Dose finding study of ladademstat in combination with azacitidine in newly diagnosed Acute Myeloid Leukemia: The ALICE study

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Abstract

Background: Iadademstat is a potent, selective, oral inhibitor of both the enzymatic and scaffolding activities of the transcriptional repressor Lysine-Specific Demethylase 1 (LSD1 aka KDM1A). In a Phase 1 study in R/R AML iadademstat monotherapy induced myeloblast differentiation with manageable toxicity. This, together with strong preclinical synergy observed with azacitidine in AML cell lines, provided the rationale to study this combination clinically.

Methods: The completed Phase 2a ALICE study (EudraCT 2018-000482-36) enrolled unfit ND AML adult patients with ECOG 0-2. Two doses of iadademstat (60 μg/m^2/d (n=17) or 90 μg/m^2/d (n=19) PO, 5 days ON, 2 days OFF weekly) were evaluated with azacitidine (75 mg/m^2 SC, 7 out of 28 days. Primary objectives were safety (SAS population) and RP2D; secondary objectives included efficacy in the evaluable (EAS) subpopulation.

Findings: Between November 12, 2018 and September 30, 2021, 36 patients with ND AML were accrued in the study; median age was 76 [Interquartile Range (IQR) 74-79] years, all Caucasian with 50% sex distribution, and all with intermediate or adverse risk AML. The median follow-up was 22 months [IQR 16-31]. The most frequent (>10%) G3/4 AEs considered related to treatment were decreases in platelet (25 patients, 69%) and neutrophil (22 patients, 61%) counts and anemia (10 patients, 28%). Three patients experienced treatment related serious AEs (one G5 intracranial hemorrhage, one G3 differentiation syndrome and one G3 febrile neutropenia). The ORR in the evaluable patient subpopulation (n=27) was 82%. CR/CRi rate was 52% (14 patients) of whom 10 out of 11 evaluable for MRD achieved negativity. Responses were rapid (86% by the

second assessment) and durable (30% for ≥18 months). In the ITT population (n=34) ORR was 65%. Based on safety, PK/PD and efficacy, 90 μg/m^2/d iadademstat with azacitidine was the RP2D.

Interpretation: The combination of iadademstat and azacitidine has a manageable safety profile and produces robust, rapid, and durable responses in ND AML patients, including those with high-risk prognostic factors.

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Keywords: iadademstat; azacitidine; acute myeloid leukemia; LSD1; epigenetics

Introduction

Acute myeloid leukemia (AML) is a heterogenous disease with a broad spectrum of cytogenetic and molecular abnormalities. The highest incidence and lowest survival rates occur in the elderly, where the option for potentially curative treatments is limited. In this unfit population, previously reported response rates to hypomethylating agents (HMA) in monotherapy are less than 30%.[1,2] Emerging targeted therapies have improved overall survival (OS) for some specific subgroups, however outcomes remain poor. Combinations of venetoclax with HMA are the standard of care (SoC) for unfit patients. Azacitidine plus venetoclax showed an OS of 14.7 months and a complete remission or complete remission with incomplete hematological recovery (CR/CRi) rate of 66% in the VIALE-A trial.[3] Nevertheless, the great majority of patients relapse, with only 30% alive at 3 years.[4] AML with mutations in *TP53*, the *RAS* pathway, or *FLT3*, along with the monocytic subtype, are identified as particularly resistant to this combination.[5-7] Patients with *TP53* mutations have consistently poor outcomes with median OS of only 5-6 months.[8] Overall, 90% of unfit AML patients relapse after first line treatment, due to the persistence of leukemic stem cells (LSCs) and/or their clonal evolution, emphasizing the need to develop new strategies targeting LSCs to improve outcomes.[3,9]

One such investigational strategy is iadademstat (aka ORY-1001), an oral, potent, and selective inhibitor of the Lysine-Specific Demethylase 1 (LSD1 aka KDM1A) enzyme.[10] LSD1 works as a master regulator of transcription by: 1) removing mono- or dimethyl groups from Histone 3 lysine 4 (epigenetic eraser); and 2) serving as a scaffold in assembly of multiprotein transcriptional complexes repressing expression of genes governing cell differentiation and stemness. In myeloid cells, LSD1 provides an essential scaffold for assembly of the GFI1b/CoREST transcriptional repressor complex, which regulates hematopoietic differentiation. Iadademstat-induced shifts in gene expression from a

proliferative to a differentiation signature have been demonstrated preclinically in AML cells,[10] and clinically in a Ph1 monotherapy study in relapsed/refractory (R/R) AML.[11] In that study, 27 patients were treated with iadademstat per os (PO) on days 1 to 5 (5-220 μg/m^2/d) weekly. The 140 μg/m^2/d dose was determined as the recommended phase 2 dose (RP2D) for monotherapy, and the treatment proved to be both safe and effective in decreasing blast percentages in peripheral blood (PB) and bone marrow (BM), inducing blast cell differentiation, and achieving CRi in one patient.[11]

Iadademstat shows preclinical synergistic activity with a broad category of agents effective for the treatment of AML including azacitidine and decitabine.[10]

This paper reports the results of the multicenter, open-label, ALICE study investigating the combination of iadademstat and azacitidine for the treatment of newly diagnosed (ND) adult AML patients who were not candidates for intensive chemotherapy.

Methods

Study design and participants

ALICE was designed as an open label study to investigate the safety, RP2D and preliminary efficacy of iadademstat in combination with azacitidine for the treatment of patients 18 years or older, ECOG 0-2, with ND AML (according to WHO criteria, with blast counts of at least 20% in BM and/or PB) considered unfit per investigator assessment or refusing standard chemotherapy and with a life expectancy of at least 3 months in the opinion of the investigator. In the course of the study seven amendments were made but only one (amendment 4) affected eligibility, specifically to include patients ≥ 18 years unfit for intensive chemotherapy and clarify prior treatments allowed. Full eligibility criteria, and additional methods are available in the Supplemental Material

Six hospitals in Spain (details in Supplemental Material) conducted the study in accordance with the ethical principles of the International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki, and all other applicable local regulatory requirements. The ALICE study protocol, the subject information sheet, and the informed consent form were reviewed and approved by the CEIm of Hospital La Fe, Valencia. All protocol amendments were also submitted to and approved by the same institutional review board (IRB) prior to implementation.

Written informed consent was obtained for each participant subject prior to any study-specific procedures being performed and to collect any study data.

At the time the study initiated and until September 2023 the SoC treatment for this patient population in Spain was azacitidine monotherapy.

