Groupe Francophone des Myélodysplasies

TRIAL PROTOCOL

A phase I-II study to assess venetoclax + azacitidine and donor lymphocyte infusion in patients with MDS or AML (blasts < 30%) in relapse after allo hematopoietic stem cell transplantation

Study of phase I/II, not randomized, open label multicenter
EUDRACT Nr : 2021-000632-56

STUDY DRUG	**VENETOCLAX**
SHORT TITLE	**VENTOGRAFT study**
EudraCT NUMBER	**2021-000632-56**
VERSION	**5**
STUDY	**Open label multicenter, Phase I/II, not Randomized**
DATE	**20/04/2022**

SPONSOR SIGNATURE PAGE

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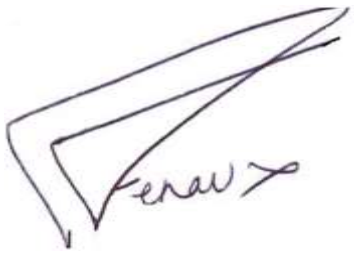

June 16, 2022

_____ _____
Signature of Sponsor Date

Pierre FENAUX
_____
Printed Name

By my signature, I agree to supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines or local regulations governing the conduct of clinical studies.

INVESTIGATOR SIGNATURE PAGE

Investigator :

Signature of Investigator | Date

Printed Name of Investigator

We, the undersigned, agree to conduct this trial according to this protocol. We commit ourselves to treat, to follow-up, and to document all included participants according to the study protocol.

Study Personnel

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Supported by	**AbbVie**

Abbreviations

AE	Adverse Event
Allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplantation
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
AST	Aspartate aminotransferase
AZA	Azacitidine
BCL2	B-cell lymphoma-2
BM	Bone Marrow
BMA	Bone Marrow Aspirate
BP	Blood Pressure
CBC	Complete Blood Count (including hemoglobin, platelets, leukocytes, neutrophils)
CI	Coordinating investigator
CLL	Chronic Lymphocytic Leukemia
CMML	Chronic Myelomonocytic Leukemia
CNS	Central Nervous System
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DLI	Donor Lymphocyte Infusion
DLT	Dose Limiting Toxicities
DMC	Data Monitoring Committee
DOR	Duration of response
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

EFS	Event-Free Survival
EMA	European Medicines Agency
EPO	Erythropoietin
FAB	French-American-British Classification System
FCBP	Females of Childbearing Potential
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical PracticeGastrointestinal
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
G-CSF	Granulocyte-Colony Stimulating Factor
GvHD	Graft-versus-Host-Disease
GvL	Graft-versus-leukemia
HI	Hematologic Improvement
HI-E	Hematologic Improvement of Erythrocytes
HI-N	Hematologic Improvement of Neutrophils
HI-P	Hematologic Improvement of Platelets
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating Agent
HR	Heart Rate
HSCT	Hematopoietic Stem Cell Transplantation
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International normalized ratio
IPSS	International Prognostic Scoring System
IPSS R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
IWG	International Working Group

MDS	Myelodysplastic Syndrome
MDS-EB1	Myelodysplastic Syndrome with Excess Blasts type 1
MDS-EB2	Myelodysplastic Syndrome with Excess Blasts type 2
MDS-MLD	Myelodysplastic Syndrome with Multilineage Dysplasia
MDS-RS	Myelodysplastic Syndrome with Ring Sideroblasts
MDS-SLD	Myelodysplastic Syndrome with Single Lineage Dysplasia
MDS-U	Myelodysplastic Syndrome Unclassifiable
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NR	No Response
OIR	Overall Improvement Rate
ORR	Overall Response Rate
OS	Overall Survival
PB	Peripheral Blood
PD	Progressive Disease
PFS	Progression-Free Survival
PLT	Platelets
PR	Partial Remission
PT	Prothrombin Time
Pts	Patients
PTT	Partial Thromboplastin Time
QD	Once a day
RA	Refractory Anemia
RAEB	Refractory Anemia with Excess of blasts
RAEB-T	RAEB in Transformation
RARS	Refractory Anemia with Ringed Sideroblasts
RBC	Red Blood Count
REB	Research Ethics Board
RPTD	Recommended Phase II Dose
SAE	Serious Adverse Event
SC	Subcutaneous
SCT	Stem Cell Transplantation
SLL	Small Lymphocytic Lymphoma

SmPC	Summary of Product CharacteristicsSuspected Unexpected Serious
SUSAR	Adverse Reaction
TLS	Tumor lysis syndrome
ULN	Upper Limit of Normal
WBC	White Blood Cells

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1 PROTOCOL SYNOPSIS

PROTOCOL TITLE Phase I-II study to assess venetoclax + azacitidine and donor lymphocyte infusion in patients with MDS or AML (with marrow blasts < 30%) in relapse after allogeneic hematopoietic stem cell transplantation (VENTOGRAFT study)	
STUDY DRUGS	Venetoclax
EudraCT NUMBER	2021-000632-56
Number of Patients	Approximately 48 adult patients will be enrolled into the study
Study Population	Adult patients with MDS or AML with less than 30% blasts in relapse after Allo-SCT
STUDY PHASE	I/II
Study Sites	Approximately 20 sites

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Documented relapse of MDS or AML with marrow blasts < 30% (with WBC < 15000/mm^3) after allo-SCT.
2. Age ≥ 18 years.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
4. Patient must have adequate organ function as indicated by the following laboratory values:

System	Laboratory Value
Renal	
Serum creatinine or calculated creatinine clearance[a]	< 2 mg/dl **OR** ≥ 30 mL/min for patients with creatinine levels > 1.5 x institutional ULN
Hepatic	
Serum total bilirubin	≤ 2.5 x ULN **OR** direct bilirubin ≤ ULN for patients with total bilirubin levels ≥ 2 mg/dL.
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN
Alkaline Phosphatase	≤ 5 x ULN

	If > 2.5 x ULN, then liver fraction should be ≤ 2.5 x ULN

[a] Creatinine clearance should be calculated per institutional standard.

5. Patient not refractory to platelet transfusions.
6. Female subject of childbearing potential must practice at least one protocol specified method of birth control (**see Appendix 3**), starting on Study Day 1 through at least 30 days after the last dose of venetoclax or 3 months after the last dose of azacitidine.
   Not being of childbearing potential is defined as:
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause, or
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L, or
   - Permanent surgical sterility (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
7. Female subjects of childbearing potential must have negative results for pregnancy test performed:
   - At Screening with a serum sample obtained within 14 days prior to the first study drug administration, and
   - Prior to dosing with urine sample obtained on Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy test results.

   Female subjects who are not of childbearing potential at Screening do not require pregnancy testing.
8. Male subjects sexually active with female partner(s) of childbearing potential, must agree from first dose of study drug(s) through at least 30 days after the last dose of venetoclax or 3 months after the last dose of azacitidine, whichever is later, to practice the protocol specified contraception (**see Appendix 3**).
9. Patient is available for periodic blood sampling, study related assessments, and appropriate clinical management at the treating institution for the duration of the study.
10. Patient has the ability to understand and willingness to sign an informed consent form indicating the investigational nature of the study.
11. Patient is able to swallow capsules.

Exclusion Criteria

Patients with any one of the exclusion criteria listed below are not eligible for the study:

1. Patient has active and uncontrolled infection.
2. Patient has active acute or chronic GVHD.
3. Patient receives more than 1mg/kg/day prednisolone.
4. Patient has uncontrolled intercurrent illness or circumstances that could limit compliance with the study, including but not limited to the following: symptomatic

congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, pancreatitis, or psychiatric or social conditions that may interfere with patient compliance.

5. Patient is currently participating or has participated in a study with an investigational compound or device within 30 days of initial dosing with study drug.
6. Patient has known human immunodeficiency virus (HIV) infection or HIV-related malignancy.
7. Patient has clinically active hepatitis B or hepatitis C infection.
8. Patient has a known allergy or hypersensitivity to any component of VENETOCLAX or AZA.
9. Patient with a "currently active" second malignancy, other than non-melanoma skin cancer and carcinoma in situ of the cervix, should not be enrolled. Patients are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy, are disease free from prior malignancies for > 5 years or are considered by their physician to be at less than 30% risk of relapse.
10. Patient has received growth factors such as erythropoietin alfa (EPO) or granulocyte colony-stimulating factor (G-CSF) or has received non cytotoxic agents (including low dose oral chemotherapy) in the 30 days before inclusion. In case of previous cytotoxic treatment, an interval of 3 months is required.
11. Patient is on any systemic steroids that have not been stabilized to the equivalent of ≤ 10 mg/day prednisone during the 4 weeks prior to the start of the study drugs.
12. Patients with clinical evidence of CNS leukemia.
13. Patient has a history of GI surgery or other procedures that might interfere with the absorption or swallowing of the study drugs.
14. Subject enrolled in a Dose-Escalation cohort has received strong or moderate CYP3A inhibitors (**see appendix 2 for examples**) within 3 days prior to the first dose of study drug.
15. Patient is unable to take and/or tolerate oral medications on a continuous basis.
16. Patient is pregnant or breastfeeding within the projected duration of the study.
17. Subject has a malabsorption syndrome or other condition that precludes an enteral route of administration.
18. Absence of social security.

STUDY OBJECTIVES

Objectives

The objectives of this study are to assess the safety, and efficacy, of venetoclax in combination with AZA/DLI in patients with MDS and AML with marrow blasts < 30% (myeloid neoplasms) in relapse after allogeneic hematopoietic stem cell transplantation.

Phase I:

- Assess the safety profile of venetoclax in combination with AZA/DLI

- Determine the recommended Phase II dose (RPTD)

Phase II: Determine the efficacy of venetoclax in combination with AZA/DLI

STUDY ENDPOINTS

Primary endpoint:

Phase I: To determine toxicity profile and safety of the combination

Phase II: Overall hematological response rate of venetoclax in combination with AZA/DLI
Response assessment will be performed for MDS according to modified IWG 2006 criteria and according to European LeukemiaNet criteria for AML.

Secondary endpoints:

- ✓ Toxicity as measured by NCI CTCAE 5.0
- ✓ Acute and chronic GVHD rate
- ✓ Duration of response (DOR)
- ✓ Overall survival (OS)
- ✓ Progression-free survival (PFS)
- ✓ Event-free survival (EFS)

Exploratory endpoint:

- ✓ Study the correlation between patient overall mutational status before treatment and response
- ✓ The prognostic impact of MRD on outcome

STUDY DESIGN

This is an open label multicenter phase I/II study. Patients will be treated with venetoclax during 14 days in combination with AZA at 75 mg/m²/day for 5 days for each cycle or 50 mg/m²/day for 5 days each cycle if relapse occurred less than 4 months after allo SCT.

Patients who meet eligibility criteria will be administered VENETOCLAX orally at starting dose in phase I part and at MTD in phase II part on days 1-14 in combination with AZA at 75 mg/m²/day for 5 days for each cycle (on days 1-5) or 50 mg/m²/day for 5 days each cycle if relapse occurred less than 4 months after allo SCT.

Following cycles must be administered on day 28 or delayed until day 42 in cases of hematological toxicity. Each cycle will last 28 days starting on day 1 of each cycle when ANC > 1 G/L and platelet > 50 G/L without transfusion or when recovery of baseline level.

In the phase I part, VENETOCLAX will be given once daily orally on days 1-14 for all cycles at escalating doses starting at Dose Level 1 (defined below) in combination with AZA +/- DLI. Patients will receive at least 8 cycles of VENETOCLAX/AZA/DLI unless progression occurs. Response will be assessed after 4, 6 and 8 cycles. Patients achieving a response (defined below) will be able to continue on protocol with VENETOCLAX + AZA until 12 cycles maximum then with AZA alone. In the absence of response, patients will stop treatment.

Dose Levels for Treatment in Phase I

Dose Level	**VENETOCLAX (mg)**	**Azacitidine (mg/m²)**
-1	50 mg*	75 (50 if relapse < 4 months)
1 (Starting dose)	100 mg*	75 (50 if relapse < 4 months)
2	200 mg*	75 (50 if relapse < 4 months)
3	400 mg*	75 (50 if relapse < 4 months)

*VENETOCLAX will be given once daily orally during 14 days.

In the phase II part, VENETOCLAX will be given once daily orally on days 1-14 for all cycles at MTD defined in the phase I part of the study in combination with AZA/DLI. Patients will receive at least 8 cycles of VENETOCLAX/AZA/DLI unless progression occurs. Response will be assessed after 4, 6 and 8 cycles. Patients achieving a response (defined below) will be able to continue on protocol with VENETOCLAX + AZA until 12 cycles maximum then AZA alone. In the absence of response, patients will stop treatment.

