SUPPLEMENTAL MATERIAL

ALICE Study Protocol v.7.0

Statistical Analysis Plan (SAP)

I. METHODS

I.1. Eligibility criteria: (Protocol v.7.0)

Inclusion criteria:

1. Subjects ≥ 18 years of age with AML according to World Health Organization (WHO) classification, who are considered by the investigator ineligible for intensive chemotherapy regimen at that time or have refused standard chemotherapy.
2. Blasts at least 20% in bone marrow and/or ≥ 20 % in peripheral blood.
3. Subjects must not have received azacitidine or prior treatment for AML other than hydroxyurea.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
5. Platelets ≥ 10 $x10^9$/ L without transfusion
6. Chemical laboratory parameters within the following range:
    a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x the upper limit of normal (ULN).
    b. Total bilirubin ≤ 1.5 x the ULN; patients with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits.
7. Patients with preserved renal function: serum creatinine ≤ 1.5 mg /dl.
8. Patients must be capable of understanding and complying with protocol requirements, and they must be able and willing to sign a written informed consent, and willing to complete all scheduled visits and assessments at the institution administering.
9. Life expectancy of at least 3 months in the opinion of the investigator.

Exclusion criteria:

10. Malignancies other than AML within 1 years prior to start treatment, except for those that are in complete remission, no treatment is required and with a minimal risk of metastasis or death, such as

adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, ductal carcinoma in situ treated surgically with curative intent.

11. Patients with uncontrolled hypertension (in the opinion of the investigator).
12. Patients with uncontrolled diabetes (in the opinion of the investigator).
13. Active hepatitis C virus (HCV) or hepatitis B virus (HBV). Patients who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
14. Known positive test result for human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS).
15. Inter-current illness or social situation that will limit compliance with study requirements. Any serious underlying medical or psychiatric condition (e.g., alcohol or drug abuse), dementia or altered mental status or any issue that would impair the ability of the patient to understand informed consent or that in the opinion of the investigator would contraindicate the patient's participation in the study or confound the results of the study.
16. A physical exam or laboratory finding that contraindicates the use of investigational therapy or otherwise places the patient at excessively high risk for treatment, as determined by the Investigator.
17. Patients medicated with anti-depressants reported to have KDM1A/LSD1 inhibitory activity: Tranylcypromine or Phenelzine.
18. History of central nervous system (CNS) disease involvement or prior history of NCI CTCAE Grade ≥ 3 drug-related CNS toxicity.
19. Evidence of active uncontrolled viral, bacterial, or systemic fungal infection. Additionally, all patients should initiate anti-infection prophylactic therapy, according to institutional protocols, as said below, simultaneously with the start of the study treatment and irrespective of the neutrophil count*
    a. Antibacterial prophylaxis, with the preferred quinolone or beta-lactamic antibiotic as per institution practice, is mandatory from randomization until the completion of the second cycle,

irrespective of the neutrophil count. If a CR/CRi is achieved after the first cycle, antibacterial prophylaxis can be suspended as per investigators judgement.

b. Antifungal prophylaxis, with the preferred antifungal triazol as per institution practice, is mandatory from randomization for at least two months or until investigators judgement.

c. Antiviral prophylaxis, with the preferred antiviral as per institution practice, is mandatory from randomization for at least two months or until investigators judgement.

20. Peripheral white blood cell (WBC) count ≥ 20 x 109/L on Day 1 prior to treatment. Hydroxyurea or 6-mercaptopurine are allowed until 24 hours prior study treatment.
21. Pregnant or lactating / breast feeding women.
22. Fertile women of childbearing potential (WCBP) not willing to use double barrier methods of contraception (abstinence, oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly, or surgically sterile) during the trial and 90 days after the end of treatment. Male patients whose partners are not willing to use double-barrier methods of contraception.

I.2. Dose Limiting Toxicity (DLT)

DLTs are to be evaluated according to the NCI-CTCAE, V5.0, with the exception of cytokine release syndrome (CRS), which should be graded according to the CRS Revised Grading Scale. An AE must be judged to be at least possibly related to iadademstat to qualify as a DLT.

The DLT observation period lasts for a minimum of 28 days after the patient starts Cycle 1 of iadademstat, up to a maximum of 42 days in patients with persistent Grade 4 neutropenia or thrombocytopenia in the absence of residual leukemia. Patients eligible for DLT evaluation

must have received at least 85% of the planned dose in the first cycle.

DLT definition includes the following treatment-related non-hematologic and hematologic AEs, including laboratory abnormalities.

- Non-hematologic DLT
    - Any Grade 4 non-hematologic AE not related to underlying disease or intercurrent illness.
    - Any Grade ≥ 3 non-hematologic AE not related to underlying disease or intercurrent illness and not resolving to Grade ≤ 1 or baseline within 72 hours excluding:
        - Grade 3 nausea.
        - Grade 3 or 4 vomiting in patients who have not received optimal treatment with anti-emetics.
        - Grade 3 or 4 diarrhea in patients who have not received optimal treatment with antidiarrheals.
        - Grade ≥ 3 fatigue.
        - Grade ≥ 3 electrolyte disturbances responsive to correction within 24 hours.
    - Any treatment-related AE resulting in a dose interruption of > 7 consecutive days of iadademstat
    - Any treatment-related AE that results in withdrawal from the study, regardless of duration or grade.
    - Any other event judged by the Safety Monitoring Committee to constitute DLT.
- Hematologic DLT
    - Hematologic DLT is defined as any treatment-related clinically significant Grade 4 neutropenia or thrombocytopenia persisting to Day 42 of a cycle or later in the absence of residual leukemia.

I.3. NGS panels

The molecular analyses were performed at local laboratories by participant hospitals.

The majority of analyses were performed using the Oncomine system: An analysis of 40 genes and 29 fusion gene drivers associated with myeloid malignancies was performed by NGS using the Oncomine Myeloid Research Assay (ThermoFisher Scientific) and the ThermoFisher automated sequencing platform (Ion Chef/Ion

Torrent and Ion S5 XL systems). DNA and RNA were extracted from mononuclear cells isolated from BM aspirates and library preparation was performed using 20 ng of DNA and 100 ng of RNA. The mean sequencing depth of coverage was 2,000 to 2,500x. Pathogenic/likely pathogenic variants and variants of unknown significance were selected based on a minimum variant coverage of 25 reads and a minimum allele frequency of 1% to 5%. The limit of detection for fusion genes was transcript level 0.1%.

Samples from Hospital La Fe were analyzed based on their own system: Thirty genes were established as key genes for AML pathogenesis: ABL1, ASXL1, BRAF, CALR, CBL, CEBPA, CSF3R, DNMT3A, ETV6, EZH2, FLT3, GATA2, HRAS, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1 and WT1. ASXL1, CEBPA, FLT3, IDH1, IDH2, NPM1, RUNX1, and TP53 following a method and sequencing panel options (Ion Torrent or Illumina) previously validated by a National Spanish network.[1]

I.4 Bone Marrow assessments

For efficacy assessments, BM response was evaluated locally on days 29, 52, 80, 164 (pre-cycle 2,3,4,6 respectively), every 3 cycles thereafter, and when clinically indicated. Morphologic and cytogenetic assessments were performed during each BM evaluation.

