Abstract # TPS7075: Iadademstat in combination with gilteritinib for *FLT3*-mutated Relapsed/Refractory Acute Myeloid Leukemia patients

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Background:

- About **70% of recurring mutations in AML patients target regulators of gene expression**, underscoring the potential of epigenetic therapies to change the natural history of the disease.
- **Iadademstat (iada/ORY-1001) is a specific, oral, potent, covalent inhibitor of the epigenetic enzyme Lysine-Specific Demethylase 1 (LSD1/KDM1A)**.
- In preclinical and clinical studies **iada decreased leukemic stem cell survival and induced macrophage/monocytic differentiation of blasts** (Fig.1).
- ALICE, a Ph2 study of iada in combination with azacitidine (aza), showed impressive rates of remission (CR/CRi) and durable responses in treatment naïve, unfit AML patients without exacerbating the tolerability profile of aza[1].
- Up to **30-40% of AML patients harbor *FLT3* mutations**. Despite improvements in AML therapy, relapsed and refractory **(R/R) cases are frequent and contribute to the death of more than 50% of patients**, particularly in higher risk *FLT3* mut+ AML.
- Use of the FLT3 inhibitor (FLT3i) **gilteritinib as monotherapy for R/R pts resulted in improved outcomes, but the duration of remission achieved is transient and often brief** (CR rate: 20%; EFS: 2.8 months) per the ADMIRAL Ph3 study[2].
- Preclinically, **iada has marked synergy with FLT3i**, including gilteritinib, particularly in *FLT3* wild-type and *FLT3* mut+ AML cells and in derived cell lines resistant to venetoclax, azacitidine and FLT3is[3] (Table 1 & Fig.2).

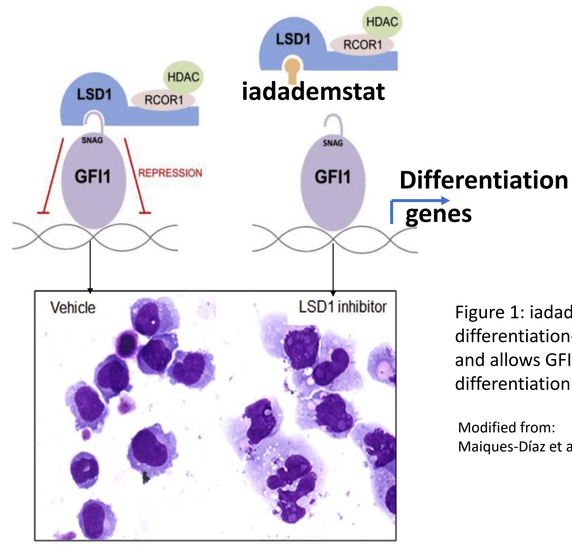

Figure 1: iadademstat blocks the differentiation-repressing RCOR complex and allows GFIi-driven myeloid differentiation

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

Cell line	Mean CI for Fa >0.75	N	Classification[4]
MOLM-13 (FLT3-mut)	0.2	3	Strong synergism
MV(4;11) (FLT3-mut)	0.45	2	Synergism
OCI-AML3 (FLT3-WT)	0.76	2	Moderate Synergism
TF1a (FLT3-WT)	0.29	3	Strong synergism
MOLM-13 VENETOCLAX-r	0.32	2	Synergism
MOLM-13 MIDOSTAURIN-r	0.60	2	Synergism
MOLM-13 AZACITIDINE-r	0.80	2	Moderate synergism

Table 1 & Figure 2: Synergism analysis for the combination of iadademstat + gilteritinib in AML cell lines and in MOLM-13 cell lines resistant to SoC agents (Calcusyn software)

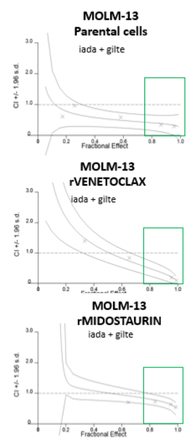

Figure.2

Methods:

Main Eligibility Criteria

- **Adult pts with Relapsed or Refractory *FLT3* mut⁺ AML**
- Refractory or relapsed to first- or second-line treatment
- ECOG 0-2
- Normal liver and renal function
- Patient can swallow oral medications
- Prior frontline midostaurin or sorafenib allowed; prior quizartinib or gilteritinib allowed if no progression on treatment

FRIDA study Ph1b is open to accrual

See note*

ESCALATION:
(up to ~6 pts/ dose level)

	Iadademstat PO 5dON-2dOFF Each week	Gilteritinib PO Every day
Dose level +1	150 µg	120 mg
Starting dose	100 µg	120 mg
Dose level -1	75 µg	120 mg

3+3 design

Pharmacologically active dose/s

EXPANSION
Up to ~ 14 pts/ dose cohort

Dose C1: **Iadademstat + Gilteritinib**

Dose C2: **Iadademstat + Gilteritinib**

Bayesian Monitoring for safety and efficacy

NCT05546580. Contact info: alimon@oryzon.com

Main Endpoints

- Primary:
  - **Safety**
  - **RP2D**
- Secondary:
  - Efficacy: CR/CRh, ORR, OS, EFS, TTR, DoR
  - Transfusion rate
- Exploratory
  - PK/PD
  - MRD
  - Gene mutation status
  - Biomarkers

Statistical Analysis: Bayesian posterior probability safety and efficacy monitoring will be performed periodically for each dose cohort. Bayesian efficacy futility and early stopping boundaries will be applied. Posterior probability criterion (Prob (CR > 0.3) ≥ 0.60) at the end of the study will justify Ph2 development.

Current Status: The study is currently accruing at the following sites: Massachusetts General Hospital; The University of Texas MD Anderson Cancer Center; University of Pittsburgh - Hillman Cancer Center; Oregon Health & Science University; Johns Hopkins Medicine - The Sidney Kimmel Comprehensive Cancer Center and is planned to open in a total of 15 US sites. First cohort in escalation phase is completed with no DLTs so far.

References
[1]Salamero et al., Oral presentation at ASH 2022; [2]Perl, et al., NEJM 2019; [3]Sacilotto et al., Abstract 190 at the 34th EORTC-NCI-AACR symposium 2022; [4]Chou TC, Pharmacol Rev, 2006, 58(3):621-681.

FLT3 mut+: fms-like tyrosine kinase 3 mutated; ECOG: Eastern Cooperative Onccology group; HSCT: Hematologic stem-cell transplant; PO: Per os (oral); RP2D: Recommended Phase 2 dose; CR: Complete Remission; CRh: Complete Remission with partial hematologic recovery; ORR: Overall Response Rate; OS: Overall survival; EFS: Event-free survival; TTR: Time To Response; DoR: Duration of Response; MRD: Measurable Residual Disease; PK: Pharmacokinetics; PD: Pharmacodynamics