Procedures

The study started with a 3+3 dose-finding phase (starting dose 90 μg/m^2/d with de-escalation to 60 and escalation up to 140 μg/m^2/d) of iadademstat PO given 5-days ON, 2-days OFF weekly[11] with azacitidine SC (75 mg/m^2) 7 days in a 28-day cycle, followed by an expansion phase. Iadademstat was provided in aqueous solution (20 μg of iadademstat free base per ml) in oral syringes loaded with the daily dose. Treatment continued until disease progression or unacceptable toxicity. Criteria for removal from the study included: disease progression, intercurrent illness, unacceptable toxicity, withdrawal of consent, non-compliance, major eligibility deviation, pregnancy or investigator's decision. Safety assessments consisting of monitoring and recording all adverse events (AEs), including serious adverse events (SAEs) and non-serious AEs of special interest were assessed continuously during the study. Laboratory measurements (biochemistry, hematology and coagulation) were assessed weekly in the first cycle and on the first day of every subsequent cycle. Urinalysis was

assessed during screening. Details on criteria for dose reductions and interruptions can be found in the protocol (section 5.9 and 5.10) provided in the Supplemental Material.

Outcomes

Primary objectives of the study were safety and establishing the RP2D. Safety endpoints included DLTs during first cycle (up to 42 days after starting treatment), AEs and changes from baseline in the patient's vital signs, weight, and clinical laboratory results as per CTCAE v 5·0.[12] See Supplemental Material for full dose limiting toxicity (DLT) criteria. Of note, hematologic DLT was defined as any treatment-related clinically significant G4 neutropenia or thrombocytopenia persisting to Day 42 of a cycle or later in the absence of residual disease.

Secondary objectives included evaluation of the treatment efficacy and pharmacodynamic (PD, measured as LSD1 target engagement (TE)) and pharmacokinetic (PK) determinations. Efficacy endpoints included responses (as reported by the investigator according to ELN 2010[13]) and presented here as Overall Response Rate (ORR=CR+CRi+Partial Response (PR)), Time to Response (TTR), Duration of Response (DOR), Event Free survival (EFS), and OS, all detailed in the Supplemental Material. Hematologic improvement (HI) although specified as an endpoint in the protocol is not reported here because there are no standardized criteria in AML.

In patients achieving remission, measurable residual disease (MRD) was investigated as an optional exploratory endpoint. Additionally, ad-hoc analyses of response per most recent ELN2022 criteria and Transfusion Independence (TI) as well as post-hoc efficacy in frequently represented subpopulations with recurrent AML mutations are also presented.

Statistical Analysis

There is no formal hypothesis testing in this study. No formal sample size estimation was performed. The assumption concerning reasonable sample size was based on the dose-escalating scheme applied

for determination of DLTs and the RP2D. Approximately 36 patients were planned to be enrolled in this study. Exact sample size could not be specified given the dynamic features of dose escalation. A Safety Monitoring Committee (SMC) was responsible for the decisions related to dose escalation. Prespecified populations as per the Statistical Analysis Plan (SAP): (i) Safety Analysis Set (SAS) defined as all patients who received at least one dose of the study treatment; (ii) Dose Limiting Toxicity (DLT) Analysis Set (DAS) defined as patients evaluable for the determination of dose escalation who met either one of the following criteria: experienced a DLT during the first cycle (28 to 42 days) (DLT evaluation period) or completed the DLT evaluation period and received at least 85% of planned doses; (iii) Full Analysis Set (FAS, equivalent to ITT) defined as all patients who met eligibility criteria and signed the Informed Consent; (iv) Efficacy Analysis Set (EAS) defined as all patients who met eligibility criteria, have been treated, have baseline disease assessment and at least one available post baseline efficacy assessment; (v) PK Analysis Set (PKAS): defined as all PK-evaluable patients for whom at least one plasma concentration data is available; (vi) PD Analysis Set (PDAS) defined as all PD-evaluable patients or whom at least one PD data point is available. Statistical analysis was conducted following the principles as specified in International Conference on Harmonization (ICH) Topic E9 (CPMP/ICH/363/96). The significance level (two-sided) will be α=0.05 for all tests. All report outputs were produced using SAS® version 9.4 or higher in a secure and validated environment. Point estimates of binary endpoints were provided along with the corresponding two-sided 95% CI using the Clopper-Pearson method. Continuous scores or values, change from baseline and % change from baseline were summarized with non-missing values, mean, SD, 95% CI of mean (using normal approximation), median, range and interquartile range. Time to event data were summarized using the K-M method. The number and proportion of events, median survival time and survival rates, with corresponding 95% Cl were calculated. These CI was calculated

based on Greenwood ‘s formula. All analyses were performed by dose cohort and overall patients. This study was registered as EUDRACT #2018-000482-36.

Role of funding source

Oryzon Genomics was the sponsor of the study. The Translational and Clinical team at Oryzon Genomics, in collaboration with the study investigators contributed to the study design, data collection, data analysis, and interpretation and writing the report, as reflected in the authorship. The first and last authors (OS and PM) are investigators with full access to all the data and are ultimately responsible for submission of the manuscript.

Results

Between November 12, 2018 and September 30, 2021, 36 patients with ND AML unfit as per investigator assessment were accrued in the ALICE trial, categorized according to the WHO 2017 classification[14]. Median age was 76 years [IQR 74-79], with 20 (56%) ≥75 years old; all were Caucasian with 50% balance between males and females. ELN 2017[15] cytogenetic risk was either intermediate in 13 (36%) or adverse in 23 (64%). Thirty-one patients (86%) required transfusions and the majority of patients presented with G3/G4 neutropenia (26, 72%) or thrombocytopenia (22, 61%). The mutational profiles demonstrated the characteristic heterogeneity observed in AML. The most frequent mutations and other demographic details are presented in Table I.

Figure I shows the CONSORT diagram for the ALICE study. Out of 36 patients treated (Safety Analysis Set or SAS), 34 were enrolled per protocol (according to eligibility criteria/ITT) and of those, a total of 27 patients underwent baseline and at least one BM assessment after screening and were evaluable for efficacy constituting the Efficacy Analysis Set (EAS). Seven patients died before assessments could be performed: three with intracranial hemorrhages (ICH) (one traumatic) and four

due to infection (one COVID). At database lock (one year after last patient in), nine patients were alive and as of February 2024, five patients remain alive, with three continuing treatment (and in CR) under compassionate use. Reasons for discontinuation are summarized in Table S1: 11 patients (31%) because of death, 12 (33%) due to progression of disease, five (14%) per investigator decision, four (11%) per patient decision, three (8%) transitioned to compassionate use program, and only one (3 %) due to treatment toxicity (platelet count decrease).