Measurable residual disease (MRD assessments were performed by Multiparametric flow cytometry (MFC) with whole BM samples incubated with quadruple combinations of antibodies in a 5-tube combination assay with a sensitivity of 10^{-4} and analyzed following a previously described methodology.[2]

One patient had MRD monitored in BM samples by NPM1 quantitative reverse transcription polymerase chain reaction (RT-PCT) (sensitivity 10^{-5} to 10^{-6}) as previously described[3]. After each treatment cycle, absolute transcript reduction was estimated, and its logarithm (log10) reduction from diagnosis was also determined. Based on the latest ELN MRD working party recommendations[3], MRD positivity was considered when NPM1

transcripts were amplified in at least 2 of 3 replicates with cycle threshold values of ≤40 at a cycling threshold of 0.1.

I.5. Iadademstat PK determinations

Iadademstat concentrations were determined in human plasma using a highly sensitive GLP-validated HPLC-MS/MS method (LLOQ: 1pg/mL) with ESI in positive ion mode and deuterated iadademstat as internal standard, developed at Pharm-Analyt Labor GmbH. Sample analysis was GLP compliant.

I.6 LSD1 target engagement

PD studies were performed on Leucosep-separated PBMNCs from 10 ml PB sampling following the method described by Mascaro et al.,[4]

I.7 Statistical Methods

Sample size calculations:

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.

Phase 1: Dose escalation part: 12 to 18 evaluable patients to be enrolled in this part of the study.

Phase 2: Dose expansion part: A total of 18 evaluable patients to be enrolled in this part of the 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.

-Safety Monitoring Committee:

A Safety Monitoring Committee (SMC) was responsible for the decisions related to dose escalation. Additionally, the committee was responsible for decisions regarding stopping the trial in case of unacceptable toxicities. The committee was formed by a Medical Monitor, representatives of the sponsor and the

investigators from all participating sites to review safety data on an ongoing basis. The committee met virtually to make decisions on each dose escalation step.

Data Handling:

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. There is no formal hypothesis testing in this study. 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.

Prespecified populations as per SAP and ad-hoc assessments:

- Safety Analysis Set (SAS) defined as all patients who received at least one dose of the study treatment. Safety analysis set was used for all safety analysis.
- 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)
    - Completed the DLT evaluation period and received at least 85% of planned doses.

  Patients who did not meet either of the above criteria were not evaluable for the dose escalation assessment and could be replaced as needed to permit dose escalation. DLT analysis set was used for DLT related analysis.
- Full Analysis Set (FAS): defined as all patients who met eligibility criteria and signed the Informed Consent. Full analysis set was used for sensitivity analyses, including safety and efficacy analysis.

- Efficacy Analysis Set (EAS) defined as all patients who met eligibility criteria, have been treated, have baseline disease assessment and at least 1 available post baseline efficacy assessment. Efficacy analysis set was used for efficacy analyses.
- PK Analysis Set (PKAS): defined as all PK-evaluable patients for whom at least one plasma concentration data is available. PK analysis set was used for PK analyses.
- PD Analysis Set (PDAS) defined as all PD-evaluable patients or whom at least one PD data point is available. PD analysis set was used for PD analyses.

Ad-hoc analyses contemplated in the SAP included:

- Exposure-response relationships (per dose received, according to specific baseline characteristics, per response achieved etc.). The PK, PD, safety and/or efficacy populations will be used for this exploratory endpoint.
- Optional MRD analysis on patients achieving remission
- Responses based on ELN 2022 criteria
- Subgroup analysis on specific categories (a post-hoc analysis was performed in subgroups of 5 or more patients harboring AML recurrent mutations)

Software package used for statistical analyses was SAS v. 9.4

This study was registered as EUDRACT #2018-000482-36

I.8. Response Definitions

Endpoint	Per protocol/SAP	Per ELN 2022
Complete Remission (**CR**)	The patient must be free of all symptoms related to leukemia and have an absolute neutrophil count > 1 x 10^9/L (1000/µL) and platelet count ≥ 100 x 10^9/L (100,000/µL), and normal bone marrow differential (<5 % leukemic blasts with no Auer rods) in a normo- or hypercellular marrow with a count of at least 200 cells (i.e., the marrow is evaluable for response). The patient must be independent of transfusion and there should be no evidence of residual extramedullary leukemia (EL) neither in the peripheral blood or elsewhere. *BM blasts < 5%; no Auer rods; ANC >1,000; platelets ≥100,000; TI, No EL* Note: All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5-7 days; a BM biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.	Bone marrow blasts < 5%; absence of circulating blasts; absence of extramedullary disease; ANC ≥1.0 x 10^9/L; platelet count ≥ 100 x 10^9/L. *BM blasts < 5%; ANC ≥1,000/µL; platelets ≥100,000/µL, No EL* Notes*^&.
Complete Remission with partial hematologic recovery **(CRh)**		ANC ≥ 0.5 x 10^9/L and platelets ≥ 50 x 10^9/L, no evidence of extramedullary leukemia (NEL) otherwise all other criteria for CR met. *BM blasts < 5%; ANC ≥500/µL; platelet ≥50,000/µL No EL* Notes*^&. If CRh used, CRi should only include patients not meeting the definition of CRh.
Complete Remission with incomplete hematologic recovery **(CRi)**	All criteria for CR must be fulfilled, but with residual neutropenia (≤1 x 10^9/L [1.000/µL]) or thrombocytopenia (<100 x 10^9/L [100.000/µL]). A CRi should only be declared if a CR cannot be attained within d 14 of the response determining bone marrow (i.e., neutrophil and platelet counts should be recorded up until this date). *BM blasts < 5%; ANC ≤ 1,000/L OR platelet < 100,000/µL; No EL*	All CR criteria except for residual neutropenia <1 x 10^9/L or thrombocytopenia <100 x 10^9/L. *BM blasts < 5%; ANC >1,000/µL OR platelet > 100,000/µL; NEL* Notes*^&
Morphologic Leukemia-Free State (**MLFS**)		BM blasts <5%; absence of circulating blasts; N EL, no hematologic recovery required. *BM blasts < 5%; NEL* Note: BM should not merely be "aplastic"; BM spicules should be present; at least 200 cells should be enumerated in the aspirate or cellularity should be at least 10% in the biopsy.

Endpoint	Per protocol/SAP	Per ELN 2022
Partial Response (**PR**) *(called partial remission in protocol)*	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pre-treatment bone marrow blast percentage by at least 50%. *BM blasts 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%, ANC >1,000; platelet >100,000; No EL*	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pre-treatment BM blast percentage by at least 50%. *BM blasts 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%* *ANC >1,000; platelet >100,000; No EL*
Response	Objective response (OR): OR is defined as number of subjects achieving CR, CRi, or PR, confirmed by repeat assessments ≥4 weeks after initial documentation	Patients evaluable for response meeting the criteria for CR, CRh, CRi, MLFS or PR by the response landmark.
Stable disease (SD) *(called Resistant disease in the protocol (RD))* **No response (ELN)**	Failure to achieve CR, CRi or PR (phase I trials); includes patients following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination. SAP classified these patients with a "Stable disease" (SD) response provided they do not qualify for progressive disease (PD).	**No response**: Patients evaluable for response but not meeting the criteria for CR, CRh, CRi, MLFS or PR prior to the response landmark.
Non- evaluable for response	Patients without baseline BM assessment and at least 1 post-dose BM assessment.	Patients lacking an adequate BM response evaluation. This category will include patients with early death, withdrawal prior to response assessment, or a technically suboptimal BM sample precluding assessment.
Response if includes MRD[$] **CR MRD$^-$,** **CRh MRD$^-$,** **CRi MRD$^-$**		CR, CRh or CRi with MRD below a defined threshold for a genetic marker by qPCR, or by MFC. Response without MRD should be confirmed with a subsequent assessment at least 4 weeks apart. The date of response without MRD is the first date in which the MRD was below the defined threshold. Response with MRD detection at low-level (CRMRD-LL) is included in this category of CR, CRh or CRi without MRD. CRMRD-LL is currently only defined for NPM1-mutant and CBF- AML. Note: Sensitivities vary by marker tested, and by method used; therefore, test used, tissue source and minimum assay sensitivity for evaluability should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Refractory Disease		Patients failing to achieve response by the designated landmark are designated as having refractory disease.
Relapsed disease (after CR, CRh or CRi)	BM > 5%; or reappearance of blasts in the blood; or development of extramedullary disease. Note: In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related AML.	BM blasts ≥ 5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least one week apart; or development of extramedullary disease (ED).