Ramp-up** will be performed at the beginning of cycle 1 :

Dose Level	**VENETOCLAX D1C1**	**VENETOCLAX D2C1**	**VENETOCLAX D3C1 and beyond**
-1	10 mg*	20 mg*	50 mg*
1 (Starting dose)	20 mg*	50 mg*	100 mg*
2	50 mg*	100 mg*	200 mg*
3	100 mg*	200 mg*	400 mg*

*VENETOCLAX will be given once daily orally

**Therapy with CYP3A inhibitor are not allowed during the ramp up.

DLI will be infused every two cycles (C2, C4, C6, C8) at day 15 in absence of GVHD as follows, and at least 8 weeks after immunosuppressive therapy discontinuation. If the chimerism in > 90% recipient, DLI will not be performed.

	DLI dosage
Sibling-Id or Unrelated Donor-Id 10/10	0.5×10^7 CD3/kg 1×10^7 CD3/kg 0.5×10^8 CD3/kg 1×10^8 CD3/kg
Unrelated Donor-Id 9/10	1×10^6 CD3/kg 5×10^6 CD3/kg 1×10^7 CD3/kg 0.5×10^8 CD3/kg

INVESTIGATIONAL PRODUCT

Venetoclax

Venetoclax will be administered at dose levels defined for the cohort a given subject is assigned to at Screening.

Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of a meal (preferably breakfast). Exceptions may apply if food is not allowed for medical procedures. Tablets must be swallowed whole and must not be broken, chewed, or crushed. The dose should be administered at the same time each day.

On days of concomitant administration of azacitidine, venetoclax should be given prior to azacitidine.

If vomiting occurs after taking venetoclax, do not take any additional dose that day. Take the next dose at the usual time the next day. A missed dose of venetoclax should be taken with food and water within 8 hours of the missed dose. After 8 hours, the missed dose should not be taken. The next dose of venetoclax will be the regularly scheduled dose.

Azacitidine

Azacitidine will be administered at the dose of 75 mg/m²/day for 5 days for each cycle or 50 mg/m²/day for 5 days each cycle if relapse occurred less than 4 months after allo SCT and should be prepared according to the information provided in the Summary of Product Characteristics (SmPC) and will be administered, by IV infusion or SC injection.

BIOLOGICAL STUDIES

Mutational analysis (Hematology Laboratory, CHRU Lille)
Immunologic analysis (Immunology Laboratory, Saint Louis hospital, Paris and INSERM U1065, Mediterranean center of molecular medicine, Nice)

At screening and during follow up (after 4 and 8 cycles and at the end of the study) presence of all identified mutations will be investigated with the same technique. All mutation-specific primers and probes will be designed by Biorad (Hercules, CA).

OVERALL DURATION OF THE STUDY: 42 MONTHS

Recruitment months: 24 months

Duration of Treatment: 12 months

Follow-up for all patients: 6 months

2 SUMMARY OF RATIONALE

a) MDS and AML in relapse after allo hematopoietic stem cell transplantation and their current treatment
Among patients with acute myeloid leukemia (AML), allogeneic hematopoietic stem cell transplantation (allo-HSCT) used as post-remission therapy for those with high-risk molecular profiles or as salvage therapy for those with resistant disease offers the highest potential for long-term survival[1]. In addition, allo-HSCT is the only curative option for patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML)[2]. Still, relapse after allo-HSCT remains the major cause of treatment failure and is associated with a dismal prognosis[3]. Treatment options for those patients are mainly restricted to chemotherapy, donor lymphocyte infusions (DLI) or second allo-HSCT [4]. Treatment approach should ideally offer efficient antileukemic activity, acceptable toxicity and mechanisms to direct the donor immune system towards an enhanced graft-versus-leukemia effect without provoking graft-versus-host disease (GvHD). To fulfil all criteria, combination of azacitidine (AZA) to donor lymphocyte infusion (DLI) could be used in patients with relapse inferior to 2 years after allo-HSCT. AZA is approved for the treatment of patients with high-risk MDS and AML [5, 6]. Beyond its direct cytotoxic effects and ability to induce remissions even in patients refractory to chemotherapy, AZA is considered to increase the immunogenicity of AML blasts by re-expression of important antigens[7-9]. Furthermore, animal models suggest an immunomodulatory role of AZA that might attenuate GvHD after DLI [10, 11]. Combination was evaluated in AZARELA trial [12]. Treatment schedule contained up to eight AZA cycles (100 mg/m²/day, days 1–5, every 28 days) followed by DLI (from 1–5 x 10^6 to 1–5 x 10^8 CD3 cells/kg) after every second AZA cycle. A median of three courses AZA (range 1–8) were administered and 22 patients (73%) received DLI. Overall response rate was 30%, including seven complete remissions (CR, 23%) and two partial remissions (7%)[12, 13]. Incidence of acute and chronic

graft-versus-host disease was 37% and 17%, respectively. Azacitidine and DLI as salvage therapy is safe, induces long-term remission and is today a standard of care for patients in relapse after allo-HSCT [14].

b) VENETOCLAX

VENETOCLAX/GDC-0199 is a selective inhibitor of B-cell lymphoma-2 (BCL-2). The BCL-2 gene prevents apoptosis of some cells, including lymphocytes and can be highly expressed in cancers in the lymph nodes, spleen and other organs of the immune system. VENETOCLAX is designed to block the function of the BCL-2 protein by restoring the communication system that tells cancer cells to self-destruct. VENETOCLAX is approved for the treatment of patients with chronic lymphocytic leukemia (CLL), and is in clinical trials for small lymphocytic lymphoma (SLL), non-Hodgkin's lymphoma, multiple myeloma and acute myelogenous leukemia (AML). The effects of VENETOCLAX in combination with AZA in patients with MDS and AML have been reported in phase I. Ten patients received AZA + VENETOCLAX with VENETOCLAX at 400 mg (Cohort 1, n=4) and 800 mg (Cohort 2, n=6). Treatment-emergent adverse events (AEs) were febrile neutropenia, constipation, cough, nausea. The most common grade 4 AEs were a decrease in platelet count (30%), neutrophil count (20%), and white blood cell count (20%). The most frequent serious AE was febrile neutropenia (30%). Overall response rate was 70% (7/10 pts). Mutational profile of these patients weren't available[15]. Phase III is ongoing in patients ineligibles for intensive chemotherapy.

c) Use of DLI and AZA + DLI in France

In 2018, french guidelines about use of donor lymphocyte infusion were published by Francophone Bone Marrow Transplantation and Cellular Therapy (SFGTM-TC)[16]. Donor lymphocyte infusion (DLI) can be proposed to treat or prevent the relapse of malignant hemopathies following allogeneic stem cell transplantation. Doses of DLI were defined in the guidelines and were commonly used in all French centers. Response rate of DLI in AML or MDS patients were around 20-40% alone[17]. Response rate is higher in defavorable cytogenetic AML patients[18]. A german retrospective study has evaluated combination of azacitidine and donor lymphocyte infusions following relapse after allogeneic hematopoietic stem cell transplantation in AML and MDS [19]. Combination AZA + DLI showed an overall response rate of 33% including 27% and 6% of complete and partial remission, respectively. Based on these results, using of AZA + DLI in combination is the classical regimen used today in France at relapse. During the 8 past years, 64/475 (13%) DLI including 53% in combination with AZA were performed in France based from SFGM-TC data in relapsed MDS/AML.

d) Rationale for the combination of AZA + DLI and VENETOCLAX

In the present study, we will use the combination of these two drugs to try to create a synergetic effect and generate a response for patients in relapse after allo-HSCT. The rationale of combining AZA + VENETOCLAX + DLI is to increase anti leukemic effect before DLI. It was shown that the response rate after DLI is higher in low disease AML patients[18]. Moreover, VENETOCLAX was shown to induce a switch between naive and memory B-cell subsets with 80% VENETOCLAX dose-dependent decrease of autoreactive B cells in autoimmune disease like lupus. In parallel, there were no consistent or marked changes in neutrophils, natural killer cells, hemoglobin, or platelets[20]. Hypothesis will be that AZA + VENETOCLAX could induce more GvL with low GHD rate. We will begin by VENETOCLAX as single agent during 28 days before starting the combination with AZA to reduce potential hematological side effects especially in this population after allo-SCT. Overexpression of BCL-2 has been implicated in the maintenance and survival of AML cells and

associated to resistance to chemotherapy. As BCL-2 has been observed to be up-regulated in AML patients [21, 22] and blocks differentiation of myeloid progenitors, it may be considered as a potential candidate progression gene of MDS transformation. The primary antiapoptotic mechanism of BCL-2 action is interaction with proapoptotic members of the BCL-2 family to block the mitochondrial permeability transition and release of cytochrome C[23]. Bogenberger et al. showed the in vitro role of VENETOCLAX in combination with azacitidine in AML, myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML)[24]. Therefore, use of VENETOCLAX could be a good therapeutic strategy in MDS and AML.

3 HYPOTHESIS

Based on AZARELA trial results, we assume that approximately 30% of responses due to AZA/DLI effects only might be observed. The objective is to demonstrate a 20% increase in response due to the addition of VENETOCLAX (i.e. from 30% to 50% after 6 cycles of AZA/DLI + VENETOCLAX). For the phase I, a design "3+3" will be used including between 9 to 18 patients. For the phase II, a two-stage design will be used. Under H0=30% and p1=50%, the study with α=0.05 and β= 0.2, if 3 responses or less are observed in the first 14 evaluable patients, there will be no further inclusions (the inclusions would be terminated early), but all patients on treatment and that continue to derive clinical benefit according to the opinion of the investigator while tolerating study-treatment may continue to receive treatment according to the protocol.
If 4 or more responses are observed, 16 additional patients will be included in the study. If 13 responses or more are observed in evaluable patients, further investigation is warranted to compare AZA/DLI and combination of AZA/DLI and VENETOCLAX. We consider that a maximum of 10% of the population may not be evaluable for response and that a total of 48 patients will be needed to address the question.
All patients on treatment and that continue to derive clinical benefit according to the opinion of the investigator while tolerating study-treatment may continue to receive treatment at the cohort-assigned dose level.

4 STUDY OBJECTIVES

The objectives of this study are to assess the safety, and efficacy, of venetoclax in combination with AZA/DLI in patients with myeloid neoplasms in relapse after allo hematopoietic stem cell transplantation.
Phase I:

- Assess the safety profile of venetoclax in combination with AZA/DLI
- Determine the recommended Phase II dose (RPTD)

Phase II: To determine the efficacy of venetoclax in combination with AZA/DLI

5 STUDY ENDPOINTS

5.1 Primary endpoint

Phase I: To determine toxicity profile and safety of the combination

Phase II: Overall hematological response rate of venetoclax in combination with AZA/DLI

Response assessment will be performed according to modified IWG 2006 criteria for MDS and according European LeukemiaNet criteria for AML.

5.2 Secondary endpoints

- ✓ Toxicity as measured by NCI CTCAE 5.0
- ✓ Acute and chronic GVHD rate
- ✓ Duration of response (DOR)
- ✓ Overall survival (OS)
- ✓ Progression-free survival (PFS)
- ✓ Event-free survival (EFS)

5.3 Exploratory endpoint

- ✓ Study the correlation between patient overall mutational status before treatment and response
- ✓ The prognostic impact on outcome of MRD

6 INVESTIGATIONAL PLAN

6.1 Overall design

This is an open label multicenter phase I/II study. Patients will be treated with venetoclax during 14 days in combination with AZA at 75 mg/m²/day for 5 days for each cycle or 50 mg/m²/day for 5 days each cycle if relapse occurred less than 4 months after allo SCT.

Patients who meet eligibility criteria will be administered VENETOCLAX orally at starting dose in phase I part and at MTD in phase II part on days 1-14 in combination with AZA at 75 mg/m²/day for 5 days on days 1-5 for each cycle or 50 mg/m²/day for 5 days each cycle if relapse occurred less than 4 months after allo SCT.

Following cycles must be administered on day 28 or delayed until day 42 in cases of hematological toxicity. Each cycle will last 28 days starting on day 1 of each cycle when ANC > 1 G/L and platelet > 50 G/L without transfusion or when recovery of baseline level.