The study initiated by recruiting patients at the starting dose of 90 µg/m^2/d. After six patients were dosed with no DLTs and since TE was already approximately 90%, the decision was made to expand enrollment at that dose without need to further escalate. After a total of 10 patients accrued, antileukemic activity was encouraging but because PB count recovery was prolonged, the Safety Review Committee decided to open the 60 µg/m^2/d cohort to explore whether a lower iadademstat dose would facilitate blood count recovery. Seventeen patients were subsequently enrolled in the 60 µg/m^2/d cohort. However, prolonged cytopenias were still observed in some patients and more importantly, the proportion of early remissions was lower. This triggered the reopening of the 90 µg/m^2/d cohort and the last 9 patients were enrolled in this cohort up to the 36-patient target accrual. There were no reported DLTs during the DLT period. All patients who received study drugs experienced G ≥3 AEs (Table S2), primarily cytopenias. Only 3 (8%) SAEs were reported: ICH (G5), febrile neutropenia and differentiation syndrome (both G3). Table II (and parallel Table S3) provide the list of all AEs related to iadademstat +/- azacitidine in the ALICE study.

The most common iadademstat-related AEs occurring in ≥10% of the patients were platelet count decrease (25 patients, 69%) and neutrophil count decreased (22, 61%), anemia and dysgeusia (15 each or 42%), constipation and asthenia (nine each or 25%), nausea (six, 17%) and decreased appetite (four, 11%) (Table II).

Among the patients who experienced iadademstat-related AEs, 15 (42%) resulted in treatment delays, 10 (28%) in treatment holds, seven (20%) in dose reductions and only two (6%) in treatment discontinuation (one case of G5 intracranial bleeding, and one case of G4 thrombocytopenia) (Table S2). A list of all AEs, irrespective of relatedness, leading to iadademstat discontinuation can be found in Table S4.

Overall, there were 12 AEs leading to deaths during the treatment period (infections in eight patients and bleeding in three patients: two reported as ICH and one as post-traumatic subarachnoid hemorrhage). Only one death, due to ICH, was deemed by the investigator as possibly related to treatment (90 μg/m^2/d cohort). One additional death was reported as an AE without further characterization (Table S5).

For the 36 (SAS)/27 (EAS) patients, the median number of cycles received was 3·0 [IQR 2·0 -11·5] / 5·0 [IQR 3·0 -13·0] respectively, and the median duration of treatment was 95·0 days [IQR 53·0 - 348·5] (minimum of 15 and maximum 1,109 days) / 156·0 days [IQR 82·0 - 441·0] (minimum of 27 and maximum 1,109 days), respectively. This translates for the EAS to a median ratio of 31·2 days/cycle which is 3·6 additional days over the intended 28 day/cycle. The mean/median relative dose intensity in the EAS (meaning percentage of iadademstat given relative to assigned intended treatment) was 81% (SD 11·7) and 83% [IQR 7-90]. Most of the patients experienced dose interruptions (n=23) or delays (n=19), but dose reductions were uncommon (n=6) (85%, 70% and 22%, respectively). Median relative dose intensity was numerically lower in the 90 ug/m^2/d cohort as compared to the 60 ug/m^2/d cohort (75% [IQR 71- 88] vs 84% [IQR 83-90]), driven primarily by a higher (almost double) rate of dose reductions (29% vs 15%) as allowed per protocol after clearance of leukemia. Azacitidine dose was reduced per label when required.

Responses per investigator assessment (ELN 2010) of the 27 patients in the EAS are shown in Table III. Twenty-two patients responded (82%): nine were CR (33%), five CRi (19%), and eight PR (30%). Samples from 11 of the 14 patients achieving CR/CRi were available for MRD, and 10 (91%) achieved MRD-negativity.

Median time to first and best response was 64 days (95% CI 32, 80) and 105 days (95% CI 67, 162) respectively. Median duration of response was 269 days (95% CI 86, 529) (Table III), and the 18-month DoR rate was 30% (95% CI 12, 50). Figure II shows the EAS swimmer plot. Of the five patients who were deemed to have had no response (NR) by the investigators, four had stable disease (SD) and only one experienced progressive disease (PD) at first assessment.

Ten out the 22 patients (or 46%) who were transfusion dependent at treatment initiation reached transfusion independence at a median 6 months (190 days, 95% CI 130, 225) after treatment initiation. With a median follow-up of 22 months [IQR 16-31], the median EFS was 9 months (271 days, 95% CI 103, 358). The median OS was 11 months (338 days, 95% CI 137, 873), with 6, 12, and 18-month survival rates of 67% (95% CI 46, 81), 48% (95% CI 29, 65) and 35% (95% CI 18, 53), respectively (see KM graphs in Figure S1).

In the total 36 patient SAS population, the percentage of responses was 61% (n=22), with 39% (n=14) achieving CR/CRi and 22% (n=8) achieving PR. A total of 9 patients (25%) died before the first BM assessment. Median OS in the SAS was 8 months (175 days, 95% CI 96, 408), with 6, 12, and 18-month survival rates of 50% (95% CI 32·9, 64·9), 36% (95% CI 21, 51) and 27% (95% CI 13, 42).

Data for the most relevant subgroups in the EAS are summarized in Table S6. Among the patients achieving CR (n=9) and CR/CRi (n=14), the median DoR was 631 days (95% CI 216, NE) and 406 days (95% CI 155, NE) and the 18-month DoR rate was 56% (95% CI 20, 81) and 40% (95% CI 15,

65), respectively. The median OS for the CR subpopulation was NE (95% CI 271, NE) with an 18-month OS rate of 52% (95% CI 16, 79); median OS for the CR/CRi subpopulation was 471 days (95% CI 271, NE) and 18-month OS rate was 48% (95% CI 20, 71).

Among the eight patients with AML FAB of myelomonocytic/monocytic subtype (M4/M5), seven (88%) responded (and all six with CR/CRi were MRD negative). This subpopulation had sustained responses (median NE; 95% CI (16, NE) with an 18-month DoR rate of 67% (95% CI 20, 90) and 18-month survival rate of 54% (95% CI 13, 83).