Endpoint	Per protocol/SAP	Per ELN 2022
If including MRD[$] **(MRD relapse after CR, CRh or CRi without MRD)**		• Conversion from MRD $^{-}$→MRD^{+}, independent of method, or • Increase of MRD copy numbers ≥ 1 log10 between any two positive samples in patients with CR MRD-LL, CRh MRD-LL or CRi MRD-LL by qPCR The result of 1. or 2. should be rapidly confirmed in a second consecutive sample from the same tissue source
Progressive Disease **(PD)**	Per SAP: Evidence for an increase in BM blast percentage and/or increase of absolute blast counts in the blood and/or new EL. • >50% increase in marrow blasts over baseline (a minimum of 15%-point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (>0.5 x 10^9/L and/or platelet count to > 50 x 10^9/L (non-transfused); OR • > 50% increase in peripheral blasts (WBC x % blasts) to > 25 x 10^9/L (in the absence of differentiation syndrome) Note: In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse.	
Hematologic Improvement **(HI)**	Relevant hematologic improvements of some cellular line that allow patients improve their quality of life. A percent of increase in count would be: $PERCENT\ INCREASE\ IN\ COUNT = (after) - (before)/(before) * 100$ **Erythroid response (HI-E)** • Major → hemoglobin increased more than 2g/dL compared with pretreatment status (must be <11 g/dL) or becoming transfusion-independent when pretreatment status was RBC transfusion- dependent. • Minor → hemoglobin increased between 1 – 2g/dL compared with pretreatment status (when must be <11 g/dL), or transfusion requirement decreased at least 50% when pretreatment status was RBC transfusion-dependent. **Platelet Response (HI-P)** • Major → platelet count has absolute increase of at least 30,000 cells /μL when pretreatment status was <100,000/μL or being transfusion independent with stabilized counts when pretreatment status was platelet transfusion-dependent. • Minor → platelet count has absolute increase between 10.000 to 30.000 cells/μL, having increased at least 50% compared to pretreatment status. **Neutrophil response (HI-N)**	

Endpoint	Per protocol/SAP	Per ELN 2022
	• Major → neutrophils have increased at least 100% compared to pretreatment status and an absolute neutrophil count increase of more than 500 cells/μL. • Minor → neutrophils have increased at least 100% compared to pretreatment status and an absolute neutrophil count increase < than 500 cells/μL	
Overall survival **(OS)**	Mean time from first study treatment to death from any cause.	Measured from day 1 of randomization or day 1 of registration in nonrandomized trials (or from the date of diagnosis, e.g., for correlative science studies) to the date of death from any cause.
Event-free survival **(EFS)**	EFS of combo therapy: Mean time from first study treatment to disease progression or death. Kaplan-Meier method will be used for survival analysis.	Measured from day 1 of randomization or day 1 of registration in nonrandomized trials to the date of treatment failure, hematologic relapse from CR/CRh/CRi or death from any cause, whichever occurs first. • Treatment failure is defined as not achieving either CR, CRh or CRi by a pre-defined landmark. • Patients evaluable for response but not achieving either CR, CRh or CRi by the defined landmark and patients who die before the defined landmark without response assessments are considered an event at day 1 of registration. • Patients alive who are non-evaluable for response should be censored at day 1 of the registration. • Patients achieving either CR, CRh or CRi by the defined landmark but do not relapse or die should be censored on the date they were last assessed for response.
Relapse (or Disease)-free survival **(RFS)**		Measured from the date of achievement of CR, CRh, or CRi until the date of hematologic relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date they were last known to be alive.
Cumulative incidence of relapse **(CIR)**		Defined for all patients achieving CR, CRh, CRi; measured from the date of achievement of a remission until the date of hematologic relapse; patients not known to have relapsed are censored on the date they were last assessed for response; patients who died without relapse are counted as a competing cause of failure.
Cumulative incidence of death **(CID)**		Defined for all patients achieving CR, CRh, CRi; measured from the date of achievement of a remission to death without prior relapse; relapse is considered as competing risk.
If including assessment of MRD relapse **EFS$_{MRD}$, RFS$_{MRD}$, CIR$_{MRD}$, CID$_{MRD}$**		EFS $MRD^{\%}$ Measured from day 1 of randomization or day 1 of registration in non-randomized trials to the date of failure to achieve CR, CRh or CRi by a defined landmark (e.g., after two cycles of intensive chemotherapy or 180 d for non-intensive therapy), hematologic relapse, MRD relapse (for patients achieving CR, CRh or CRi without MRD) or death from any cause. $RFS_{MRD}^{\%}$ Measured from the date of achievement of a remission (CR, CRh, or CRi) until the date of hematologic relapse, MRD relapse, or death from any cause. $CIR_{MRD}^{\%}$ Measured from the date of achievement of a

Endpoint	Per protocol/SAP	Per ELN 2022
		remission (CR, CRh or CRi) until the date of hematologic relapse, or molecular MRD relapse; patients who died without relapse are counted as a competing cause of failure. CIDMRD Measured from the date of achievement of a remission (CR, CRh, or CRi) to death without prior relapse; morphologic or molecular MRD relapse is considered as competing risk.
Early death		Death from any cause within a timeframe relevant for the therapy being investigated (e.g., 30 and 60 d from commencing therapy)

To recognize the potential for continuing improvements in blood counts after myelosuppressive therapy, response definitions for patients with marrow blast clearance (<5%) may be adjusted to reflect the best hematologic response achieved prior to commencement of the next treatment cycle. Aspirate reports that include MLFS, CRh, or CRi should note the potential for post-marrow blood counts to alter the final response designation. Patients should not have received G-CSF, nor platelet transfusions within 7 days prior to hematologic response determination.

^For patients with CR, CRh, or CRi, the presence of a low percentage of circulating blasts in the blood may represent a regenerating marrow and should not be interpreted as persistent disease. In such cases the blasts generally disappear within a week.

&A response landmark for CR, CRh, or CRi should be stated, e.g., after 2 cycles of intensive therapy; this landmark may be longer for non-intensive based treatment options, e.g., 180 days.

$ MFC-MRD positivity is defined as $ 0.1% of CD45 expressing cells with the target immunophenotype. MRD test positivity by qPCR is defined as cycling threshold (Ct), 40 and is negative if Ct ≥ 40 in ≥ 2 of 3 replicates. In NPM1-mutated and CBF-AML, CR with molecular MRD detectable at low-level (CRMRD-LL) defined as, 2% is designated as negative for MRD, because when measured at the end of consolidation treatment, is associated with a very low relapse rate.