In the phase I part, VENETOCLAX will be given once daily orally on days 1-14 for all cycles at escalating doses starting at Dose Level 1 (defined below) in combination with AZA +/- DLI. Patients will receive at least 8 cycles of VENETOCLAX/AZA/DLI unless progression occurs. Response will be assessed after 4, 6 and 8 cycles. Patients achieving a response (see appendix 11 and 12) will be able to continue on protocol with VENETOCLAX + AZA until 12 cycles maximum then with AZA alone. In the absence of response, patients will stop treatment.

Dose Levels for Treatment in Phase I

Dose Level	VENETOCLAX (mg)	Azacitidine (mg/m²)
-1	50 mg*	75 (50 if relapse < 4 months)
1 (Starting dose)	100 mg*	75 (50 if relapse < 4 months)
2	200 mg*	75 (50 if relapse < 4 months)
3	400 mg*	75 (50 if relapse < 4 months)

*VENETOCLAX will be given once daily orally during 14 days.

In the phase II part, VENETOCLAX will be given once daily orally on days 1-14 for all cycles at MTD defined in the phase I part of the study in combination with AZA/DLI. Patients will receive at least 8 cycles of VENETOCLAX/AZA/DLI unless progression occurs. Response will be assessed after 4, 6 and 8 cycles. Patients achieving a response (defined below) will be able to continue on protocol with VENETOCLAX + AZA until 12 cycles maximum then AZA alone. In the absence of response, patients will stop treatment.

Ramp-up** will be performed at the beginning of cycle 1:

Dose Level	**VENETOCLAX D1C1**	**VENETOCLAX D2C1**	**VENETOCLAX D3C1 and beyond**
-1	10 mg*	20 mg*	50 mg*
1 (Starting dose)	20 mg*	50 mg*	100 mg*
2	50 mg*	100 mg*	200 mg*
3	100 mg*	200 mg*	400 mg*

*VENETOCLAX will be given once daily orally.

**Therapy with CYP3A inhibitor are not allowed during the ramp up.

DLI will be infused every two cycles (C2, C4, C6, C8) at day 15 in absence of GVHD as follows, and at least 8 weeks after immunosuppressive therapy discontinuation. If the chimerism in > 90% recipient, DLI will not be performed.

	DLI dosage
Sibling-Id or Unrelated Donor-Id 10/10	0.5 x 10^7 CD3/kg 1 x 10^7 CD3/kg 0.5 x 10^8 CD3/kg 1 x 10^8 CD3/kg
Unrelated Donor-Id 9/10	1 x 10^6 CD3/kg 5 x 10^6 CD3/kg 1 x 10^7 CD3/kg 0.5 x 10^8 CD3/kg

Patients with Complete Remission (CR), Partial Remission (PR), marrow CR or Hematological Improvement (HI) after 8 Cycles of therapy (IWG 2006 criteria or Cheson et al. criteria for AML) continue on protocol with VENETOCLAX + AZA until 12 cycles maximum then AZA alone. Patients with no response (NR) to treatment will be withdrawn from the protocol after the last treatment Cycle.

6.2 Dose Escalation Guidelines

Subjects in part of phase I will be enrolled into a dose-escalation study, and in 3 expansion cohorts evaluating venetoclax combined with azacitidine in subjects with MDS with myeloid neoplasms (blasts < 30%) in relapse after allo hematopoietic stem cell transplantation.

The dose escalation portion is expected to enroll approximately 9 – 18 subjects.

The first venetoclax dose-level to be evaluated in combination with azacitidine will be 100 mg QD at a dosing duration of 14 days per cycle. A cycle is defined as a time period of 28 days.

For this study, the dose limiting toxicities (DLT) observation period is defined as the first treatment cycle (Cycle 1) of venetoclax combined with azacitidine.

Dose limiting toxicities for dose escalation purposes will be determined based on adverse events that occur during the DLT observation period.

Adverse events occurring after the DLT observation period criteria will also be reviewed and may be taken into consideration for dose escalation decisions.

Any of the following events will be considered a DLT unless the event can be attribute by the investigator to a clearly identifiable cause such as underlying illness or disease progression, concurrent other illness, or concomitant medication:

- ANC < 1×10^9/L (Grade ≥ 3) which does not recover as defined below:
  - Recovery is defined an increase in ANC from nadir by ≥ 50% of the reduction from baseline to nadir or any increase to an ANC of ≥ 1×10^9/L within 42 days from Day 1 of Cycle 1
  - Delayed recovery should only be deemed a DLT if due to treatment induced toxicity as confirmed by a bone marrow sample showing an overall bone marrow cellularity of < 5%
- Grade ≥ 3 thrombocytopenia associated with clinically significant bleeding that requires transfusion of platelets over routine or baseline transfusion needs based on investigator opinion
- Grade ≥ 4 non-hematologic toxicity deemed related to venetoclax per investigator opinion.
- Grade 4 infections or complications related to infections (e.g., sepsis) should only be deemed DLTs if due to treatment-induced neutropenia as confirmed by a bone marrow sample showing an overall bone marrow cellularity of < 5%

6.3 Dose modification for TLS and other toxicities

Venetoclax-associated tumor lysis syndrome (TLS) is predominantly seen in patients with CLL with high tumor burden. The risk of TLS in MDS is considered small. Additionally, limiting the white blood cell (WBC) as implemented by the inclusion criteria will further mitigate TLS risk.

Additional safety and efficacy data are described in more detail in the current version of the venetoclax Investigator's Brochure.

For patients who have had a dosing interruption lasting more than 2 weeks, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose; see Table 3).

Table 3: Dose modification for TLS and other toxicities

Dose at interruption (mg)	Dose at restart (mg*)
400	300
300	200
200	100
100	50
50	20
20	10
* The modified dose should be continued for 1 cycle before increasing the dose.	

6.4 Prohibited Medications and Therapy

The Following Medications and Therapy are not allowed during the study:

- Strong cytochrome P450 3A (CYP3A) inducers (consider alternative treatments with less CYP3A induction)
- Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) and star fruit (carambola) 3 days before starting study drug in each cycle.

Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

6.5 Concomitant Therapy permitted

The following concomitant medications/therapy are permitted as needed and per institutional guidelines:

•supportive care medications;

•antibiotics, antifungals, anti-emetics, and other standard supportive care medications; Tavanic and Noxafil are recommended in case of ANC < 0.5 G/L;

•transfusion of blood and blood products;

•Granulocyte colony-stimulating factor (G-CSF) (may be administered when Grades 3 to 4 neutropenia occurs per clinical practice).

•Herbal supplements should be discouraged unless known not to be CYP3A active.

•If a P-glycoprote in (P-gp) inhibitor must be used, monitor closely for signs of toxicities or follow local label as applicable.

•Concomitant use of narrow therapeutic index P-gp substrates should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.

•Concomitant use of a moderate CYP3A inducer should be avoided. Alternative treatments with less CYP3A induction should be considered.

•In subjects receiving concomitant use of warfarin, closely monitor the international normalized ratio (INR).

CYP3A inhibitors and inducers should only be used when no appropriate therapeutic alternative exists.

Table 4 describes venetoclax dosage modifications based on concomitant use with a strong or moderate CYP3A inhibitor.

Table 4: Dose Modifications for Venetoclax when Co-Administered with Moderate or Strong CYP3A Inhibitors

Initial Target Venetoclax Dose*	Venetoclax Dose if Co-Administered with a Moderate CYP3A Inhibitor	Venetoclax Dose if Co-Administered with a Strong CYP3A Inhibitor
100 mg	50 mg	10 mg
200 mg	100 mg	20 mg
300 mg	150 mg	30 mg
400 mg	200 mg	50 mg

* For an initial target dose not listed in the table, reduce venetoclax dose by at least 8-fold for strong inhibitors and by at least 2-fold for moderate inhibitors. Therapy with CYP3A inhibitor are not allowed if initial target dose is less than 100 mg.

The Investigators Coordinators should be contacted if there are any questions regarding concomitant or prior therapy(ies).

Examples of clinical CYP3A inhibitors or inducers, or clinical substrates or inhibitors of transporters are provided on the Food and Drug Administration (FDA) website for Drug Development and Drug Interactions: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-druginteractions-table-substrates-inhibitors-and-inducers

6.6 Inclusion *Criteria*

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Documented relapse of MDS or AML with marrow blasts < 30% (with WBC < 15000/mm^3), after allo-SCT. Relapse of MDS or AML is defined as:
   - ✓ Return to pretreatment bone marrow blast percentage
   - ✓ Decrement of at least 50% from maximum remission
2. Age ≥ 18 years.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
4. Patient must have adequate organ function as indicated by the following laboratory values:

System	Laboratory Value
Renal	
Serum creatinine or calculated creatinine clearance[a]	< 2 mg/dl **OR** ≥ 30 mL/min for patients with creatinine levels > 1.5 x institutional ULN
Hepatic	
Serum total bilirubin	≤ 2.5 x ULN **OR** direct bilirubin ≤ ULN for patients with total bilirubin levels ≥ 2 mg/dL.
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN
Alkaline Phosphatase	≤ 5 x ULN If > 2.5 x ULN, then liver fraction should be ≤ 2.5 x ULN
[a] Creatinine clearance should be calculated per institutional standard.	

5. Patient not refractory to platelet transfusions.
6. Female subject of childbearing potential must practice at least one protocol specified method of birth control (**see appendix 3**), starting on Study Day 1 through at least 30 days after the last dose of venetoclax or 3 months after the last dose of azacitidine.
   Not being of childbearing potential is defined as:
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause, or
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L, or
   - Permanent surgical sterility (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
7. Female subjects of childbearing potential must have negative results for pregnancy test performed:
   - At Screening with a serum sample obtained within 14 days prior to the first study drug administration, and
   - Prior to dosing with urine sample obtained on Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy test results.

   Female subjects who are not of childbearing potential at Screening do not require pregnancy testing.

8. Male subjects sexually active with female partner(s) of childbearing potential, must agree from first dose of study drug(s) through at least 30 days after the last dose of venetoclax or 3 months after the last dose of azacitidine, whichever is later, to practice the protocol specified contraception (**see appendix 3**).
9. Patient is available for periodic blood sampling, study related assessments, and appropriate clinical management at the treating institution for the duration of the study.
10. Patient has the ability to understand and willingness to sign an informed consent form indicating the investigational nature of the study.
11. Patient is able to swallow capsules.

6.7 Exclusion Criteria

Patients with any one of the exclusion criteria listed below are not eligible for the study:

1. Patient has active and uncontrolled infection.
2. Patient has active acute or chronic GVHD.
3. Patient receives more than 1mg/kg/day prednisolone.
4. Patient has uncontrolled intercurrent illness or circumstances that could limit compliance with the study, including but not limited to the following: symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, pancreatitis, or psychiatric or social conditions that may interfere with patient compliance.
5. Patient is currently participating or has participated in a study with an investigational compound or device within 30 days of initial dosing with study drug.
6. Patient has known human immunodeficiency virus (HIV) infection or HIV-related malignancy.
7. Patient has clinically active hepatitis B or hepatitis C infection.
8. Patient has a known allergy or hypersensitivity to any component of VENETOCLAX or AZA.
9. Patient with a "currently active" second malignancy, other than non-melanoma skin cancer and carcinoma in situ of the cervix, should not be enrolled. Patients are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy, are disease free from prior malignancies for > 5 years or are considered by their physician to be at less than 30% risk of relapse.
10. Patient has received growth factors such as erythropoietin alfa (EPO) or granulocyte colony-stimulating factor (G-CSF) or has received non cytotoxic agents (including low dose oral chemotherapy) in the 30 days before inclusion. In case of previous cytotoxic treatment, an interval of 3 months is required.
11. Patient is on any systemic steroids that have not been stabilized to the equivalent of ≤ 10 mg/day prednisone during the 4 weeks prior to the start of the study drugs.
12. Patients with clinical evidence of CNS leukemia.
13. Patient has a history of GI surgery or other procedures that might interfere with the absorption or swallowing of the study drugs.

14. Subject enrolled in a Dose-Escalation cohort has received strong or moderate CYP3A inhibitors (see Appendix 2 for examples) within 3 days prior to the first dose of study drug.
15. Patient is unable to take and/or tolerate oral medications on a continuous basis.
16. Patient is pregnant or breastfeeding within the projected duration of the study.
17. Subject has a malabsorption syndrome or other condition that precludes an enteral route of administration.
18. Absence of social security.