Figure S2 displays the mutational profile of all patients in the EAS and the responses achieved as well as percentage of responses in the most frequent mutational subgroups. Responses were observed in patients with a very diverse array of mutations. Of note, six (75%) of eight patients with mutated *TP53* responded with a median DoR of 239 days (95% CI 155, NE) and a median OS of 305 days (95% CI 55, 471), and five patients achieved CR/CRi. Also, all of the seven patients harboring mutation/s in the RAS pathway (*N-, K-, H-RAS, B-RAF, PTPN11* or *NF1*) responded with median OS of 467days (95% CI 137, NE). Patients harboring *DNM3TA* (n=7), *NPM1* (n=4) and *RUNX* mutations had 100% response rates, mostly CR/CRi (Table S6).

Additional ad-hoc efficacy analysis per ELN 2022 criteria shows that a response was achieved in 14 patients (52%) in the EAS population with nine CR, three CRh, and two MLFS; therefore 44% (12 patients) achieved high quality (CR/CRh) responses. All evaluable responses except one CRh were MRD negative (overall 91%). Table S62 shows further details of this ad-hoc analysis in all subpopulations.

Plasma trough concentrations showed that iadademstat accumulated in the plasma after repeated dosing, with a mean accumulation at Day 5 vs. Day 2 of 3·1 (95% CI 2·3, 3·9) pg/mL for patients treated with 60 μg/m^2/d, and of 5·0 (95% CI 3·6, 6·3) pg/mL for patients treated with 90 μg/m^2/d.

Mean plasma concentrations increased in an approximately dose-proportional manner comparing patients treated at both doses, and the differences in exposure between doses were statistically significant at day 5 (60 μg/m^2/d - 8·7 (95% CI 3·9, 13·6) pg/mL vs 90 μg/m^2/d - 13·6 (95% CI 10·4, 16.7] pg/mL; p=0·013) (Table S7 and Figure S3B).

Iadademstat pharmacodynamics was evaluated in terms of LSD1 target engagement (TE) in peripheral blood mononuclear cells (PBMCs).[16] LSD1 engagement could be detected on day 2, reaching the maximum effect on day 5. Differences observed between doses were statistically significant on day 5, with a mean LSD1 TE for the 60 μg/m^2/d cohort of 77% (95% CI 66·0, 88·2) and 91.7% (95% CI 89·3; 94·1] for patients treated with 90 μg/m^2/d; p=0.017 (Table S8 and Figure S3C).

Analysis of the best response rate in each study cohort revealed that the 90 μg/m^2/d generated deeper responses (64 % CR/CRi vs 39 % in the lower dose cohort), as assessed per the investigators (Figure S3A). Exposure/response analysis showed that the majority of patients reaching CR had iadademstat Ctrough values within the 25-75% percentile range achieved by the 90 μg/m^2/d dose while most of the CRi and PR responders fell within the same percentiles as the 60 μg/m^2/d dose (Figure S3D). Based on the statistically significant differences in PK and TE achieved in the higher versus the lower iadademstat dose cohort, the correlation between Ctrough and better response, and the lack of statistical difference between the two cohorts in the number of AEs per month, the 90 μg/m^2/d dose of iadademstat was selected as the RP2D in combination with azacitidine (Figure S3).

Discussion

To date, iadademstat has been administered to more than 130 oncology patients in Ph1 and Ph2 trials, showing manageable toxicity and encouraging preliminary activity. In this report, iadademstat was

tested at two different doses, in combination with azacitidine administered according to label. At the selected RP2D of 90 μg/m^2/d the combination generated no new safety signals and promising antileukemic activity.

The rates of AEs, particularly cytopenias, were high in this trial wherein the majority of patients had grade 3-4 cytopenias at baseline, as expected in AML and exacerbated when combining with azacitidine. Thirty-day mortality in the study was 11% (four out of 36 patients: two cases of ICH, one COVID infection and one PD) which is within the expected early mortality range for low intensity AML regimens in the current era (6 to 15%).[17,18] Overall, there were three cases of fatal ICH, all in patients who entered the study with profound thrombocytopenia (2 contributing to the early mortality and one occurring later as a consequence of trauma). It is worth noting that ICH is the second most common cause of early death in AML, reported at frequencies up to 10%.[19,20]

Grade 3 or higher treatment-related AEs occurred in 97% of patients and were generally attributed to both study drugs, but only three were considered serious events, and only one (an ICH) was lethal and possibly related to iadademstat by the investigator. The most frequent G3/4 treatment related AEs were myelosuppression, particularly affecting platelet (69%) or neutrophil (61%) counts, which may be somewhat higher than expected for azacitidine alone and may reflect a contribution of iadademstat. Thrombocytopenia is a known on-target toxicity of LSD1 inhibitors due to reversible suppression of megakaryocyte maturation. However, once leukemia was controlled in this study, cytopenias were mild and transient. Accordingly, only two patients discontinued treatment because of AEs (one case of platelet count decrease and one case of ICH). The protocol allowed for reductions in iadademstat and azacitidine doses once patients had achieved remission, at the investigator's discretion. The combination appears tolerable over long-term administration, as three patients remain on treatment through compassionate use (and in CR) for three to four years after initiating treatment.

ORR was 82% (22 out of 27 patients in the EAS). Sensitivity analysis of ORR in the SAS population was 61% for all 36 patients enrolled and 65% in the ITT population (34 patients who met eligibility criteria). Overall, and within the limitations of comparing dose finding trials with large Phase 3 trials, remission rates to the azacitidine/iadademstat combination in this trial appear to be higher than would be expected for azacitidine monotherapy. Of note, the CR/CRi rate in this trial was 52% in the EAS and 41% in the ITT. For comparison, CR/CRi rates of 28%, 28%, and 27% for the ITT azacitidine arms were reported in the AML-001,[1] VIALE A[3], and Monarch[21] trials. Although inclusion requirements for each of these large trials differed, the rates of CR/CRi are very similar, establishing a baseline for expected responses to azacitidine monotherapy.

The time to reach hematological response is important for patient safety in AML. Most of the responses in the ALICE trial occurred rapidly (87% by the second assessment) and 36% lasted ≥12 months (30% for ≥18 months).

The CR/CRi responses achieved in this study were generally deep, as determined by the high rate of MRD negativity (91% in the evaluable samples) which is associated with improved survival.[22,23]

Achieving transfusion independence (TI) provides patient benefit and economic savings. In this study, 46% of transfusion-dependent patients became independent and remained transfusion free for a median duration of about six months.

This dose finding study was not powered to assess OS, was single-armed and was compromised by the COVID pandemic (9 patients contracted COVID, which caused death in 3 of them). However, with these considerations, the median OS in the EAS was 11·1 months with 6, 12, and 18-month survival rates of 67%, 48%, and 35%, respectively.