I.9 Drug Manufacture

Iadademstat: Hoffmann-La Roche Ltd. Grenzacherstrasse 124, CH-4070 Basel, Switzerland.

Azacitidine: commercially available as Vidaza® or as generic azacitidine Betapharm Azacitidine®.

- Based on the SmPC, manufacturer of VIDAZA® is Celgene Distribution B.V. Orteliuslaan 1000; 3528 BD Utrecht - The Netherlands.
- Based on the SmPC, the manufacturer is Betapharm Arzneimittel GmbH. Kobelweg 95: 86156 Augsburg -Germany

The two sources of azacitidine were: 1) directly from the Site's Pharmacy Services or 2) from the distributor DISTEFAR in Sevilla, Spain (contracted by Oryzon)

II. ACCRUAL PER SITE

The table below lists the accrual, Principal Investigator and sites in Spain that accrued patients in the ALICE study.

Site	Investigator	Patients recruited
Hospital Vall d' Hebron, Barcelona, Spain	Dr. Olga Salamero	18
Hospital La Fe, Valencia, Spain	Dr. Pau Montesions Fernández	7
Hospital Virgen del Rocío, Sevilla, Spain	Dr. José Antonio Pérez Simon	3
ICO Hospitalet. Hospital Duran i Reynals, Barcelona Spain	Dr. Montserrat Arnan Sangerman	3
ICO Girona. Hospital Dr. Josep Trueta, Girona, Spain	Dr. Rosa Coll	3
Hospital del Mar, Barcelona, Spain	Dr. Sara García Ávila	2

III. SUPPLEMENTAL TABLES

Table S1. Reasons for Treatment Discontinuation

Table S1. Reasons for treatment discontinuation (SAS)

	Iadademstat 60 µg/m²/d + azacitidine n=17	**Iadademstat 90 µg/m²/d + azacitidine n=19**	**Overall n=36**
Progression of disease	8 (47%)	4 (21%)	12 (33%)
Treatment Toxicity	0	1 (5%)	1 (3%)
Patient decision	2 (12%)	2 (11%)	4 (11%)
Investigator decision	2 (12%)	3 (16%)	5 (14%)
Sponsor decision*	1 (6%)	2 (11%)	3 (8%)
Death	4 (24%)	7 (37%)	11 (31%)

Results expressed as n (%). (*) Patients transitioned to compassionate use program.

Table S2. Safety Summary

Table S2. Safety Summary (SAS)

	AEs related to iadademstat +/- azacitidine			All AEs		
	Iadademstat 60 µg/m²/d + azacitidine n=17	Iadademstat 90 µg/m²/d +azacitidine n=19	Overall SAS (n=36%)	Iadademstat 60 µg/m²/d +azacitidine n=17	Iadademstat 90 µg/m²/d + azacitidine n=19	Overall SAS (n=36%)
Subjects with AEs	16 (94%)	17 (90%)	33 (92%)	17 (100%)	19 (100%)	36 (100%)
Subjects with SAEs	1 (6%)	2 (11%)	3 (8%)	16 (94%)	18 (95%)	34 (94%)
Subjects with AEs ≥G3	15 (88%)	16 (84%)	31 (86%)	17 (100%)	19 (100%)	36 (100%)
Subjects with AEs leading to treatment reduction	2 (12%)	5 (26%)	7 (19%)	2 (12%)	7 (37%)	9 (25%)
Subjects with AEs leading to treatment delay	7 (41%)	8 (42%)	15 (42%)	10 (59%)	11 (58%)	21 (58%)
Subjects with AEs leading to treatment hold	6 (35%)	4 (21%)	10 (28%)	10 (59%)	13 (68%)	23 (64%)
Subjects with AEs leading to treatment discontinuation	0	2 (11%)	2 (6%)	5 (29%)	7 (37%)	12 (33%)
Subjects with Fatal AEs	0	1 (5%)	1 (3%)	4 (24%)	8 (42%)	12 (33%)*

Results expressed as n (%).
(*) Includes a death, reported as AE.
AEs with onset date/time ≥date of first iadademstat dose up to 30 days after last dose are presented in this table.·
A related AE is an adverse event judged as Certain, Possible, Probably/likely, Conditional/unclassified, Unassessable/unclassifiable related to iadademstat. A SAE is an AE judged as serious· Seriousness was missing and imputed to serious for one event.

Table S3. Iadademstat related AEs by patient's sex

Table S3. Iadademstat related AEs by patient's sex (SAS)

Number of Subjects (%) SAS								
System Organ Class Preferred Term	G1/2		G3		G4		G5	
	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE
Investigations								
Platelet count decreased	8 (22%)	5 (14%)	8 (22%)	9 (25%)	9 (25%)	13 (36%)	·	·
Neutrophil count decreased	7 (19%)	6 (17%)	10 (28%)	9 (25%)	6 (17%)	11 (31%)	·	·
Lymphocyte count decreased	·	1 (3%)	1 (3%)	1 (3%)	·	·	·	·
Hemoglobin abnormal	·	·	2 (6%)	1 (3%)	·	·	·	·
White blood cell count decreased	·	·	·	1 (3%)	·	1 (3%)	·	·
White blood cell count abnormal	·	·	2 (6%)	·	·	·	·	·
Lymphocyte count abnormal	·	·	1 (3%)	1 (3%)	·	·	·	·
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	5 (14%)	4 (11%)	1 (3%)	·	·	·	·	·
Illness	1 (3%)	·	·	·	·	·	·	·
Pyrexia	1 (3%)	·	·	·	·	·	·	·
Gastrointestinal disorders								
Constipation	2 (6%)	6 (17%)	1 (3%)	·	·	·	·	·
Nausea	4 (11%)	2 (6%)	·	·	·	·	·	·
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	6 (17%)	7 (19%)	2 (6%)	7 (19%)	1 (3%)	1 (3%)	·	·
Febrile neutropenia	·	·	1 (3%)	·	·	·	·	·
Leukocytosis	1 (3%)	·	·	·	·	·	·	·
Infections and infestations								
Abscess	·	·	·	1 (3%)	·	·	·	·
Metabolism and nutrition disorders								
Decreased appetite	3 (8%)	1 (3%)	·	·	·	·	·	·
Hyponatremia	2 (6%)	·	·	·	·	·	·	·

Number of Subjects (%) SAS								
	G1/2		G3		G4		G5	
System Organ Class Preferred Term	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE
Hypomagnesemia	2 (6%)	·	·	·	·	·	·	·
Hypoalbuminemia	1 (3%)	·	·	·	·	·	·	·
Hypophosphatemia	1 (3%)	·	·	·	·	·	·	·
Nervous system disorders								
Dysgeusia	8 (22%)	7 (19%)	1 (3%)	·	·	·	·	·
Hemorrhage intracranial	·	·	·	·	·	·	1 (3%)	·
Skin and subcutaneous tissue disorders								
Rash	·	2 (6%)	·	·	·	·	·	·
Erythema	·	1 (3%)	·	·	·	·	·	·
Onychoclasis	·	1 (3%)	·	·	·	·	·	·
Pruritus	·	1 (3%)	·	·	·	·	·	·
Skin hemorrhage	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 S4. AEs leading to iadademstat discontinuation.