6.8 Patient Withdrawal Criteria

Patients are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any patient from the study if that patient requests to be withdrawn. The patient's participation in this study will be discontinued due to the following reasons:

- Death
- Withdrawal of the patient's consent
- Occurrence of AEs for which permanent discontinuation of study medication is desired by the patient or considered necessary by the Investigator or by the Sponsor
- Use of illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise skewing results
- Development of an intercurrent illness or situation which would, in the judgment of the Investigator or the Sponsor, affect assessments of clinical status and study endpoints to a significant degree
- Development of a second cancer that requires treatment
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- Lack of patient compliance
- Serious protocol deviation that affects patient safety and accuracy and/or validity of data
- Patient is lost to follow-up
- Inability to continue in the study for any reason
- Intake of disallowed medication
    - Initiation of any experimental therapy in any period of the study until study treatment failure has been established.
    - Initiation of any anti MDS or AML therapy until study treatment failure has been established.
- Pregnancy

- Study terminated by the Sponsor

If a patient is discontinued from the study for any reason, the date of discontinuation and the reason for the discontinuation must be recorded and all evaluations specified in the EOS visit (**See the visit schedule** (**Appendix 1**)) must be completed. In cases of discontinuation due to an AE (including death) or pregnancy, the relevant pages of the (electronic Case Report Form) eCRF must be completed. If possible, all patients who discontinue study medication due to an AE should be followed until the medical condition returns to baseline or is considered stable or chronic.
Patients unwilling to be treated with all of the courses they are eligible for, will not be withdrawn from the study if they complete at least one treatment course, and will be followed to the full extent of the study period.

7 DATA ANALYSIS SUMMARY

The primary objective of this study is to determine the safety in phase I part and efficacy in phase II part of VENETOCLAX administered with AZA/DLI in patients with myeloid neoplasms in relapse after allo hematopoietic stem cell transplantation. Summary statistics (median and range) will be provided. Adverse experiences and lab assessments will be summarized.

8 VISIT STUDY PROCEDURES

8.1 Screening Period

The investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures must take place within 2 weeks prior to initiation of therapy. A maximum of 48 subjects will be included.

Screening visit can be accomplished over one or multiple visits over a 2-week period (14 days), unless specifically noted otherwise (ie, bone marrow sample collection). Protocol specific tests or procedures not considered standard of care can only be done after the patient has signed the Informed Consent document. See the Flow Chart for a complete list of assessments and procedures to be collected during the screening visit.
A patient who signs an ICF but fails to begin treatment for any reason will be considered as a screen failure. The reason for not beginning treatment and the demographic information should be entered in the screening eCRF page. Information on death or withdrawal of consent, if applicable, must also be completed. No other data will be entered into eCRF for patients who are screen failures, unless the patient experienced a serious or nonserious adverse events considered by the investigator to be causally related to the study-required procedures.

8.2 Study Period

See the visit schedule (Appendix 1) for a detailed list of the assessments and procedures to be collected. Study entry is defined as when the patient is enrolled.

8.3 Treatment

See the visit schedule (Appendix 1) for a detailed list of the assessments and procedures to be collected.

8.4 Before Each Course

See the visit schedule (Appendix 1) for a detailed list of the assessments and procedures to be collected.

8.5 Assessment at Evaluation

See the visit schedule (Appendix 1) for a detailed list of the assessments and procedures to be collected.

8.6 End-of-Study (EOS) Visits

See the visit schedule (Appendix 1) for a detailed list of the assessments and procedures to be collected.

8.7 Follow-Up

Follow-up after treatment discontinuation for all patients.
Patients will be followed at 3 months and 6 months after treatment discontinuation. Date of death or last follow-up, disease status, and ongoing hematological treatments will be collected.

8.8 Early Discontinuation Study Visit

If a patient discontinues prematurely from the study, the same procedures planned for the EOS visit will be performed. Other procedures and evaluations will be completed as deemed necessary by the Investigator. If an early discontinued patient refuses to participate in the scheduled EOS visit, and an AE that started during or within 30 days of the last study drug dose and assessed as possibly or probably related to study drug was present at last visit, the patient will be followed until the medical condition returns to baseline or is considered stable or chronic.

8.9 Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording will be performed by the Investigator. Other procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but not limited to) laboratory tests, BM evaluations, ECG, vital signs, and physical examination.

8.10 Bone Marrow Aspirate

Please see the visit schedule (Appendix 1) specific assessment timepoints for Bone Marrow Aspirate collection. For MDS patients' CR or PR need to be confirmed at least 28 days after the BM evaluation by assessing the stability of improved counts on PB according to the IWG criteria; the need for an additional marrow confirmatory specimen is not required.
The importance of timely and complete disease assessments (including BM and PB assessments) at screening and during the study, whenever clinically indicated, cannot be understated. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point and have the potential to weaken the conclusions of this study.

8.11 Safety Assessments

Safety assessments will be based on changes from baseline of AEs reported by the patients or observed by the Investigator, concomitant medication and blood product use, treatment discontinuation due to AEs, vital signs, ECG, physical examination, laboratory assessments (hematology, blood chemistry), and evaluation of the performance status by the ECOG.
AEs and SAEs will be graded according to the CTCAE, version 5. All AEs (serious and non-serious) occurring between Study Day 1 and 30 days following the last dose of study treatment of each course will be documented in the trial subject's medical records. The following AEs will additionally be documented in the eCRF if:

- Serious (SAE) as defined in 13.2, whether or not related to study drug,
- Related to study drug, regardless of grade and clinical significance,
- Unrelated to study drug but grade ≥ 3 and clinically significant.

AEs and SAEs occurring after 30 days of the last study treatment dose in each course, should only be recorded if considered at least possibly related to study treatment by the local investigator. SAEs and Grade 3 or higher AEs that are ongoing at the end of this period (30 days from last study treatment administration) will be followed until each event is resolved or is assessed as chronic. Serious and nonserious adverse events occurring after the study-specific informed consent is signed but prior to Study Day 1 will be collected only if they are considered by the investigator to be causally related to the study-required procedures.

8.12 Laboratory assessments

Adverse Events
A detailed definition for AEs is provided in (Section 13.1).
Concomitant Medication Use
Use of concomitant medications will be recorded according to the Visit schedule (Appendix 1).
Vital Signs
Vital sign measurements will be recorded according to the schedule specified in Appendix 1 and will include BP, HR, body temperature, weight, and height. Weight will be measured without shoes and having removed

all outwear such as jackets, sweaters or sweatshirts and heavy pocket items. Height will be measured once-during screening without shoes.

Physical Examination

A complete physical examination will be performed according to the schedule specified in Appendix 1.
The physical examination will include appearance, eyes, ears, nose, head, throat, neck, chest, lungs, heart, abdomen, extremities, skin, musculoskeletal system.

Electrocardiogram (ECG)

A 12-lead ECG will be performed according to the schedule specified in Appendix 1.
Initially, ECG output will be evaluated by the Investigator at time of performance (signed and dated) and the printout should be kept in the source documentation file. When potentially clinically significant findings are detected by the Investigator. All communications and diagnoses should be filed in the source documentation file.
The final decision as to whether or not the ECG findings are of clinical significance to the patient is the Investigator's responsibility.

Eastern Cooperative Oncology Group (ECOG) Performance Status

Evaluation of this 5-point scale will be performed according to the schedule specified in Appendix 1. The ECOG performance scale is used by doctors and researchers to assess how a patient's disease is progressing and assess how the disease affects the daily living abilities of the patient. The ECOG definitions are presented in Appendix 5.

Laboratory Assessments

All routine clinical laboratory assessments will be performed by a local laboratory according to the schedule specified in Appendix 1. The laboratory evaluations will include:

1. Hematology (CBC)
2. Coagulation
3. Serum biochemistry
4. Urine analysis
5. Pregnancy test for women of childbearing potential
6. Bone marrow aspirate (or bone marrow biopsy when needed)
7. Karyotype (if initially abnormal)

9 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

9.1 Efficacy Outcome Measures

Primary Endpoint:

For MDS patients:

Overall response rate (ORR), defined as the proportion of patients who achieve a CR or PR per proposal for modification of the International Working Group (IWG) criteria for MDS, 2006 (Appendix 11):

1. CR is defined as bone marrow blasts ≤ 5%, without persistent dysplasia will be noted with normal maturation of all cell lines peripheral blood: Hgb ≥ 11 g/dL platelets ≥ 100 x 10^9/L, ANC ≥ 1.0 x 10^9/L, blasts 0%.
2. PR is defined as all CR criteria if abnormal before treatment except for bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% cellularity.

For AML patients:

CR Rate, defined as the proportion of patients who achieve a CR per the ELN2017 criteria: CR is defined as BM blasts < 5%, absence of circulating blasts and blasts with Auer rods, absence of extramedullary disease, ANC ≥ 1.0 x 10^9/L (1,000/µL); platelet count ≥ 100 x 10^9/L (100,000/µL).

Secondary Endpoints:

For MDS patients:

1. Overall improvement rate (OIR), defined as the proportion of patients reaching a CR, Marrow CR, PR, or hematologic improvement (HI) per proposal for modification of the IWG criteria for MDS, 2006 (Appendix 11). Marrow CR is defined as bone marrow blasts ≤ 5% and decreased by 50% over pretreatment. Peripheral blood: if HI responses, they will be noted in addition to marrow CR.
   HI is defined as:
   a. Erythroid response (pretreatment, < 11 g/dL) is defined as Hgb increase by ≥ 1.5 g/dL. Relevant reduction of units of red blood cells (RBC) transfusions by an absolute number of at least 4 RBC transfusions/8 weeks, compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL will count in the RBC transfusion response evaluation.
   b. Platelet response (pretreatment < 100 x 10^9/L) is defined as absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L platelets, and an increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%.
   c. Neutrophil response (pretreatment, < 1.0 x 10^9/L) is defined as at least 100% increase and an absolute increase > 0.5 x 10^9/L

2. Duration of Response (DOR), defined as time from the date of the first observed PR/CR to the date of the first subsequent documented disease progression or relapse per IWG 2006 criteria, or death from any cause.
3. Progression Free Survival (PFS), for patients with at least a PR, defined as time from the date of the first dose of study treatment to the date of the first documented disease progression or relapse per IWG 2006 criteria, or death from any cause.
4. Overall Survival (OS), defined as time from the date of the first dose of study treatment to the date of death from any cause.
5. Event-Free Survival (EFS) defined as the number of days from the date of the first dose of study drug to the date of earliest disease progression or death of any cause.
6. Rate of bone marrow blast response, defined as the proportion of patients with a reduction in bone marrow blast counts following treatment.
7. Time to AML transformation, defined as time from first treatment dose to the first date in which AML is established.
8. CR Rate, defined as the proportion of participants who achieved a CR per the IWG 2006 Criteria.
9. Rate of HI, defined as the proportion of patients reaching a HI per the IWG 2006 Criteria.

<u>For AML patients:</u>

1. Overall response rate (ORR) including; CR and CRi according to the Diagnosis and Management of AML in Adults: 2017 ELN Recommendations from an International Expert Panel Revised (see Appendix 12) (Döhner et al., 2017)
    a. CR is defined as bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥ 1.0 x 10^9/L (1000/µL); platelet count ≥ 100 x 10^9/L (100 000/µL)
    b. CRi is defined as all CR criteria except for residual neutropenia (< 1.0 x 10^9/L (1,000/µL)) or thrombocytopenia (< 100 x 10^9/L (100,000/µL)).
2. Duration of Response (DOR), defined as time from the date of the first observed CR/CRi to the date of the first subsequent documented disease progression or relapse per IWG 2006 criteria, or death from any cause.
3. Progression Free Survival (PFS) for patients with at least CRi, defined as time from the date of the first dose of study treatment to the date of the first documented disease progression or relapse per IWG 2006 criteria, or death from any cause.
4. Overall Survival (OS) defined as time from the date of the first dose of study treatment to the date of death from any cause.

5. Event-Free Survival (EFS) defined as the number of days from the date of the first dose of study drug to the date of earliest disease progression or death of any cause.
6. Rate of CR without Minimal Residual Disease (CR-MRD-), defined as the proportion of patients reaching a CR with BM blast negativity by multi-color flow cytometry.
7. Time to neutrophil recovery in patients with CR or PR, defined as:
    a. Number of days from Day 1 of commencing induction therapy to first day of neutrophils 0.5 x 10^9/L
    b. Number of days from Day 1 of commencing induction therapy to first day of neutrophils 1 x 10^9/L
8. Time to platelet recovery in patients with CR or PR, defined as:
    a. Number of days from Day 1 of commencing induction therapy to first day of platelets 50 x 10^9/L
    b. Number of days from Day 1 of commencing induction therapy to first day of platelets 100 x 10^9/L
9. Rate of patients who become platelet transfusion-independent, defined as the proportion of patients who become platelet transfusion-independent based on the comparison of the PLT transfusion requirements in the 8 weeks prior to study Day 1 to the transfusion requirements in the 8 weeks following the last treatment course.
10. Rate of patients who become red blood cell (RBC) transfusion-independent, defined as the proportion of patients who become RBC transfusion-independent based on the comparison of the RBC transfusion requirements in the 8 weeks prior to study Day 1 to the transfusion requirements in the 8 weeks following the last treatment course.

