 1**
Dysgeusia	8 (42.1) 12	6 (31.6) 10	0 (0.0) 0	0 (0.0) 0
Haemorrage intracranial	2 (10.5) 2	1 (5.3) 1	2 (10.5) 2	1 (5.3) 1
Other	5 (26.3) 8	0 (0.0) 0	1 (5.3) 1	0 (0.0) 0
Skin and subcutaneous tissue disorders	**10 (52.6) 13**	**3 (15.8) 4**	**0 (0.0) 0**	**0 (0.0) 0**
Rash	3 (15.8) 4	2 (10.5) 3	0 (0.0) 0	0 (0.0) 0
Other	9 (47.4) 9	1 (5.3) 1	0 (0.0) 0	0 (0.0) 0
Other	**12 (63.2) 36**	**2 (10.5) 3**	**5 (26.3) 6**	**1 (5.3) 1**
Differentiation syndrome	1 (5.3) 1	1 (5.3) 1	1 (5.3) 1	1 (5.3) 1
Other	11 (57.9) 35	1 (5.3) 2	4 (21.1) 5	0 (0.0) 0

A patient with more than one finding in the specific category Preferred Term or System Organ Class was only counted once

Preliminary Pharmacodynamic data

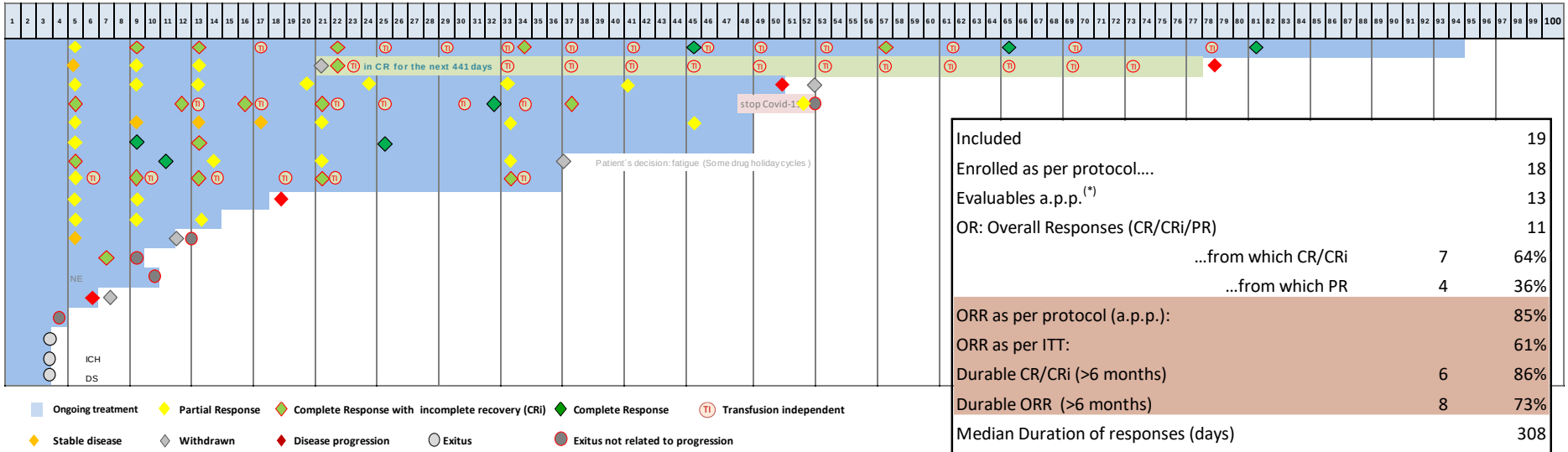
- PK levels revealed similar Ctrough for 90 and 60 µg/sqm/d doses
- PBMC LSD1 Target engagement in leukemia patients is equivalent at both doses
- In the light of the above data and aiming for a better safety and tolerability, the dose of 60 µg/sqm/d was selected as the preferred dose in this patient population





- The results obtained so far suggest that the therapeutic efficacy between the two doses is equivalent, with current ORRs of 85% at 90 µg/sqm/d and 83% at 60 µg/sqm/d

Preliminary Efficacy Results



Included		19
Enrolled as per protocol….		18
Evaluables a.p.p.(*)		13
OR: Overall Responses (CR/CRi/PR)		11
…from which CR/CRi	7	64%
…from which PR	4	36%
ORR as per protocol (a.p.p.):		85%
ORR as per ITT:		61%
Durable CR/CRi (>6 months)	6	86%
Durable ORR (>6 months)	8	73%
Median Duration of responses (days)		308
Current mPFS (of evaluable a.p.p.) (days)		270
TTR (days)		34
Current mOS per eval a.p.p. (days)		269
Transfusion independent on pts >3 months treat.	4	44%
Current longest response (days)		666

(*) a.p.p., as per protocol; Evaluable a.p.p., patients with available BM assesment after C1

- ✓ Robust ORR: 85%(*) a.p.p.; 61% as per ITT; durable responses
- ✓ Growing median duration of response as the study progresses: 308 days
- ✓ Fast time to response: 1 cycle

(*) The results presented at ASH-2020 had an error in the reported ORR data due to one patient being included by mistake in the evaluable a.p.p. population. This error was only detected after uploading the communication to the ASH-2020 IT platform. Due to congress rules, it has not been possible to amend the communication after submission.

Data presented correspond to patient cut-off as per October 30th (New patients included after cut-off not shown). Patient follow up as per November 18th

Conclusions

- Data to-date support that iadademstat has a good safety profile compared with reported data of other anti-leukemic agents
- Toxicity appears to be predictable, manageable and restricted only to those hematologic events expected by the mechanism of action
- With historical response rates of 27% in AML patients receiving AZA monotherapy, the current results are supportive of a significant synergistic effect for its combination with iadademstat
- With different MoA compared to pro-apoptotic BCL2 inhibitors, iadademstat combinations may be an additional therapeutic option for first line and also an alternative for rescue treatment in refractory or intolerant patients treated with venetoclax in first line
- ALICE is still recruiting patients and if the current responses are confirmed, these data warrant further trials with combination therapy with iadademstat