Iadademstat dosing at the higher dose of 90 μg/m^2/d generated numerically more deep responses (CR/CRi) (64 %) than did 60 μg/m^2/d dosing (39 %) without significantly increasing toxicity.

Therefore, considering all safety, PK/PD, and efficacy data, the 90 μg/m^2/d dose iadademstat was selected as the RP2D in combination with azacitidine.

Bearing in mind the small number of each type of AML-defining mutations in this trial, the anti-leukemic activity of the combination of iadademstat and azacitidine appears to be mutation-agnostic. Of note are the responses in specific subgroups: iadademstat plus azacitidine generated a 100% CR/CRi rate in M5 AML (a population primary-refractory to venetoclax/azacitidine[6]) with 100% MRD-negativity. AML with TP53 mutations in combination with complex karyotype and/or high VAF (variant allele frequency) achieved a CR/CRi rate of 63%, with a DoR of 7·9 months and a median OS of 10 months. Responses in leukemias harboring other poorer-prognosis mutations including *RAS*-pathway and *RUNX1* were also encouraging.

In preclinical studies, strong synergy of iadademstat with venetoclax (as well as azacitidine) has been observed, raising the possibility that adding iadademstat to the current AML SoC could provide additional anti-leukemic activity, and perhaps better address those subcategories of AML with poor or no responses. Dose-finding studies for such a triplet combination will commence shortly. In addition, the synergy of iadademstat in combination with FLT3 inhibitors, seen in preclinical studies, is currently being explored in an ongoing clinical trial combining iadademstat with gilteritinib in patients with R/R FLT3-mutated AML (FRIDA, NCT05546580).

Limitations of this study included those common to dose-finding studies, such as small patient numbers limiting statistical analyses, open label design, lack of racial diversity among patients and no control arm for comparisons.

In summary, the combination of iadademstat with azacitidine showed substantial anti-leukemic activity, with deep responses, in ND AML patients and with a manageable safety profile, therefore potentially expanding future treatment options for this disease.

Supplemental Material

Refer to the Supplemental Material package to access additional information.

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Appendix

Prior Presentation:

Part of this data or preliminary related data was presented at the 61st (2019), 62nd (2020), 63rd (2021) and 64th (2022) Annual Meetings of the American Society of Hematology, and at the European Hematology Association meetings in 2019, 2020, 2021 and 2022.

Data sharing:

The protocol will be available upon request. At this time, we will not be able to share individual patient level data outside of the participating institutions.

Contributors statement:

Conception and design: OS, JX, CB, PM

Provision of study materials or patients: All authors

Collection and assembly of data: All authors

Data analysis and interpretation: AL, DVF, OS, AM, JX, CB, SG, MIA, TS, PM

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Critical revision for important intellectual content: All authors

Final Approval of Manuscript: All authors reviewed and approved the final version of the manuscript.

Academic authors who accessed and verified the underlying data: OS, PM

Conflict of Interests

OS: none

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Research in Context

Evidence before this study:

Acute Myeloid Leukemia (AML) is a blood cancer predominantly affecting older adults, with a high fatality rate. We searched MEDLINE and PubMed databases with the terms "acute myelogenous leukemia OR acute myeloid leukemia", for clinical trials published 10 years before 30 September 2011. The output shows that many investigational agents have been tested in this disease but until recently, few agents have been approved or demonstrated to show clinical relevance. Older drugs that continue to be used include hypomethylating agents (azacitidine and decitabine), anthracyclines, and cytosine arabinoside, sometimes in new formulations. Although several novel targeted agents have been approved for AML in the last five years, such as IDH1, IDH2 and FLT3 inhibitors, the disease is characterized by genetic and epigenetic heterogeneity, thus limiting the applicable populations for targeted therapeutics. The Bcl-2 inhibitor venetoclax, in combination with azacitidine, has increased the survival of a broad spectrum of patients with AML. However, this approach does not appear to be curative, with most patients not surviving more than 18 months, and some sub-populations showing resistance.

Added value of this study:

New agents are needed for the treatment of AML. Ideally, such agents would have broad activity across mutational sub-types of the disease. In addition, a novel mechanism of action, which might complement, or synergize with, the activity of existing anti-leukemic agents (or evade the resistance arising from AML epigenetic and genetic clonal evolution after exposure to current therapies), would be desirable. Lysine-specific Demethylase 1 (LSD1), an epigenetic enzyme regulating histone H3 methylation, serving as an essential scaffold for transcriptional repressor complexes controlling myeloid differentiation, and a critical mediator preserving leukemic stem cell "stemness" represents a novel target in AML. This study demonstrates activity of a highly-potent and -specific inhibitor of LSD1, iadademstat, in combination with

azacitidine, in the treatment of newly-diagnosed AML in adults. Within the limitations of a small single-arm study, the combination induced a high proportion of responses, the majority of which were very deep, as assessed by residual disease negativity, and were durable, with predictable and manageable safety. Responses were also seen across the entire adverse prognostic mutational landscape.

Implications of all available evidence:

Targeting LSD1 in myeloid malignancies may represent a new therapeutic approach, with a fully novel antileukemic mechanism of action in myeloid malignancies. Ongoing development of iadademstat in combination with current standards to confirm its activity may provide a new and novel agent for the treatment of AML.