9.2 Safety and Tolerability Outcome Measures

Safety outcomes:

1. AEs analyzed by frequency, NCI-CTC grade, and causality
2. Serious Adverse Events (SAEs) and events of special interest (injection site reactions, infections, new malignancy, tumor lysis syndrome)
3. Withdrawal rates, days and reasons for withdrawal
4. Dose modifications and treatment delays
5. Serum chemistry and hematology laboratory values; change from baseline and worst NCI-CTC grade

10 STATISTICAL METHODS

10.1 Descriptive Statistics

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics.

For categorical variables, summary tables will be provided giving sample size, absolute and relative frequency and 95% CI (Confidence Interval).

For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum and 95% CI (Confidence Interval) for means of variables.

The data will be analyzed using SAS/R.

10.2 Efficacy Endpoints

Efficacy will be evaluated by the investigator according to the 2006 IWG response criteria in MDS and for AML according to AML in Adults: 2017 ELN Recommendations from an International Expert Panel Revised (Döhner et al., 2017).

The analyses for efficacy will be performed for the following endpoints.

Overall Response Rate

The proportion of subjects with overall response (OR = CR + mCR + PR + HI) will be calculated. The 95% confidence interval for OR rate based on binomial distribution will be constructed.

Complete Remission Rate

The proportion of subjects with complete remission (CR) will be calculated. The 95% confidence interval for CR rate based on binomial distribution will be constructed.

Marrow Complete Remission Rate

The proportion of subjects with mCR with or without hematological improvement will be calculated. The 95% confidence internal for mCR rate based on binomial distribution will be constructed.

Partial remission (PR)

The proportion of subjects with PR with or without hematological improvement will be calculated. The 95% confidence internal for PR rate based on binomial distribution will be constructed.

Hematologic Improvement

The proportion of subjects with HI (erythroid/platelet/neutrophil responses) will be calculated. The 95% confidence interval for the rate of HI based on binomial distribution will be constructed.

Time to AML Transformation

Time to AML transformation will be defined as the number of days from the date of the first dose of study drug to the date of documented AML transformation. AML transformation will be defined as the presence of blast count ≥ 20% in either the peripheral blood or bone marrow. Time to AML transformation will be summarized as median (range). Subjects who do not show transformation to AML will not be included in the analysis.

Duration of Response

Duration of response (DOR) will be defined as the number of days from the date of first response (CR, mCR, PR or HI) to the earliest documentation of progressive disease (PD). Duration of response will be analyzed by Kaplan-Meier methodology. Median DOR will be calculated and 95% confidence interval for median DOR will be presented.

If the response is still ongoing at the time of analysis, the subject's data will be censored at the date of the subject's last available disease assessment. For subjects who never experience a response, the subject's data will not be included in the analysis.

Overall Survival

Overall survival (OS) will be defined as the number of days from the date of the first dose of study drug to the date of death. Overall survival will be analyzed by Kaplan-Meier methodology. Median OS will be calculated and 95% confidence interval for median OS will be presented. Data from subjects that are alive at the time of analysis will be censored at the date of last study visit or the last known date the subject was alive, whichever is later.

Progression-Free Survival

Progression-free survival (PFS) will be defined as the number of days from the date of the first dose of study drug to the date of earliest disease progression or death due to disease progression or febrile neutropenia. Progression-free survival will be analyzed by Kaplan-Meier methodology. Median PFS will be calculated and 95% confidence interval for median PFS will be presented. All events of disease progression will be included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. Refer to Appendix 11 and 12 for the definition of disease progression. If the subject has not experienced disease progression or death, the subject's data will be censored at the date of last disease assessment. Data for subjects without any disease assessments performed after the first dose of study drug will be censored at the time of the first dose of study drug.

Event-Free Survival

Event-free survival (EFS) will be defined as the number of days from the date of the first dose of study drug to the date of earliest disease progression or death of any cause.

Event-free survival will be analyzed by Kaplan-Meier methodology. Median EFS will be calculated and 95% confidence interval for median EFS will be presented. All events of disease progression will be included regardless whether the event occurred while the subject was taking the study drug or had previously

discontinued the study drug. If the subject has not experienced disease progression or death, the subject's data will be censored at the date of last disease assessment. Data for subjects without any disease assessments performed after the first dose of study drug will be censored at the time of the first dose of study drug.

Safety assessments

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidence tables will be presented for all AEs by maximum grade graded according to the CTCAE, version 5). AEs, SAEs, deaths on study, AEs assessed as related to study drug and AEs resulting in dose reduction, interruption or discontinuation of study drug will be tabulated. Time-to-onset and duration of selected events will also be tabulated.

Laboratory assessments will be presented in shift tables of baseline grade vs. maximum grade on study, and summarized descriptively.

Study Drug Exposure

The number of days and/or cycles that subjects were exposed to study drug will be summarized.

General statistical considerations

Missing values will not be imputed. Outliers will be identified prior to the analyses of the efficacy endpoints and have to be checked by the study physician. According to the decision of the data management, the statistician and the study physician, outliers will be kept in the database or set to “missing”.

Analysis datasets

Full analysis set (FAS)

All efficacy analyses will be conducted with the full analysis set (FAS). The full analysis set consists of all patients who were included in the study.

Per protocol analysis set (PPS)

The secondary dataset for analysis is derived from the per-protocol (PP) population. This dataset includes all trial subjects who were treated without major protocol violations**.**

Safety analysis set

The safety analysis set comprises all trial subjects who received any IMP or other trial treatment.

Sample size calculation

Based on AZARELA trial results, we assume that approximately 30% of responses due to AZA/DLI effects only might be observed. The objective is to demonstrate a 20% increase in response due to the addition of VENETOCLAX (i.e. from 30% to 50% after 6 cycles of AZA/DLI + VENETOCLAX).

For the phase I, a design "3+3" will be used, the number of subjects required for dose escalation will depend upon the occurrence of DLTs as the study progresses. Approximately 9 - 18 subjects may be enrolled to identify the MTD for venetoclax in combination with azacitidine.

For the phase II, a two-stage design will be used. With the assumption that the AZA/DLI gives 30 % of ORR, with the assumption that AZA/DLI + VENETOCLAX gives 50 % of ORR, and with an alpha risk of 0.05 and a beta risk of 80% with a drop-out of 10%, to confirm the safety and evaluate efficacy, for the phase II, 30 patients should be treated at the optimal dose (27 patients + drop-out of 10%).

Overall, a maximum of 48 patients will be treated: 9 - 18 in phase I and 30 in phase II.

Statistical analysis plan

Analysis will be based on an intent-to-treat basis, whether or not the patient receives the protocol treatment.

It will be performed once the sample size has been reached in each group, separately.

It will be based on the computation of response rate, with 95% confidence interval.

Randomization / Stratification

Not applicable for this trial.

Methods of Statistical analysis

A summary of the planned statistical analyses are described. Structured analyses will be specified in a separate statistical analysis plan (SAP) prior to the end of the data management process and before receiving final study data. If analyses should be conducted deviating from the following descriptions, these deviations also will be specified in the SAP prior to receiving final study data.

Descriptive Statistics

For continuous variables mean, standard deviation (SD), median, interquartile range, minimum and maximum will be presented.

For categorical variables absolute and relative frequencies will be presented.

Interim analysis

An interim analysis is planned during the phase II to evaluate the effectiveness of treatment.

If 3 responses or less are observed in the first 14 evaluable patients, there will be no further inclusions (the inclusions would be terminated early), but all patients on treatment and that continue to derive clinical benefit according to the opinion of the investigator while tolerating study-treatment may continue to receive treatment according to the protocol.

If 4 or more responses are observed, 16 additional patients will be included in the study.

Final analysis

The final report of the study and the compilation of the statistical report will be performed within 12 months after completion and correction of all case report forms (database lock).

11 BIOLOGICAL STUDY

11.1 *Mutational analysis (Hematology Laboratory, CHRU Lille)*

Mutational screening will be performed by NGS (Illumina platform) and all genes most frequently mutated in myeloid disorders (*TP53, ASXL1, CBL, CEBPA, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, PHF6, PTPN11, RIT1, RUNX1, SETBP1, SF3B1, SRSF2, TET2, U2AF1, WT1, ZRSR2, CAL-R*) will also be studied. Variant allele frequency (VAF) will be determined for each mutation.

At screening and during follow up (after 4 and 8 cycles and at the end of the study or premature termination) presence of all identified mutations will be investigated with the same technique. All mutation-specific primers and probes will be designed by Biorad (Hercules, CA).

11.2 *Immunologic analysis (Immunology Laboratory, Saint Louis hospital, Paris and INSERM U1065, Mediterranean center of molecular medicine, Nice)*

Sequential phenotypic analysis of NK- and T-cell subsets will be performed on patients with 16-color flow-cytometry. Healthy donors blood samples will be used a control. Supervised analysis on NK cells will include

a study of triggering receptors (NK receptors, activation and proliferation markers) functional proteins (perforin, granzymes, cytokines) whereas T-cell analysis will focus on subpopulations (Th1, Th2, Treg, naïve and memory subsets) and checkpoint receptors (PD-1, CTLA-4, Tim-3, LAG-3, CD96). This work will be coupled to unsupervised dimensionality reduction analysis (t-SNE) and cell-events clustering (SPADE) allowing visualization of complex multi-dimensional data. Such unsupervised analysis will allow identifying non-expected defects in particular subsets, or arrival/disappearance of rare cell subpopulations in patients compared to controls. In function of sample availability and richness, molecular analysis (either on bulk or sorted subsets) could be planned.

12 TREATMENTS

12.1 Treatments Administered

Venetoclax

Venetoclax will be administered at dose levels defined for the cohort a given subject is assigned to at Screening.

Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of a meal (preferably breakfast). Exceptions may apply if food is not allowed for medical procedures. Tablets must be swallowed whole and must not be broken, chewed, or crushed. The dose should be administered at the same time each day.

On days of concomitant administration of azacitidine, venetoclax should be given prior to azacitidine.

If vomiting occurs after taking venetoclax, do not take any additional dose that day. Take the next dose at the usual time the next day. A missed dose of venetoclax should be taken with food and water within 8 hours of the missed dose. After 8 hours, the missed dose should not be taken. The next dose of venetoclax will be the regularly scheduled dose.

Azacitidine

Azacitidine will be administered at the dose of 75 mg/m²/day for 5 days for each cycle or 50 mg/m²/day for 5 days each cycle if relapse occurred less than 4 months after allo SCT and should be prepared according to the information provided in the Summary of Product Characteristics (SmPC) and will be administered, by IV infusion or SC injection.

12.2 Identity of Investigational Products

Information about the venetoclax and azacitidine formulations to be used in this study is presented below:

Identity of Investigational Products

Study Drug	Formulation	Route of Administration
Venetoclax	10 mg tablet	Oral
Venetoclax	50 mg tablet	Oral
Venetoclax	100mg tablet	Oral

Packaging and Labeling

Venetoclax tablets will be packaged in bottles or blister cards to accommodate the study design. Each bottle or blister card will be labeled per local regulatory requirements. Each tablet contains 10 mg, 50 mg, or 100 mg of venetoclax.

Storage and Disposition of Study Drugs

Venetoclax must be stored at 15° to 25°C (59° to 77°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to sponsor.

For more information about Venetoclax, please refer to the IB

Identity of Non-Investigational Products

Study Drug	Formulation	Route of Administration
Azacitidine	100 mg lyophilized powder for injection	SC or IV[a]

a. According to local regulations.

For more information about azacitidine, please refer to SmPC

13 SAFETY AND PHARMACOVIGILANCE

13.1 Adverse Event

An AE is defined as any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

In this study, any event occurring after the Study Day 1 and within 30 days of the last study treatment dose of each course should be recorded and reported as an AE. AEs and SAEs occurring after 30 days should only be recorded if considered at least possibly related to study treatment by the local Investigator. Serious and non-serious adverse events occurring after the study-specific informed consent is signed but prior to Study Day 1 will be collected only if they are considered by the investigator to be causally related to the study-required procedures

Laboratory values related to AML, HR MDS and AML, HR MDS progression such as anemia, neutropenia, thrombocytopenia, should not be classified as AEs as long as they are within the expected progression of the disease or expected duration/severity.