Table S4. AEs leading to iadademstat discontinuation (SAS)

System Organ Class Preferred Term	AEs leading to iadademstat discontinuation
Infections and infestations	
Abdominal sepsis	**1 (3%)**
Bacteremia	**1 (3%)**
COVID-19 pneumonia	**1 (3%)**
Fungal infection	**1 (3%)**
Pneumonia	**1 (3%)**
Respiratory tract infection	**1 (3%)**
Sepsis	**1 (3%)**
Septic shock	**1 (3%)**
General disorders and administration site conditions	
Fatigue	**1 (3%)**
Pyrexia	**1 (3%)**
Nervous system disorders	
Hemorrhage intracranial	**1 (3%)**
Subarachnoid hemorrhage	**1 (3%)**
Blood and lymphatic system disorders	
Anemia	**1 (3%)**
Hepatobiliary disorders	
Drug-induced liver injury	**1 (3%)**
Investigations	
Platelet count decreased	**1 (3%)**
Respiratory, thoracic, and mediastinal disorders	
P leural effusion	**1 (3%)**
Grand Total	**12 (33·3%)**

Results provided as number of patients n (%) in the SAS (Safety Analysis Set).

Table S5. Cause of Death

Table S5. Cause of death (SAS)

System Organ Class Preferred Term	**60 ug/m^2/d iadademstat N=16**	**90 ug/m^2/d iadademstat N=19**	**Overall N=36**
Infections and infestations			
COVID-19 pneumonia	1 (6%)	2 (11%)*	3 (8%)
Fungal infection		1 (5%)	1 (3%)
Pneumonia	1 (6%)*	1 (5%)	2 (6%)
Septic shock	1 (6%)*		1 (3%)
Nervous system disorders			
Hemorrhage intracranial		2 (11%)*	2 (6%)
Subarachnoid hemorrhage		1 (5%)*	1 (3%)
Gastrointestinal disorders			
Neutropenic colitis	1 (6%)*		1 (3%)
General disorders and administration site conditions			
Death		1 (5%)	1 (3%)
Total	**4 (25%)**	**8 (42%)**	**12 (33·3%)**

Results provided as number of patients (%) experiencing Adverse events (AEs) that lead to death in the SAS (Safety Analysis Set). (*) Indicate the patients experiencing death before the first BM assessment on study with the exception of 1 fatal COVID case that occurred after several cycles on study.

Table S6. Efficacy in Subgroups

Table S6. Efficacy in Subgroups of patients (EAS)

	(EAS n=27)											
SUBGROUPS	**Response**				**DoR Median days (95%CI)**	**DoR rate 6 mos (95%CI)**	**DoR rate 12 mos (95%CI)**	**MRD^{neg} n out of evaluable**	**MRD^{pos} n out of evaluable**	**OS Median days (95%CI)**	**OS 12 mos rate (95%CI)**	**OS 18 mos rate (95%CI)**
Responses by investigator n(%%)	**CR**	**CRi**	**PR**	**n(%) of EAS**								
EAS (n=27%)	9 (33%)	5 (19%)	8 (30%)	22 (82%)	269 (86, 529)	68% (45, 83)	36% (17, 55)	.	.	338 (137·873)	48% (29, 65)	35% (18, 53)
CR/CRi/PR n (=22%)	9 (41%)	5 (23%)	8 (36%)	22 (82%)	269 (86, 529)	68% (45, 83)	36% (17,55)	.	.	467 (215, NE)	59·1% (36, 76)	43% (22, 63)
CR/CRi (n=14%)	9 (64%)	5 (36%)	.	14 (52%)	406 (155, NE)	79% (47, 93)	50% (23, 72)	10 out of 11	1 out of 11	471 (271, NE)	71% (41, 88)	48% (20, 71)
CR (n=9%)	.	.	.	9 (33%)	631 (216, NE)	100% (100, 100)	56% (20, 81)	7 out of 7	0 out of 7	NE (271, NE)	78% (37, 94)	52% (16, 79)
Responses by ELN 2022	**CR**	**CRh**	**MLFS**	**n(%) of EAS**								
EAS (n=27%)	9 (33%)	3 (11%)	2 (7%)	14 (52%)	280 (21, 455)	64·3% (34, 83)	40% (15, 64)	.	.	338 (137,873)	48% (29, 65)	35% (17·8, 53·4)
CR/CRh/CRi/PR/MLFS (n=14%)	9 (64%)	3 (21%)	2 (14%)	14 (52%)	280 (21, 455)	64% (34, 83)	40% (15, 64)	10 out of 11	1 out of 11	471 (271, NE)	71% (41, 88)	48% (20·3, 70·8)
CR/CRh/CRi (n=12%)	9 (75%)	3 (25%)	.	12 (44%)	282 (111, NE)	75% (41, 91)	47% (18, 72)	9 out of 10	1 out of 10	NE (338, NE)	83% (48, 96)	56% (24, 79)
CR (n=9%)	.	.	.	9 (33%)	414 (111, NE)	89% (43, 98)	64% (24, 87)	7 out of 7	0 out of 7	NE (271, NE)	89% (43, 98)	64% (24, 87)
AML Type	**CR**	**CRi**	**PR**	**n(%) of subtype**								
	CR	**CRh**	**MLFS**									

	(EAS n=27)											
SUBGROUPS	**Response**				**DoR Median days (95%CI)**	**DoR rate 6 mos (95%CI)**	**DoR rate 12 mos (95%CI)**	**MRD^{neg} n out of evaluable**	**MRD^{pos} n out of evaluable**	**OS Median days (95%CI)**	**OS 12 mos rate (95%CI)**	**OS 18 mos rate (95%CI)**
Not otherwise categorized (n=4%)	1	1	2	4 (100%)	NC	NC	NC	1 out of 1	0 out of 1	NC	NC	NC
	1	0	1	2 (50%)	NC	NC	NC					
With MRC (n=14%)	3	4	5	12 (86%)	210 (78, 326)	67% (34, 86)	17% (3, 41)	5 out of 6	1 out of 6	305 (96, 873)	43% (18, 66)	26% (7, 51)
	3	3	1	7 (50%)	183 (16, 282)	43% (10, 73)	14% (1, 47)					
With recurrent genetic abnormalities (n=5%)	4	0	1	5 (100%)	1084 (71, NE)	80% (20, 97)	60% (13, 88)	4 out of 4	0 out of 4	NE (102, NE)	80% (20, 97)	53% (7, 86)
	4	0	0	4 (80%)	NC	NC	NC					
Therapy related (n=4%)	1	0	0	1 (25%)	NC	NC	NC	.	.	NC	NC	NC
	1	0	0									
FAB	**CR**	**CRi**	**PR**	**n(%) of subtype**								
	CR	**CRh**	**MLFS**									
Monocytic M4/M5 (n=8%)	4	2	1	7 (88%)	748 (16, NE)	86% (33, 98)	71% (26, 92)	6 out of 6	0 out of 6	NE (50, NE)	75% (32, 93)	60% (20, 85)
	5	0	1	6 (75%)	455 (16, NE)	83% (27, 98)	63% (14, 89)	6 out of 6	0 out of 6			
ELN 2017 risk	**CR**	**CRi**	**PR**	**n(%) of subtype**								
	CR	**CRh**	**MLFS**									
Intermediate (n=12%)	3	2	5	10 (83%)	231 (5, 748)	60% (25, 83)	27% (5, 56)	5 out of 5	0 out of 5	276 (61, NE)	50% (21, 74)	40% (14, 66)
	3	0	2	5 (42%)	280 (5, NE)	60% (13, 88)	30% (1, 72)					
Adverse risk (n=15%)	6	3	3	12 (80%)	272 (86, 631)	75% (41, 91)	42% (15, 67)	5 out of 6	1 out of 6	338 (137, NE)	47% (21, 69)	33% (12, 56)
	6	3	0	9 (60%)	282 (21, 455)	67% (28, 88)	44% (14, 72)					
With selected mutations (n≥5%)	**CR**	**CRi**	**PR**	**n(%) of subtype**								
	CR	**CRh**	**MLFS**									
TP53 (n=8%)	4	1	1	6 (75%)	239 (155, NE)	83% (27, 98)	17% (1, 52)	3 out of 3	0 out of 3	305 (55, 471)	38% (9, 67)	13% (1, 42)