Figures

Figure I. CONSORT diagram

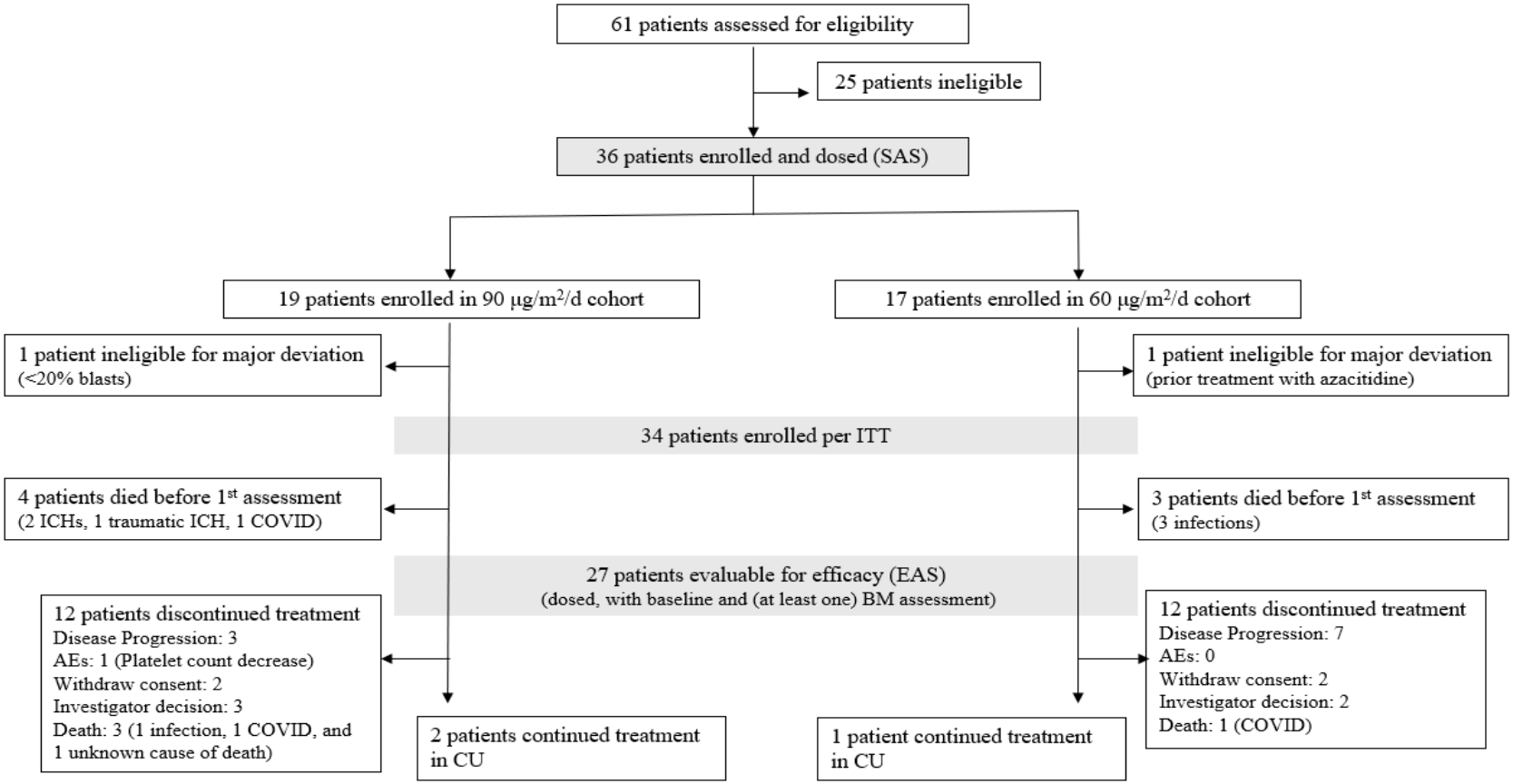

Figure I. CONSORT diagram. SAS: Safety Analysis Set; EAS; ITT: Intent-to-treat; Efficacy Analysis Set; ICH: Intracranial hemorrhage; AEs: Adverse Events; CU: Compassionate use program. Out of the 3 deaths in the EAS 90 µg/m2/d cohort, one occurred in a patient who achieved CR, but then relapsed and died from COVID, the other 2 patients achieved SD (stable disease) per investigator criteria. The COVID death in the 60 µg/m2/d cohort was in a patient who achieved PR by investigator criteria. As of February 2024, 5 patients remain alive: four in the 90 µg/m2/d cohort (2 in CU with 876 and 998 days on treatment; and 2 off treatment 1,867 and 1,853 days after treatment initiation) and one in the 60 µg/m2/d cohort (in CU, with 1,449 days on treatment)