The reporting of abnormal laboratory values from unscheduled tests should be avoided unless they lead to clinical consequences or are associated with an AE.

AEs occurring during the study, whether or not attributable to the study treatment, observed by the investigator or reported by the patient spontaneously or in response to a direct question, will be recorded in the patient's source documents as long as they occurred during study treatment administration or within 30 days of last study treatment dose of each course. AEs occurring after 30 days should only be recorded if considered at least possibly related to study treatment by the local Investigator. AEs will be graded in accordance with NCI CTCAE version 5.

For adverse events not captured by the Common Terminology Criteria, the following should be used:

Grade 1: The adverse event is transient and easily tolerated by the subject (mild).

Grade 2: The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).

Grade 3: The adverse event causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe).

Grade 4: The adverse event is life threatening requiring urgent intervention (severe).

Grade 5: The adverse event resulted in death of the subject (severe).

The investigator will document, according to his/her opinion, the relationship of the AE to the study treatment using the criteria outlined in visit schedule (Appendix 1). The nature of each event, start and end date, action taken in response to the event, outcome, NCI CTCAE toxicity grade, relationship to study treatment, and whether the event is serious, should be established and recorded on the AE eCRF. All entries must be clearly documented in the source documents. AEs documented in the eCRF without a stop date should be reviewed at subsequent visits. Documentation on AEs should be updated as necessary. In case of worsening of an AE (i.e. AE grade increase) the event should be captured with the maximal severity observed providing that the AE is ongoing while the AE grade increased.

13.2 Serious Adverse Events

An SAE is defined as an AE that results in any of the following:

- Death
- Life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongs existing inpatient hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- An important medical event that requires medical intervention to prevent any of the above outcomes

Important medical events are those that may not be immediately life-threatening, but may jeopardize the patient and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened, or to diagnostic procedure.
The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
Any new SAE that occurs during the study period should be recorded and reported immediately (See Section 8.11) if it occurred after the patient has signed the ICF and within 30 days of the last study treatment dose of each course. Serious and non-serious adverse events occurring after the study-specific informed consent is signed but prior to Study Day 1 will be collected only if they are considered by the investigator to be causally related to the study-required procedures.

13.3 Study-Specific Exceptions

Cytopenias (anemia, neutropenia, or thrombocytopenia) are part of the natural history of MDS and AML. Persistent cytopenia at the same CTCAE grade as at baseline are not to be reported as adverse events, unless the investigator had an identifiable cause other than the underlying disease.
Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be subject to expedited reporting.
Serious and nonserious adverse events occurring after the study-specific informed consent is signed but prior to the initial dose of study drug will be collected only if they are considered by the investigator to be causally related to the study-required procedures.

13.4 Assessment of Causality

The causal relationship between an AE and study treatment will be determined and documented by the responsible Investigator or designee, according to best medical judgment, as presented in table below.

Adverse Event Relationship Criteria

Term	Definition	Clarification
No Reasonable Possibility	This category applies to those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those AEs, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to study treatment	An adverse experience may be considered "No Reasonable Possibility" if it is clearly due to extraneous causes or when (at least 2 of the following): • It does not follow a reasonable temporal sequence from the administration of study treatment • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient

		• It does not follow a known pattern of response to study treatment • It does not reappear or worsen when the study treatment is re-administered
Reasonable Possibility	This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with STUDY TREATMENT administration cannot be ruled out with certainty or which are felt with a high degree of certainty to be related to study treatment.	An adverse experience may be considered "Reasonable Possibility" if or when (at least 2 of the following): • It follows a reasonable temporal sequence from administration of study treatment • It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists • It follows a known pattern of response to study treatment

13.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a Suspected Unexpected Serious Adverse Reaction. An Adverse Reaction is defined as any AE caused by a drug. A suspected Adverse Reaction is defined as an AE for which there is a reasonable possibility that the drug caused the AE. The "reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. Unexpected Adverse Reaction means a reaction which is not included in the Adverse Reaction section of the relevant Reference Safety Information by its specificity, severity, outcome or frequency. The relevant Reference Safety Information of this study is provided in the study treatment IB.

13.6 Reporting of AE/SAE that occur before treatment

For this trial, the only adverse events that will be counted will be treatment-emergent events. These events are those that started after the start of the treatment period, or were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected to be due to study drug, or developed into an SAE after the start of the treatment period.

Each AE will be counted once according to the date of onset. If the AE onset was prior to the first dose of study drug and the event does not increase in severity after initiation of study drug, the AE is then considered to be a pretreatment adverse event and will not be counted in the treatment emergent adverse event incidence tables. If the onset is prior to the first dose of study drug and the severity increases thereafter, the event is counted as a treatment emergent AE. An AE with onset after the first dose of study drug will be counted as a treatment emergent AE. This rule is consistent with the treatment emergent signs and symptoms convention for counting AEs.

All AEs (ie, pretreatment AE and treatment emergent AEs) will be reported separately. All AEs will be split between pretreatment and post treatment phases.

13.7 Recommendations related to contraception and pregnancy

Subjects with reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy or tubal occlusion or who have not been naturally postmenopausal (i.e., who have not menstruated at all) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

If of childbearing potential (males and females), willing to use an effective form of contraception such as latex condom, hormonal birth control, intrauterine device or double barrier method during chemotherapy treatment and for at least three months thereafter.

Pregnant women are excluded from this study. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with venetoclax, breastfeeding should be discontinued if the mother is treated with venetoclax.

Contact information for Safety reporting

Sponsors contact department:

Fatiha Chermat
Directrice du GFM
Hôpital Saint Louis
Service Hématologie Séniors
1, avenue Claude Vellefaux
75475 Paris Cedex 10
Phone : + 33 (0)1 71 20 70 59
Fax : + 33 (0)1 71 20 70 38
Email : fatiha.chermat-ext@aphp.fr

Each SAE and pregnancy must be followed up until resolution or stabilization by submission of updated reports (FU-report) to the designated recipient.
The sponsor will inform AbbVie about all serious adverse events, SUSARs and all suspected pregnancies within 24 hours of their knowledge of the event. Reports to AbbVie must be submitted via email to frpv@abbvie.com

The sponsor will also provide to AbbVie
- A listing of non-serious AEs, if requested
- Final study report

13.8 *Investigator reporting responsibilities*

Any fatal or life-threatening event should be reported immediately to GFM. These preliminary reports will be followed within 24 hours by detailed descriptions that include a completed SAE form, copies of hospital case reports, autopsy reports and other documents, when requested and applicable.
The investigator must complete the SAE Report Form in English, assess the relationship to study treatment and submit it via fax or email within 24 hours to GFM listed above.
Follow-up information is to be submitted on a new SAE form. The new form should clearly state that it is a follow-up to the previously-reported SAE and give the date of the original report. The follow-up SAE report should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or discontinued study participation.

The following information should be provided in the SAE form to accurately and completely record the event:
1. Investigator name and site address
2. Patient study identification number
3. Patient demographics (gender, year of birth or age, weight, height)
4. Clinical Event:

- Description
- Date and time of onset, stop date, or duration
- Severity
- Treatment (including hospitalization)
- Relationship to study treatment (causality)
- Action(s) taken regarding study treatment
- Information on recovery and any sequelae
- If the SAE resulted in death, cause of death (whether or not the death was related to study treatment)
- Autopsy findings (if available)
- Medical History case report form (copy)
- Concomitant Medication case report form (copy)
- Any relevant reports (laboratory, discharge, etc.)

Accompanying documentation, such as copies of hospital case reports, autopsy reports and other documents when applicable, should be summarized on the SAE form and a copy of the source document may be sent if required. The patient's personal details will be removed and replaced with study identifiers i.e. study number and initials, if applicable.
In addition, all AEs / SAEs / SUSARs will be reported to the ethics committee (EC/IRB) and regulatory authorities as required by local regulations and International Conference on Harmonization (ICH)-GCP guidelines.
Minimal information should include:

- An identifiable patient (e.g., patient study code number)
- An identifiable reporting sources
- All related AEs

Follow-up of SAEs / SUSARs
Follow-up of SAEs / SUSARs that occur during the study will continue until their satisfactory resolution or stabilization.
If supplementary information becomes available, a follow-up SAE Report Form must be completed by the site and faxed or emailed within 24 hours to GFM.
The contact information for follow-up SAE reporting is the same as for initial SAE reports (as detailed in the section above).

Once faxed or emailed, the SAE form and accompanying documentation should be placed in the SAE section of the Investigator's file. If supplementary information on a SAE has to be sent, the SAE form to be used must be marked as "follow-up report".

13.9 *Sponsors reporting responsibilities*

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to treatment with the study medication.

Every SUSAR that becomes known in a clinical trial will be reported by the sponsor to the competent authority and the Ethics Committee.

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

The sponsor will inform AbbVie about all serious adverse events, SUSARs and all suspected pregnancies within 24 hours of their knowledge of the event, as outlined in section 13.7.

13.10 *Notification of SAEs to the Ethics Committee*

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions (SUSARs)) will be performed by the sponsor according to all applicable regulations.

13.11 *Contact information of the competent authority*

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

13.12 *Annual safety report (DSUR) of trial subjects*

Once a year or on demand, the sponsor will supply a report on the safety of trial subjects with all relevant information during the reference period to the competent authority and the ethics committee.

The reference period for the annual report on the safety of trial subjects begins with the date that the trial is approved by competent authority. This date is the reference date for the start of the year of the annual safety report. The sponsor will supply the report within 60 days of one year after the reference date.

13.13 *PREMATURE TREATMENT DISCONTINUATION (Discontinuation of Individual Subjects)*

Treatment will continue until the occurrence of any of the following events:

- No response after 8 cycles of therapy
- Major violation of the study protocol (violations that affect the right and safety of patients and the integrity of collected data)

- Unacceptable AE or failure to tolerate study therapy
- All grade 4 toxicities
- Persistent myelosuppression and/or cardiac toxicity
- Disease progression
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy
- Administrative decision by the investigator or the sponsor
- If the patient manifests exclusion criteria during the trial
- Subject noncompliance (deliberate protocol violations)
- A subject requires the use of a proscribed medication; the subject will need to be discontinued from treatment and end of treatment and end of study visits performed.

Where possible, patients who have discontinued their treatment prematurely will receive the same follow-up as other patients.

13.14 *PREMATURE STUDY TERMINATION (Discontinuation of Entire Study)*

Both the sponsor and the investigator reserve the right to terminate the study according to the study contract. The sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. The sponsor decides on whether to discontinue the trial in consultation with IDMC.

If such action is taken, the reasons for terminating the trial must be documented in detail in the trial master file. The sponsor will inform the IEC/IRB and the competent authorities in writing of the study's completion or early termination at the time and send a copy of the notification to all investigators.

Premature termination of the trial will be considered if:

- The risk-benefit balance for the trial subject changes markedly
- It is no longer ethical to continue treatment with the IMP
- The sponsor considers that the trial must be discontinued for safety reasons

- It is no longer practicable to complete the trial

If the investigator decides a termination of a single subject or has any ethical concerns about continuation of the trial, the investigator must inform the sponsor. All information about the termination must be documented in the investigator site file. All trial subjects still under treatment at the time of termination must undergo a final examination which must be documented.

13.15 *Continuation of treatment after the end of trial*

After conclusion of the clinical trial, patients will receive further standard medical care as usual for this kind of disease.

13.16 *Emergency management*

In case of an emergency the coordinating investigator can be approached via the following phone/fax connection:

Pr. Thomas CLUZEAU
CHU de Nice - Hôpital L'Archet I
Service d'Hématologie clinique
151 Route Saint Antoine de Ginestière
06200 Nice
Phone : +33(0)4 92 03 58 39
Fax : +33(0)4 92 03 58 95
Email : cluzeau.t@chu-nice.fr

Pr. Pierre FENAUX
Service hématologie séniors
Hôpital Saint Louis
1, Avenue Claude Vellefaux
75475 Paris Cedex 10
Phone : +33(0)1 71 20 70 22
Fax : + 33(0)1 71 20 70 20
Email : pierre.fenaux@aphp.fr

13.17 Study Stopping Rules

Study Stopping Rules in the phase I

The dose limiting toxicities (DLT) observation period is defined as the first treatment cycle (Cycle 1) of venetoclax combined with azacitidine.

Dose limiting toxicities for dose escalation purposes will be determined based on adverse events that occur during the DLT observation period.

Adverse events occurring after the DLT observation period criteria will also be reviewed and may be taken into consideration for dose escalation decisions.