	(EAS n=27)											
SUBGROUPS	**Response**				**DoR Median days (95%CI)**	**DoR rate 6 mos (95%CI)**	**DoR rate 12 mos (95%CI)**	**MRD^{neg} n out of evaluable**	**MRD^{pos} n out of evaluable**	**OS Median days (95%CI)**	**OS 12 mos rate (95%CI)**	**OS 18 mos rate (95%CI)**
	3	2	0	5 (63%)	264 (111, NE)	60% (13, 88)	20% (1, 58)	3 out of 3	0 out of 3			
TET2 (n= 7%)	2	1	2	5 (71%)	262 (66, NE)	60% (13, 88)	40% (5, 75)	3 out of 3	0 out of 4	144 (50, NE)	43% (10, 73)	29% (4, 61)
	3	0	0	3 (43%)	NC	NC	NC	3 out of 3	0 out of 3			
RAS pathway* (n= 7%)	2	3	2	7 (100%)	205 (16, NE)	57% (17, 84)	43% (10, 73)	5 out of 5	0 out of 5	467 (85, NE)	57% (17, 84)	38% (6, 72)
	3	1	1	5 (71%)	455 (16, NE)	60% (13, 88)	60% (13, 88)	5 out of 5	0 out of 5			
DNM3TA (n=7%)	1	4	2	7 (100%)	186 (16, NE)	57% (17, 84)	29% (4, 61)	4 out of 5	1 out of 5	467 (85, NE)	71% (26, 92)	38% (6, 72)
	2	2	1	5 (71%)	183 (16, NE)	40% (5, 75)	20% (1, 58)	4 out of 5	1 out of 5			
SRSF2 (n=5%)	1	1	1	3 (60%)	NC	NC	NC	2 out of 2	0 out of 2	102 (50, NE)	0	0
	0	1	1	2 (40%)	NC	NC	NC	2 out of 2	0 out of 2			

Response per Investigator criteria and per the Ad-Hoc analysis (according to ELN 2022) is shown in white and blue colored cells respectively. Results are expressed as n (%) unless specified. Time to event is only calculated for subgroups with n≥5. CR: Complete Remission; CRi: CR with incomplete hematologic recovery; PR: Partial Response; CRh: CR with partial hematologic recovery; MLFS: Morphologic Leukemia Free State; MRD: Measurable Residual Disease; ELN: European Leukemia Net; ORR: Overall Response Rate; DoR: Duration of Response; OS: Overall Survival; MRC: Myelodysplastic Related Changes; SE: Standard Error; CI: Confidence Interval. (*) Including *K-N-H RAS, BRAF, PTPN11 and NF1 mutations.*

Table S7. PK Analysis

Table S7. Pharmacokinetic analysis (PKAS)

	60 µg/m²/d iadademstat N=16	90 µg/m²/d iadademstat N=19	Overall N=35
Plasma Concentration - Cycle 1 Day 1			
n	16	19	35
Mean (SD)	0·0 (0·0)	0·23 (1·0)	0·1 (0·7)
95% CI	(0,0)	(-0·3, 0·71)	(-0·13, 0·4)
Median	0	0	0
Q1; Q3	0·0; 0·0	0·0; 0·0	0·0; 0·0
Min; Max	0·0; 0·0	0·0; 4·4	0·0; 4·4
P-value between doses			0·40
Plasma Concentration - Cycle 1 Day 2			
n	15	17	32
Mean (SD)	2·4 (1·9)	4·6 (5·0)	3·6 (4·0)
95% CI	(1·4, 3·5)	(2·1, 7·1)	(2·2, 5·0)
Median	2·1	3·5	2·6
Q1; Q3	1·1; 3·2	2·0; 4·0	1·6; 3·8
Min; Max	0·0; 7·5	1·2; 22·0	0·0; 22·0
P-value between doses			0·073
Plasma Concentration - Cycle 1 Day 5			
n	13	16	29
Mean (SD)	8·7 (8·1)	13·6 (5·9)	11·4 (7·2)
95% CI	(3·9, 13·6)	(10·4, 16·7)	(8·6, 14·1)
Median	6·0	13·0	11·3
Q1; Q3	3·2; 11·3	8·0; 17·9	6·2; 15·0
Min; Max	2·6; 31·1	6·3; 24·6	2·6; 31·1
P-value between doses			0·013
Ratio of accumulation at nominal day 5 (Ctrough (Day 5)/Ctrough (Day 2))			
n	10	14	24
Mean (SD)	3·1 (1·2)	5·0 (2·3)	4·2 (2·1)
95% CI	(2·3, 3·9)	(3·6, 6·3)	(3·3, 5·1)
Median	2·6	5·2	4·3
Q1; Q3	2·3; 4·2	3·2; 6·6	2·3; 5·5
Min; Max	1·8; 5·0	0·8; 8·9	0·8; 8·9
P-value Day 5 versus Day 2	0·002	0·0001	<·0001
P-value between doses			0·055

Plasma levels of iadademstat were assessed in the PKAS (PK Analysis set) by High-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) in serial PB samples (10 mL) collected in Cycle 1, days 1,2 and 5 before the administration of the daily dose of the drug on available samples. The two-tailed Mann-Whitney test with continuity correction was used for statistics.

Table S8. LSD1 Target Engagement Analysis

Table S8. LSD1 target engagement (PDAS)

	60 µg/m2/d iadademstat n=13	**90 µg/m2/d iadademstat n=16**	**Overall n=29**
Averaged LSD1 TE (%) - Baseline			
n	11	15	26
Mean (SD)	0	0	0
95% CI	0	0	0
Median	0	0	0
Q1; Q3	0	0	0
Min; Max	0	0	0
P-value between doses			1
Averaged LSD1 TE (%) - Cycle 1 Day 2			
n	11	11	22
Mean (SD)	56·8 (15·2)	70·8 (14·4)	63·8 (16·1)
95% CI	(46·7, 67·0)	(61·1, 80·6)	(56·7, 71·0)
Median	62·3	71·8	63·6
Q1; Q3	45·6; 67·7	59·7; 84·4	53·4; 72·5
Min; Max	29·3; 79·2	45·4; 93·1	29·3; 93·1
P-value between doses			0·10
Averaged LSD1 TE (%) - Cycle 1 Day 5			
n	9	12	21
Mean (SD)	77·1 (14·4)	91·7 (3·8)	85·5 (12·1)
95% CI	(66·0, 88·2)	(89·3, 94·1)	(79·9, 91·0)
Median	80·1	91·6	89·0
Q1; Q3	67·4; 89·0	88·9; 95·2	84·6; 93·1
Min; Max	53·8; 92·1	84·6; 96·7	53·8; 96·7
P-value between doses			0·017

Results of the LSD1 target engagement (TE) analysis performed in PDAS (PD Analysis set). Peripheral blood (10 mL) was used to isolate Peripheral blood Mononucleated cells (PBMCs) in Leucosep tubes for the determinations by ELISA.4 Sampling was done on the Cycle 1 of treatment on days 1, 2 and 5 before the drug administration. The two-tailed Mann-Whitney test with continuity correction was used for statistics.