Figure II. Swimmer Plot showing responses per Investigator in the EAS

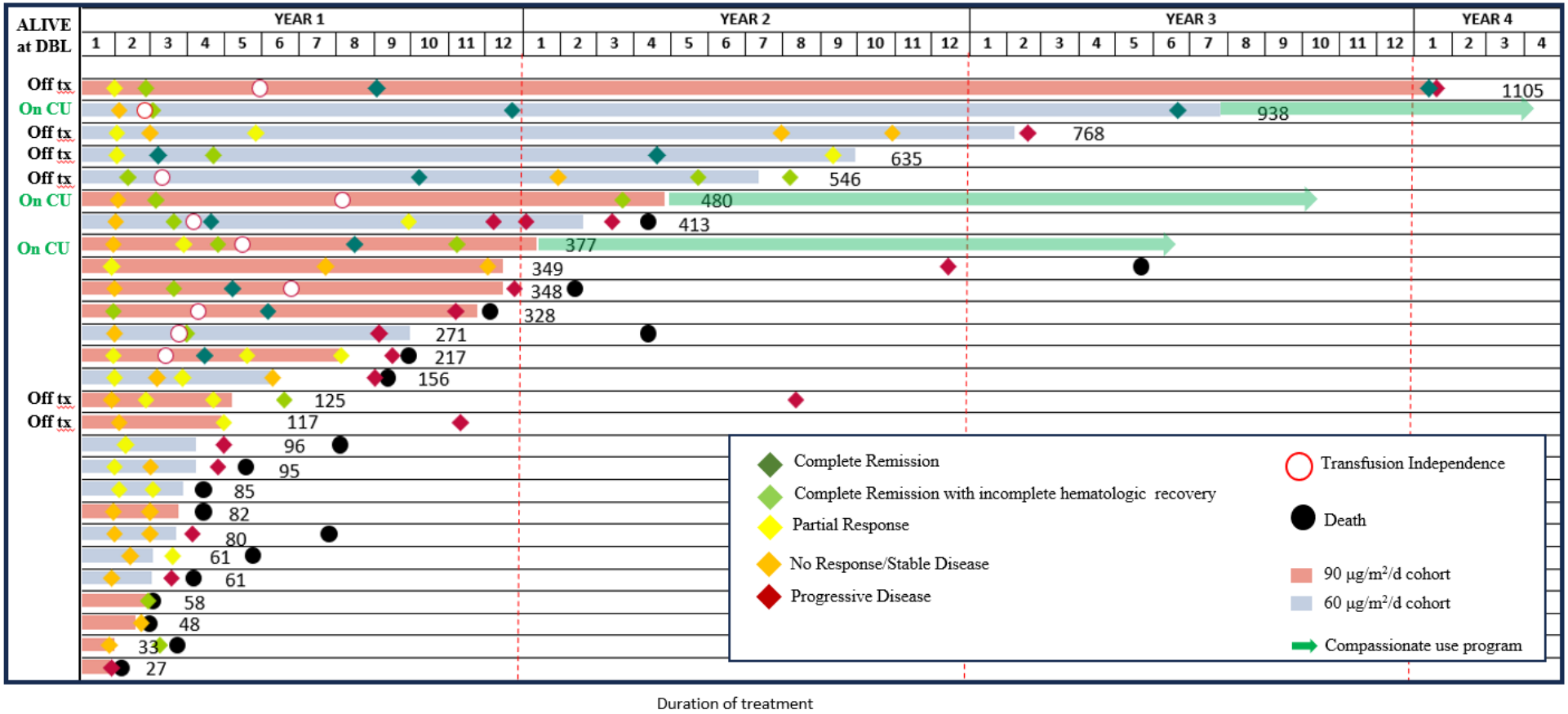

Figure II. Swimmer Plot showing responses per Investigator assessment in the EAS. The horizontal bars (blue for the 60 µg/m2/d cohort and red for the 90 µg/m2/d) and numbers at the end indicate the duration of the treatment (days from C1D1 to end of treatment) for each patient in the EAS (Efficacy Analysis Set) in the ALICE study. Diamonds colored as per the legend indicate first, subsequent changes and last disease response assessed as recorded in the eCRF by the investigators. Column on the left shows the patients alive at the time of the Database Lock (DBL). Green arrows indicate the 3 patients that transitioned to compassionate use (CU) program and continued treatment (all of them still on treatment as of February 2024). White circles indicate when patients who were transfusion dependent at baseline became transfusion independent. Black circles reflect time of recorded death. Note: At the end of the first bar the green diamond indicates the patient had a CR response in the last BM assessment but showed progression of disease (red diamond) in the CNS.

Tables

Table I. Baseline characteristics (SAS)

	SAS (n=36)	
	Iadademstat 60µg/m²/d + azacitidine n=17	**Iadademstat 90µg/m²/d + azacitidine n=19**
Age in years, median [IQR]	74·0 [73-79]	77·0 [74-79]
<75 years	9 (53%)	7 (37%)
≥75 years	8 (47%)	12 (63%)
Sex		
male	9 (53%)	9 (48%)
female	8 (47%)	10 (53%)
Race		
Caucasian	17 (100%)	19 (100%)
ECOG Performance status		
0	5 (29%)	6 (32%)
1	10 (59%)	11 (58%)
2	2 (12%)	2 (11%)
Peripheral Blood blasts		
<30%	12/15 (80%)	15 (79%)
30%-50%	2 /15 (13%)	3 (16%)
≥50%	1/15 (7%)	1 (5%)
Bone marrow blasts		
<30%	3 (18%)	6 (32%)
30%-50%	11 (65%)	6 (32%)
≥50%	3 (18%)	7 (37%)
AML subtype		
WHO 2017:		
AML with recurrent genetic abnormalities	2 (12%)	4 (21%)
AML with myelodysplasia-related changes	8 (47%)	8 (42%)
AML therapy related	2 (12%)	3 (16%)
AML not otherwise categorized	5 (29%)	4 (21%)
FAB:		
M0 (myeloblastic, minimally differentiated)	1/15 (7%)	1/17 (6%)
M1 (myeloblastic, minimal maturation)	5/15 (33%)	4/17 (24%)
M2 (myeloblastic, with granulocytic maturation)	5/15 (33%)	5/17 (29%)
M4 (acute myelomonocytic leukemia)	2/15 (13%)	4/17 (24%)
M5a (monoblastic)	0	2/17 (12%)
M5b (monocytic)	2/15 (13%)	0
M6b (pure erythroleukemia)	0	1/17 (6%)
AML Type		
AML de novo	15 (88%)	14 (74%)
AML secondary	2 (12%)	5 (26%)
ELN 2017 risk		
Favorable	0	0
Intermediate	5 (3%)	8 (42%)
Adverse	12 (71%)	11 (58%)
AML Karyotype		
Normal	3/14 (21%)	7 (37%)
Abnormal	11/14 (79%)	12 (63%)
Days since diagnosis, median [IQR]	12/15 [8-19]	8/17 [3-15]

Cytopenias (G3/4) at baseline		
Anemia	2 (12%)	2 (11%)
Neutropenia	11 (65%)	15 (79%)
Thrombocytopenia	9 (53%)	13 (68%)
Transfusion dependence^	14 (82%)	17 (90%)
Mutations identified	Number of patient samples known to harbor the specific mutation*	
TP53	5	5
TET2	6	4
DNMT3a	3	6
ASXL1	3	2
RAS (KRAS, HRAS.NRAS)	3	2
SRSF2	3	3
NPM1	1	4
FLT3-ITD	1[$]	4
IDH1/2	4	1
RUNX1	2	3
EZH2	1	4
CEBPA	1	3
ETV6	2	1
PTPN11	1	2
BCOR	1	2
WT1	1	1
NF1	1	1
KIT	1	0
JAK2	0	1

All results expressed as n (%) unless specified. SAS: Safety Analysis Set; ECOG: Eastern Cooperative Oncology Group; AML: Acute Myeloid Leukemia; WBC: White Blood Cell; ELN: European Leukemia Net; WHO: World Health Organization; FAB: French-American-British; G: Grade.
(^) A Patient with transfusion dependence is defined as a patient for whom a transfusion was reported in the 8 previous weeks before C1D15 on treatment.
(*) Not all samples were available/evaluable for mutational analysis.
($) had also a FLT3-TKD mutation.

Table II. Iadademstat related AEs. (SAS)

Number of Subjects (%) in the SAS (n=36)				
System Organ Class **Preferred Term**	**G1/2**	**G3**	**G4**	**G5**
Investigations				
Platelet count decreased	13 (36%)	17 (47%)	22 (61%)	·
Neutrophil count decreased	13 (36%)	19 (53%)	17 (47%)	·
Lymphocyte count decreased	1 (3%)	2 (6%)	·	·
Hemoglobin abnormal	·	3 (8%)	·	·
White blood cell count decreased	·	1 (3%)	1 (3%)	·
White blood cell count abnormal	·	2 (6%)	·	·
Lymphocyte count abnormal	·	2 (6%)	·	·
Weight decreased	1 (3%)	1 (3%)	·	·
Hemoglobin decreased	·	1 (3%)	·	·
Alanine aminotransferase abnormal	·	1 (3%)	·	·
Aspartate aminotransferase abnormal	·	1 (3%)	·	·
Blood sodium increased	·	·	1 (3%)	·
Blood bilirubin increase	1 (3%)	·	·	·
Leukocytosis	1 (3%)	·	·	·
General disorders and administration site conditions				
Asthenia	9 (25%)	1 (3%)	·	·
Illness	1 (3%)	·	·	·
Pyrexia	1 (3%)	·	·	·
Gastrointestinal disorders				
Constipation	8 (22%)	1 (3%)	·	·
Nausea	6 (17%)	·	·	·
Diarrhea	3 (8%)	·	·	·
Vomiting	2 (6%)	·	·	·
Mouth hemorrhage	1 (3%)	·	·	·
Aphthous ulcer	1 (3%)	·	·	·
Gastrointestinal toxicity	1 (3%)	·	·	·
Hemorrhoids	1 (3%)	·	·	·
Blood and lymphatic system disorders				
Anemia	13 (36%)	9 (25%)	2 (6%)	·
Febrile neutropenia	·	1 (3%)	·	·
Leukocytosis	1 (3%)	·	·	·
Infections and infestations				
Abscess	·	1 (3%)	·	·