Any of the following events will be considered a DLT unless the event can be attribute by the investigator to a clearly identifiable cause such as underlying illness or disease progression, concurrent other illness, or concomitant medication:

- ANC < 1×10^9/L (Grade ≥ 3) which does not recover as defined below:
    - ○ Recovery is defined an increase in ANC from nadir by ≥ 50% of the reduction from baseline to nadir or any increase to an ANC of ≥ 1×10^9/L within 42 days from Day 1 of Cycle 1
    - ○ Delayed recovery should only be deemed a DLT if due to treatment induced toxicity as confirmed by a bone marrow sample showing an overall bone marrow cellularity of < 5%
- Grade ≥ 3 thrombocytopenia associated with clinically significant bleeding that requires transfusion of platelets over routine or baseline transfusion needs based on investigator opinion
- Grade ≥ 4 non-hematologic toxicity deemed related to venetoclax per investigator opinion.
- Grade 4 infections or complications related to infections (e.g., sepsis) should only be deemed DLTs if due to treatment-induced neutropenia as confirmed by a bone marrow sample showing an overall bone marrow cellularity of < 5%

Occurrence of a DLT event will require an interruption and possible discontinuation of study treatment administration to the patient that experienced the DLT. All decisions regarding continued dosing for individual subjects will be medically managed by the investigator, per discussion with the GFM, as appropriate. These decisions will be driven by the definition of DLTs as described above.

In addition, any treatment related death will be reported to the safety committee within 24 hours, the safety committee will review discuss and provide guides to the sponsor according to the safety committee charter.

Study Stopping Rules in the phase II

Any of the following events will be considered a DLT unless the event can be attribute by the investigator to a clearly identifiable cause such as underlying illness or disease progression, concurrent other illness, or concomitant medication:

- ANC < 1×10^9/L (Grade ≥ 3) which does not recover as defined below:

○ Recovery is defined an increase in ANC from nadir by ≥ 50% of the reduction from baseline to nadir or any increase to an ANC of ≥ 1×10^9/L within 42 days from Day 1 of Cycle 1

○ Delayed recovery should only be deemed a DLT if due to treatment induced toxicity as confirmed by a bone marrow sample showing an overall bone marrow cellularity of < 5%

- Grade ≥ 3 thrombocytopenia associated with clinically significant bleeding that requires transfusion of platelets over routine or baseline transfusion needs based on investigator opinion
- Grade ≥ 4 non-hematologic toxicity deemed related to venetoclax per investigator opinion.
- Grade 4 infections or complications related to infections (e.g., sepsis) should only be deemed DLTs if due to treatment-induced neutropenia as confirmed by a bone marrow sample showing an overall bone marrow cellularity of < 5%

We will stop the enrollment of new patients at the request of the DSMB if DLT attributable to VEN > 2. Ongoing patients without toxicities and with a benefit of treatment at the investigator's discretion will be allowed to continue to receive treatment according to the protocol.

13.18 Study Safety Committee

An independent Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB) will be formed to oversee the safety of the study subjects by periodically assessing the safety of the study therapy. The DSMB will consist of three physicians who are not involved in the study and who are external to the sponsor. The study DSMB charter will elaborate the guidelines for the DSMB. Subsequently the DSMB will meet according to the intervals mentioned in the DSMB Charter.
The Safety Committee recommendations will be binding and the sponsor commits to promptly implement any safety recommendations related to changes to the eligibility criteria, dose adjustments and study discontinuation.

14 QUALITY ASSURANCE

In order to guarantee the authenticity and credibility of the data in accordance with Good Clinical Practice (GCP), the sponsor shall put in place a quality assurance system which includes:

- Management of the trial in accordance with GFM's procedures,

- Quality control of the investigator site data by the monitor, whose role is to check the data in the case report form for concordance and consistency with the source documents,

- The possible audit of investigator sites.

15 OWNERSHIP OF THE DATA AND CONFIDENTIALITY

The investigator undertakes that he/she and anyone who monitors the conduct of the trial will ensure the confidentiality of all of the information provided by GFM until the trial results are published. This confidentiality requirement shall not apply to information that the investigator gives to patients in connection with their participation in the trial or to previously published information.

The investigator undertakes not to publish, disclose, or use any trial-related scientific or technical information, in any way, either directly or indirectly.

Nevertheless, in accordance with Article R 5121-13 of the French public health code, the site and the investigator can give information about the trial:

- To the minister for health,
- To public health inspectors (medical doctors or pharmacists),
- To the General Director and inspectors of the ANSM.

No written or verbal comments can be made about the trial without the sponsor's consent, since all of the information provided or obtained while the trial is being conducted legally belongs to the sponsor, which can use the information at its own discretion.

16 PUBLICATION POLICY

All of the information arising from this trial shall be considered confidential, at least until completion of the appropriate analysis and subsequent checks by the trial sponsor, coordinating investigator, and statistician.

Any publications, abstracts or presentations that include results from the trial must be submitted to the sponsor for approval.

Any communications, articles, or presentations must also include a section mentioning the GFM and the organizations that supported the research financially.

The trial’s coordinating investigator will be the main (first or last) author.

The first or last author (depending on the position given to the coordinating investigator) will be jointly selected by the sponsor and the coordinating investigator (CI).

The following investigators will be cited in order of the number of patients recruited for multicenter trials, or based on their involvement in the protocol and/or the disease. The trial statistician will also be cited.

Similarly, publications of ancillary results (biological studies) shall include the name of the person who carried out the ancillary study, as well as the names of anyone else involved in the ancillary study.

17 ETHICAL AND REGULATORY ASPECTS

The clinical trial must be conducted in accordance with:

- The ethical principles of the current version of the Declaration of Helsinki,
- The guideline for Good Clinical Practice of the International Conference on Harmonization (ICH–E6, 07/17/96),
- European Directive 2001/20/EC on the conduct of clinical trials,
- The French Huriet Act (No. 88-1138) dated December 20, 1988 concerning the protection of clinical trial subjects, amended by the French public health law No. 2004-806 dated August 09, 2004,
- The French data protection and civil liberties law No. 78-17 dated January 06, 1978, amended by law 2004-801 of August 06, 2004 regarding the processing of personal data,
- French law No. 2004-800 dated August 06, 2004 concerning bioethics.

17.1 Research Ethics Board

Before conducting biomedical research on human subjects, the sponsor is obliged to submit the project to one of the REBs for its opinion.

The sponsor also submits applications for substantial amendments to the initial project to the REB for its opinion.

17.2 Competent Authority

Before conducting a clinical trial or having one conducted, the sponsor of the trial shall apply to the ANSM for authorization.

17.3 Subject information and consent

Before biomedical research is conducted on a person, their voluntary, written, informed consent must be obtained, after they have been fully informed by the investigator during a consultation and given enough time to consider their decision.

Information intended for trial subjects must include all of the particulars set out in the French public health law of August 09, 2004 and must be written in straightforward language that the patient can understand.

The consent form must be signed and dated personally by the trial subject and the investigator (the original copy shall be archived by the investigator, and one copy will be given to the trial subject).

The patient information leaflet and informed consent form must be combined into a single document to ensure that all of the information is given to the trial subject.

17.4 Responsibilities of the sponsor

The sponsor of the clinical trial is the individual or legal entity that takes the initiative for the biomedical research on human subjects, manages the trial, and ensures that provision has been made for its funding.

The sponsor must be established in the European Community or, failing that, have a legal representative in a member state.

The sponsor's main responsibilities are to:

- Take out civil liability insurance,

- Register the trial in the European trials database and obtain the EudraCT number (European Drug Regulatory Authorities Clinical Trials),

- Request the opinion of the REB on the initial project and substantial amendments,

- Request authorization for the initial project and substantial amendments from the competent authority,

- Provide information about the trial to the site directors, investigators, and pharmacists,

- Report any suspected unexpected serious adverse events related to any of the trial treatments to the competent authority, ANSM and EMEA (European pharmacovigilance database, Eudravigilance), and send this information to the REB and the trial investigators,

- Submit the annual safety report to the competent authority and the REB,

- Notify the competent authority of the start and end of the trial,

- Write the final clinical study report,

- Send the trial results to the competent authority, REB, and trial subjects,

- Archive essential trial documents in the sponsor's folder for a minimum of 15 years after the trial has ended.

17.5 Responsibilities of investigators

The principal investigator of each establishment concerned undertakes to conduct the clinical trial in accordance with the protocol approved by the REB and the competent authority.

The investigator must not make any changes to the protocol without the written authorization of the sponsor and unless the REB and the competent authority have approved the proposed changes.

It is the responsibility of the principal investigator to:

- Provide the sponsor with his/her curriculum vitae as well as those of his/her co-investigators, identify the members of his/her team, who are participating in the trial and define their responsibilities,

- Recruit patients once authorized to do so by the sponsor.

It is the responsibility of each investigator to:

- Obtain informed consent, personally signed and dated by the subject, before carrying out any trial-specific screening procedures,

- Regularly complete the case report form (CRF) of each patient enrolled in the trial and allow the clinical research assistant (CRA) appointed by the sponsor to have direct access to source documents, so that the latter can validate the data on the CRF,

- Date, correct, and sign corrections on the CRF of each patient enrolled in the trial,

- Accept regular visits by the monitor, and any auditors appointed by the sponsor or inspectors from the regulatory authorities.

All of the trial-related documentation (the protocol, consent forms, case report forms, investigator brochure, etc.) and source documents (laboratory results, X-rays, consultation reports, physical exam reports, etc.) are considered confidential and must be kept in a safe place. The principal investigator must store the data and a patient identification list for a minimum of 15 years after the end of the study.

18 INSURANCE

In accordance with current legislation, insurance has been taken out with the company CHUBB European Group SE contract N° FRLCSA61513 to cover any physical harm or other incapacity that may result from administration of the investigational treatment, in accordance with the study protocol.

19 PROTOCOL DEVIATIONS

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation.

20 SUBJECT CONFIDENTIALITY

The Sponsor affirms the subject's right to protection against invasion of privacy in compliance with the local legal practice.

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and / or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the Sponsor, IEC / IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strict confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

21 ARCHIVING

All documents, informed consent forms and other important study materials will be archived for at least 15 years.

Essential documents shall be archived in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the institution. Where the archiving procedures do not meet the minimum timelines required by the Sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the Sponsor if the archival arrangements change (e.g. relocation or transfer of ownership). The ISF is not to be destroyed without the Sponsor's approval. The investigator's contract will contain all regulations relevant for the study center.

22 AMENDMENTS TO THE STUDY PROTOCOL

To ensure that comparable conditions are achieved as far as possible at individual study sites and in the interests of a consistent and valid data analysis, changes to the provisions of this study protocol are not planned. In exceptional cases, however, changes may be made to the study protocol. Such changes can only be made if agreed by the Sponsor, Sponsor's representative and all authors of this study protocol. Any changes to the study procedures must be made in writing and must be documented with reasons and signed by all authors of the original study protocol.

Amendments made in accordance with GCP Regulations that require approval are submitted to the ethics committee and the supreme federal authority and will not be implemented until approved. Exceptions to this are amendments made to avoid immediate dangers.

23 REFERENCES

1. Schlenk, R.F., et al., *Prospective evaluation of allogeneic hematopoietic stem-cell transplantation from matched related and matched unrelated donors in younger adults with high-risk acute myeloid leukemia: German-Austrian trial AMLHD98A.* J Clin Oncol, 2010. **28**(30): p. 4642-8.
2. Saure, C., et al., *Upfront allogeneic blood stem cell transplantation for patients with high-risk myelodysplastic syndrome or secondary acute myeloid leukemia using a FLAMSA-based high-dose sequential conditioning regimen.* Biol Blood Marrow Transplant, 2012. **18**(3): p. 466-72.
3. Pavletic, S.Z., et al., *NCI First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: report from the Committee on the Epidemiology and Natural History of Relapse following Allogeneic Cell Transplantation.* Biol Blood Marrow Transplant, 2010. **16**(7): p. 871-90.
4. Porter, D.L., et al., *NCI First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: Report from the Committee on Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation.* Biol Blood Marrow Transplant, 2010. **16**(11): p. 1467-503.
5. Fenaux, P., et al., *Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study.* Lancet Oncol, 2009. **10**(3): p. 223-32.
6. Dombret, H., et al., *International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts.* Blood, 2015. **126**(3): p. 291-9.
7. Atanackovic, D., et al., *Cancer-testis antigen expression and its epigenetic modulation in acute myeloid leukemia.* Am J Hematol, 2011. **86**(11): p. 918-22.
8. Pinto, A., et al., *Modulation of HLA-DR antigens expression in human myeloid leukaemia cells by cytarabine and 5-aza-2'-deoxycytidine.* Lancet, 1984. **2**(8407): p. 867-8.
9. Schroeder, T., et al., *Salvage therapy with azacitidine increases regulatory T cells in peripheral blood of patients with AML or MDS and early relapse after allogeneic blood stem cell transplantation.* Leukemia, 2013. **27**(9): p. 1910-3.