IV. SUPPLEMENTAL FIGURES.

Figure S1. Event-Free-Survival and Overall Survival Analysis

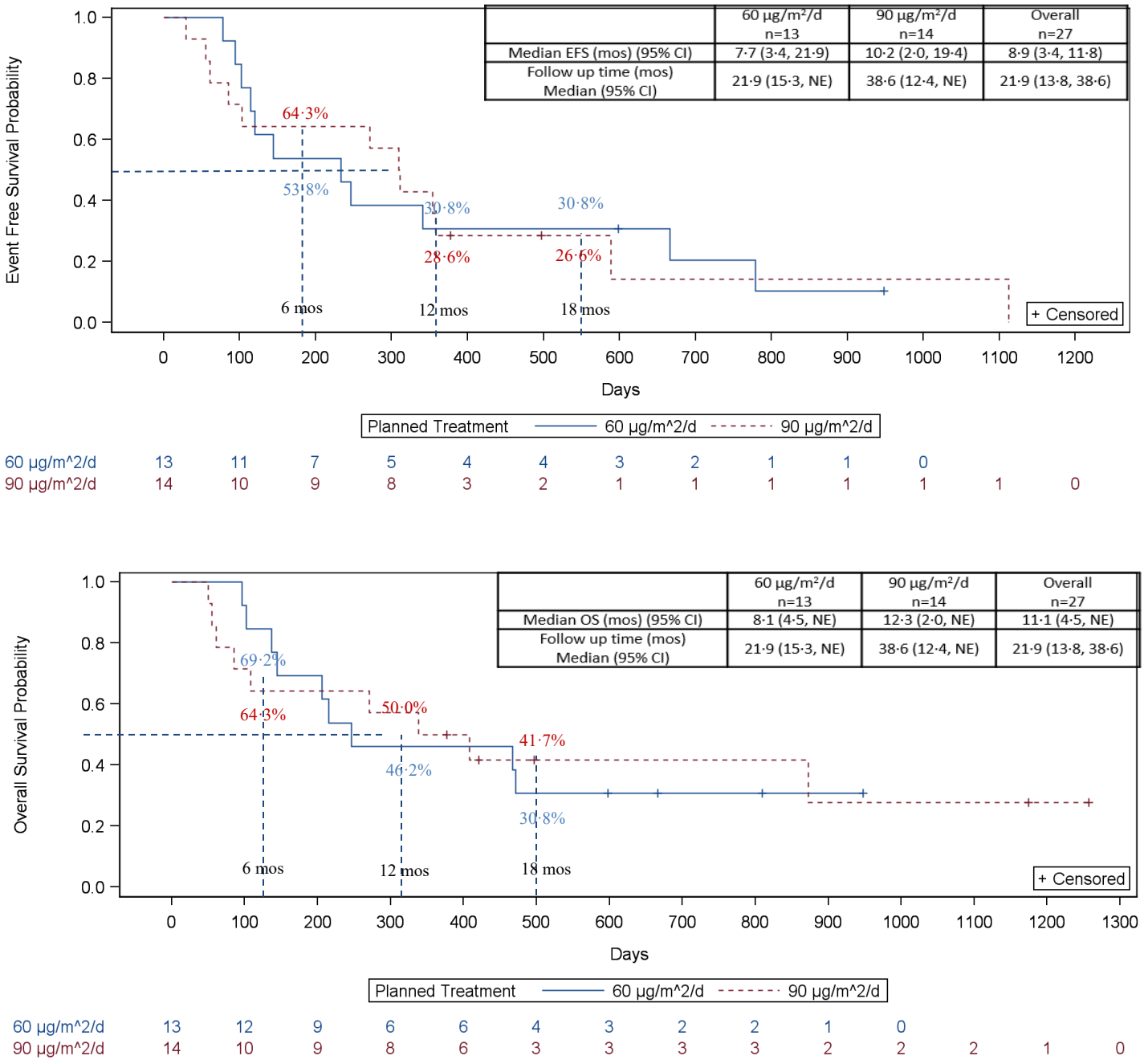

Figure S1. EFS (top) and OS (bottom) Kaplan Mayer curves for the EAS population in the ALICE study. Percentages embedded in the graphs indicate the survival rates at 6,12 and 18 months. Mos: months; NE: Not Evaluable; CI: Confidence Interval.