Number of Subjects (%) in the SAS (n=36)				
System Organ Class **Preferred Term**	**G1/2**	**G3**	**G4**	**G5**
Metabolism and nutrition disorders				
Decreased appetite	4 (11%)	·	·	·
Hyponatremia	2 (6%)	·	·	·
Hypomagnesemia	2 (6%)	·	·	·
Hypoalbuminemia	1 (3%)	·	·	·
Hypophosphatemia	1 (3%)	·	·	·
Nervous system disorders				
Dysgeusia	15 (42%)	1 (3%)	·	·
Hemorrhage intracranial	·	·	·	1 (3%)
Skin and subcutaneous tissue disorders				
Rash	2 (6%)	·	·	·
Skin hemorrhage	1 (3%)	·	·	·
Erythema	1 (3%)	·	·	·
Onychoclasis	1 (3%)	·	·	·
Pruritus	1 (3%)	·	·	·
Neoplasms benign, malignant, and unspecified (incl cysts and polyps%)				
Differentiation syndrome	·	1 (3%)	·	·
Hepatobiliary disorders				
Hyperbilirubinemia	1 (3%)	·	·	·
Reproductive system and breast disorders				
Heavy menstrual bleeding	1 (3%)	·	·	·
Intermenstrual bleeding	1 (3%)	·	·	·
Vaginal discharge	1 (3%)	·	·	·
Congenital, familial and genetic disorders				
Aplasia	1 (3%)	·	·	·
Ear and labyrinth disorders				
Hypoacusis	1 (3%)	·	·	·
Injury, poisoning and procedural complications				
Abdominal injury	1 (3%)	·	·	·
Respiratory, thoracic and mediastinal disorders				
Dyspnea	1 (3%)	·	·	·
Vascular disorders				
Hematoma	1 (3%)	·	·	·

Results shown as number of patients n (%) in the SAS (Safety Analysis Set population).Table shows iadademstat (+/- azacitidine) related Adverse Events (AEs). Related AEs include all AEs judged as certain, possible, probably/likely, conditional/unclassified, unassessable/unclassifiable related to the administration of iadademstat. G (grade).

Table III. Efficacy in the EAS population.

	Iadademstat 60 µg/m²/d + azacitidine n=13	**Iadademstat 90 µg/m²/d + azacitidine n=14**	**Overall n=27**
Response rate			
ORR (CR+CRi+PR), n (%) (95% CI)	11 (85%) (55, 98)	11 (79%) (49, 95)	22 (82%) (62, 94)
CR	4 (31%)	5 (36%)	9 (33%)
CRi	1 (8%)	4 (29%)	5 (19%)
CR/CRi	5 (39%)	9 (64%)	14 (52%)
PR	6 (46%)	2 (14%)	8 (30%)
SD	2 (15%)	2 (14%)	4 (15%)
PD	0	1 (7%)	1 (4%)
MRD negative[#] /evaluable remission samples	4/4 (100%)	6/7 (86%)	10/11 (91%)
CR MRD neg in CR responses	3/3 (100%)	4/4 (100%)	7/7 (100%)
CRi MRD negative in/CRi responses	1/1 (100%)	2/3 (67%)	3/4 (75%)
Time to first response, median days (95% CI)	43 (29, 80)	67 (30, 93)	64·0 (32, 80)
Time to best response, median days (95% CI)	79 (32, 283)	124 (67, 169)	105·0 (67, 162)
in pts achieving CR/CRi	108 (92, NE)	139 (70, NE)	124·0 (92, 283)
in pts achieving CR	196 (78, NE)	162 (139, NE)	162·0 (108, NE)
Patients achieving first/best response in	n=10	n=12	n=22
C1	7 (64%) / 5 (45%)	4 (36·4) / 1 (9%)	11 (50%) / 6 (27%)
C2	3 (27%) / 2 (18%)	5 (46%) / 4 (36%)	8 (36%) / 6 (27%)
C3	1 (9%) / 2 (18%)	1 (9%) / 1 (9%)	2(9%) / 3 (14%)
C4	-	1 (9%) / 2 (18%)	1 (5%) / 2 (9%)
C5	-	- / 1 (9%)	- / 1 (5%)
C8	- / 1 (9%)	- / 2 (18%)	- / 3 (14%)
C11	- / 1 (9%)	-	- / 1 (5%)
DoR, median days (95% CI)	n=11	n=11	n=22
in pts achieving CR	631 (262, NE)	282 (216, NE)	631 (216, NE)
in pts achieving CR/CRi	631 (155, NE)	282 (5, NE)	406 (155, NE)
in pts achieving CR/CRi/PR	205 (71, 748)	282 (16, 529)	269 (86, 529)
Transfusion dependent at baseline	n=10	n=12	n=22
Reached transfusion independence^	4 (40%)	6 (50%)	10 (46%)
Time to transfusion independence^, median days (95% CI)	149 (112, NE)	207 (125, NE)	190 (130, 225)
Duration of transfusion independence^, median days (95% CI)	191 (56, NE)	186 (8, NE)	186 (8, NE)
EFS, median days (95% CI)	233 (102, 666)	310 (61, 589)	271 (103, 358)
OS, median days (95% CI)	246 (137, NE)	373 (61, NE)	338 (137, 873)

All results expressed as n (%) unless specified. CR: Complete Remission; CRi: CR with incomplete hematologic recovery; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; MRD: Measurable Residual Disease, NE: Not Evaluable

(*) Not all samples were available/evaluable for MRD. Analysis was performed by local Multiparametric Flow Cytometry (MFC) in all but 1 patient (which sample was assessed by RT-PCR).

(^) Patients reaching transfusion independence who were transfusion dependent at baseline. Transfusion dependence at baseline is defined as the number of patients for whom no transfusions were reported during the previous 8 weeks to C1D15 on treatment.