Figure S2. EAS mutational profile and associated responses

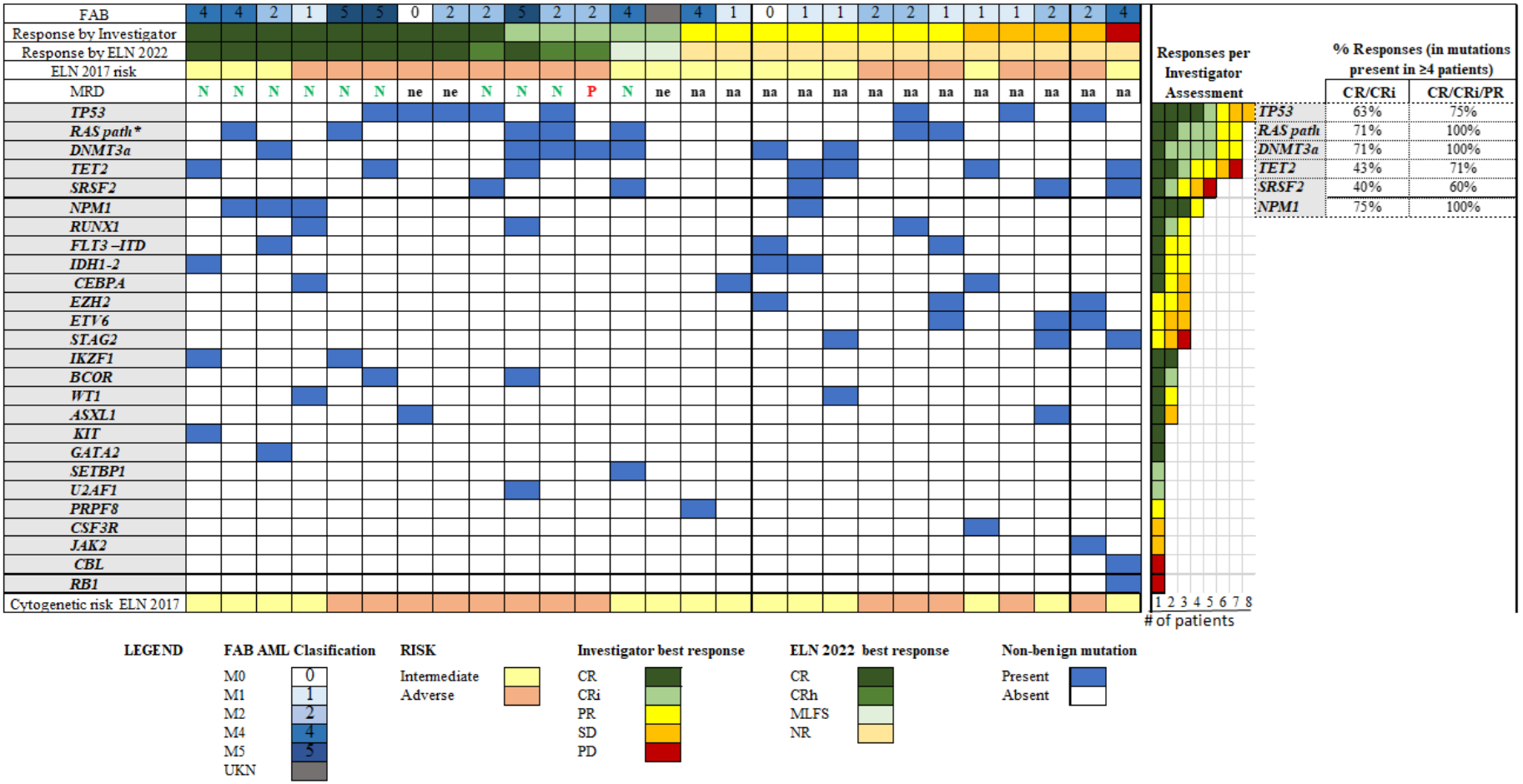

Figure S2. EAS mutational profile and associated responses. Left panel shows mutations detected by NGS considered pathogenic or probably pathogenic for each of the 27 patients in the EAS. FAB AML classification subtype, ELN 2017 and cytogenetic risk, the best response achieved (per investigator and ELN2022 ad-hoc analysis), the available MRD (P=positive, N=negative) result and the days on treatment for each patient are also shown. The right panel depicts best responses per mutation type as assessed by the investigator and % of response for the more prevalent 6 mutations (present in 4 or more patients).

CR: Complete Remission; CRi: CR with incomplete hematologic recovery; CRh: CR with partial hematologic recovery; MLFS: Morphologic Leukemia Free State; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; NR: No response; MRD: Measurable Residual Disease; FAB: French-American-British; ELN: European Leukemia Net; na: not available; ne: not evaluable; (*) Including *K-N-H RAS, BRAF, PTPN11* and *NF1* mutations.

Figure S3. Exposure and PD/Dose-response relationship and safety analysis per dose cohort

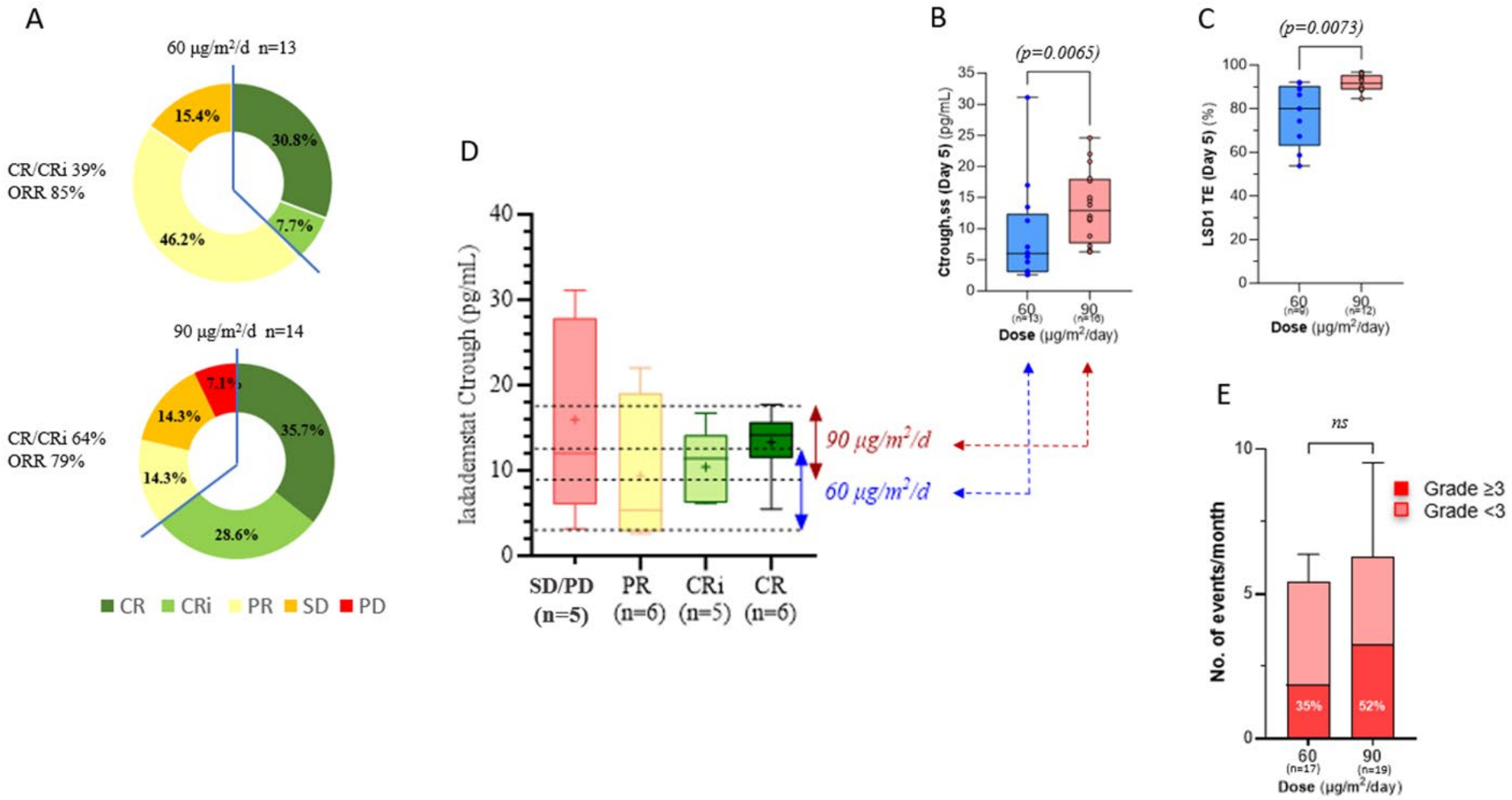

Figure S3: Exposure and PD/Dose-Response relationships and safety analysis per dose cohort. (A) Best response rate per investigator assessment in the EAS is shown in donut charts for the 60 ug/m^2/d dose cohort (top) and the 90 ug/m^2/d dose cohort (bottom) . (B) Iadademstat exposure (Ctrough) at day 5 per assigned dose in the available samples from the SAS. (C) LSD1 target engagement (TE) on day 5 per assigned iadademstat dose in the available samples from the SAS. (D) Exposure/best response relationship: dashed lines represent the 25th and 75th percentiles of the Ctrough reached at each dose in the SAS population. (E) Adverse events (Grade ≥ 3 or < Grade 3) per assigned dose cohort in the SAS. Median with interquartile range of the number of events per month is represented. Percentages of Grade ≥ 3 events with respect to the total events/month are indicated. Two-tailed Mann Whitney exact test was used for statistical comparisons.
CR: Complete Remission; CRi: CR with incomplete hematologic recovery; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ns: no statistically significant.

V. REFERENCES

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CLINICAL TRIAL

Version 7.0

17/05/2022

CL02-ORY-1001 AML	**A pilot 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.**

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