10. Goodyear, O., et al., *Induction of a CD8+ T-cell response to the MAGE cancer testis antigen by combined treatment with azacitidine and sodium valproate in patients with acute myeloid leukemia and myelodysplasia.* Blood, 2010. **116**(11): p. 1908-18.
11. Sanchez-Abarca, L.I., et al., *Immunomodulatory effect of 5-azacytidine (5-azaC): potential role in the transplantation setting.* Blood, 2010. **115**(1): p. 107-21.
12. Schroeder, T., et al., *Azacitidine and donor lymphocyte infusions as first salvage therapy for relapse of AML or MDS after allogeneic stem cell transplantation.* Leukemia, 2013. **27**(6): p. 1229-35.
13. Schroeder, T., et al., *Treatment of acute myeloid leukemia or myelodysplastic syndrome relapse after allogeneic stem cell transplantation with azacitidine and donor lymphocyte infusions--a retrospective multicenter analysis from the German Cooperative Transplant Study Group.* Biol Blood Marrow Transplant, 2015. **21**(4): p. 653-60.
14. Yafour, N., et al., *[Preventative and therapeutic relapse strategies after allogeneic hematopoietic stem cell transplantation: Guidelines from the Francophone society of bone marrow transplantation and cellular therapy (SFGM-TC)].* Bull Cancer, 2017. **104**(12S): p. S84-S98.
15. DiNardo, C.D., et al., *Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia.* Blood, 2019. **133**(1): p. 7-17.
16. De Vos, J., et al., *[Donor Lymphocyte Infusions (DLI): Guidelines from the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC)].* Bulletin du cancer, 2019. **106**(1S): p. S35-S39.
17. Castagna, L., et al., *Donor lymphocyte infusion after allogeneic stem cell transplantation.* Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis, 2016. **54**(3): p. 345-55.
18. Schmid, C., et al., *Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2007. **25**(31): p. 4938-45.
19. Schroeder, T., et al., *Treatment of acute myeloid leukemia or myelodysplastic syndrome relapse after allogeneic stem cell transplantation with azacitidine and donor lymphocyte infusions--a retrospective multicenter analysis from the German Cooperative Transplant Study Group.* Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, 2015. **21**(4): p. 653-60.
20. Lu, P., et al., *Safety and pharmacodynamics of venetoclax (ABT-199) in a randomized single and multiple ascending dose study in women with systemic lupus erythematosus.* Lupus, 2018. **27**(2): p. 290-302.
21. Karakas, T., et al., *High expression of bcl-2 mRNA as a determinant of poor prognosis in acute myeloid leukemia.* Ann Oncol, 1998. **9**(2): p. 159-65.
22. Karakas, T., et al., *The coexpression of the apoptosis-related genes bcl-2 and wt1 in predicting survival in adult acute myeloid leukemia.* Leukemia, 2002. **16**(5): p. 846-54.
23. Gross, A., J.M. McDonnell, and S.J. Korsmeyer, *BCL-2 family members and the mitochondria in apoptosis.* Genes Dev, 1999. **13**(15): p. 1899-911.
24. Bogenberger, J.M., et al., *BCL-2 family proteins as 5-Azacytidine-sensitizing targets and determinants of response in myeloid malignancies.* Leukemia, 2014. **28**(8): p. 1657-65.

24 APPENDIX

24.1 *Appendix 1:* VISIT SCHEDULE

	Screening [a]	Cycle 1					Cycle 2 and above [b]					End of Study[c]
Day	(-14 to 0)	1	7	15	21	28	1	7	15	21	28	
Visit	1	2	3	4	5	6	7	8	9	10	11	Final
Informed consent	X											
Demography and medical history	X											
Prior/concomitant medications[d]	X	X	X	X	X	X	X		X		X	X
Review inclusion/exclusion criteria	X											
Height/weight/body surface area calculation	X	X					X					X
Vital signs[e]	X	X	X	X	X	X	X		X			X
Physical examination[f]	X	X		X			X					X
ECOG performance status[g]	X	X		X			X					X
12-lead ECG	X			X			X					
CBC w/diff, platelets[h]	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive chemistry panel[i]	X	X	X	X	X	X	X		X		X	X
PT (INR) PTT	X	X					X					X
Complete urinalysis with microscopic exam	X											
Pregnancy Test[j] (if applicable)	X						X					
T/B/NK phenotype and Centralized biology	X						X				X[l]	X
Blood chimerism (CD3 sorted)	X						X					X
Medullar chimerism[k]	X										X	X
Adverse experience (AE) assessment		X	X	X	X	X	X		X		X	X
Dispense AZA		X					X					
Dispense VENETOCLAX		X					X					
Bone marrow aspirate /cytogenetics and for correlative studies[l]	X										X[l]	X

a All pre-treatment studies should be obtained within 14 days of entry into the trial. Any abnormal results (except for bone marrow aspiration) should be repeated within 48 hours of beginning therapy to establish a baseline.

b Patients may receive additional Cycles of therapy but not earlier than 4 weeks from the previous Cycle. One full cycle of treatment is defined as the administration of AZA and VENETOCLAX. During additional Cycles, patient Visits are numbered sequentially.

c To be completed within 30 days of discontinuing study drug.

d Medications will include the RBC and Platelet transfusions charts for the 8 weeks preceding inclusion and for the 8 weeks preceding beginning of AZA.

e Vital signs to include temperature, pulse, respiratory rate and blood pressure.

f A complete history and physical should be performed 48 hours before initiation of the study. A focused physical exam based on clinical assessment and AE evaluation should be conducted prior to the start of each Cycle.

g See Appendix 5. ECOG should be performed within 48 hours of study initiation and then at the start of each Cycle.

h CBC w/diff and platelet count should be completed weekly for the first 2 Cycles and then at the start of each subsequent Cycle. A sample collected on day 28 does not need to be repeated on day 1 of the next Cycle if the 2 Visits are within 72 hours of each other.

i Complete chemistry panels should be performed within 48 hours of study initiation and then weekly in the Cycle 1 and 2, and bi-weekly at the start of each subsequent Cycle. A sample collected on Day 28 does not need to be repeated on Day 1 of the next Cycle if the 2 Visits are within 72 hours of each other. The panel includes sodium, potassium, chloride, carbon dioxide, BUN, creatinine, magnesium, calcium, phosphorus, glucose, total protein, albumin, AST, ALT, uric acid, lactate dehydrogenase (LDH), alkaline phosphatase and total/direct bilirubin at the beginning of each Cycle.

j Female subjects of childbearing potential must have negative results for pregnancy test performed at Screening with a serum sample obtained within 14 days prior to the first study drug administration, and prior to dosing with urine sample obtained on Cycle 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy test results. Female subjects who are not of childbearing potential at Screening do not require pregnancy testing.

k Every 2 cycles.

l Bone marrow aspiration (BMA) should be conducted prior to study initiation and then after 4, 6 and 8 cycles of AZA + VENETOCLAX and at the end of study or Premature termination. BMA collected on Day 0 of cycle 1 will be for correlative, morphologic and cytogenetic sampling. The other BMA will be for response assessment. Cytogenetics should be repeated in case of abnormal findings at baseline.

24.2 *Appendix 2: Sample List of Excluded or Cautionary Medications*

Strong CYP3A inducers - Carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. John's Wort
Moderate CYP3A inducers - Bosentan, efavirenz, etravirine, modafinil
Strong CYP3A inhibitors - Boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir, elvitegravir/ritonavir, idelalsib,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir,nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, posaconazole, saquinavir,telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Moderate CYP3A inhibitors -Aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib,*cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib,* tofisopam,verapamil

Warfarin and coumarin derivatives (e.g., phenprocoumon)**
P-gp substrates - Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus,*fexofenadine, lapatinib,* loperamide, maraviroc, nilotinib,* ranolazine, saxagliptin, sirolimus,*sitagliptin, talinolol, tolvaptan, topotecan*
BCRP substrates - Methotrexate,* mitoxantrone,* irinotecan,* lapatinib,* rosuvastatin, sulfasalazine,topotecan*
OATP1B1/1B3 substrates - Asunaprevir, atrasentan, atorvastatin, cerivastatin, danoprevir, ezetimibe,fexofenadine, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide,telmisartan, valsartan, olmesartan **P-gp inhibitors** - Amiodarone, captopril, carvedilol, felodipine, propafenone, quercetin, quinidine,ranolazine, ticagrelor

Note that this is not an exhaustive list. For an updated list, see the following link:
https://www.fda.gov/drugs/development-resources/drug-interactions-labeling

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit,grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruits within 3 days prior to each cycle and while on venetoclax.

* These are anticancer agents; consult Investigator Coordinator before use.
** Closely monitor international normalized ratio (INR).

24.3 *Appendix 3:* Contraception Recommendations

While participating in this research study, female subjects should not become pregnant or breastfeed a baby.

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a female of childbearing potential, practicing at least one of the following highly effective methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of venetoclax or at least 3 months after the last dose of azacitidine.

● Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1.

● Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.

● Bilateral tubal occlusion/ligation at least 1 month before study participation.

● Bilateral tubal occlusion via hysteroscopy (e.g., Essure®), provided a hysterosalpingogram confirms success of the procedure at least 1 month before study participation.

● Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the Female subjects of childbearing potential (trial participant).

● Intrauterine device (IUD).

● Intrauterine hormone-releasing system (IUS).

● True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Male subjects who are sexually active with a female of child-bearing potential, must agreeto use effective contraceptive measures as defined in the protocol for female study subjects of childbearing potential from Study Day 1 through at least 30 days after the last dose of venetoclax or at least 3 months after the last dose of azacitidine, whichever is later.

Male subjects should be advised to not donate or store sperm from Study Day 1 through at least 3 months after the last dose of azacitidine.

24.4 Appendix 4: CTCAE Version 5.0

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting.

HTTPS://CTEP.CANCER.GOV/PROTOCOLDEVELOPMENT/ELECTRONIC_APPLICATIONS/DOCS/CTCAE_V5_QUICK_REFERENCE_8.5X11.PDF

CTCAE V 5.0.pdf

Article last updated on: November 27, 2017.

All Study sites will have access to a copy of the CTCAE Version 5.0.

24.5 Appendix 5: Eastern Cooperative Oncology Group (ECOG) Performance Status Grading

Olken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davi, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649-655, 1982

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50 % of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50 % of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

24.6 *Appendix 6: Risk classification according to IPSS R*

IPSS-R Cytogenetic risk groups

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 ≥abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R Prognostic Score Values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	≤ 2		> 2-< 5%		5-10%	> 10%	
Hemoglobin	≥ 10		8-< 10	< 8			
Platelets	≥ 100	50-<100	<50				
ANC	≥ 0.8	<0.8					

IPSS-R Cytogenetic risk groups

RISK CATEGORY	RISK SCORE
Very Low	≤ 1.5
Low	> 1.5 - 3
Intermediate	> 3 - 4.5
High	> 4.5 - 6
Very High	> 6

24.7 *Appendix 7: Risk classification according to IPSS*

score (points)	marrow blasts	karyotype	cytopenias* (number of affected cell lines)
0.0	< 5	normal, -Y, del 5q, del 20q	0 - 1
0.5	5 - 10	other	2 - 3
1.0		complex (≥ 3 anomalies) and/or chromosome 7 anomalies	
1.5	11 - 20		
2.0	21 - 30		

***Definition for cytopenias:**

neutrophils	< 1800/µl
hemoglobin	< 10 g/dl
platelets	< 100 000/µl

type	points	median survival
low-risk:	0	about 5.7 years
intermediate-1-risk:	0.5 – 1.0	about 3.5 years
intermediate-2-risk:	1.5 – 2.0	about 1.2 years
high-risk:	≥ 2.5	about 5 months

24.8 *Appendix 8:* Tabulated summary of dyshematopoiesis

Dyshematopoiesis in bone marrow:	
Dyserythropoiesis	Ringed sideroblasts, megaloblastic transformation, nucleus fragmentation, more than one nucleus, nuclei not round, sideroblastosis, PAS-positive erythroblasts
Dysgranulopoiesis:	Increase of blasts, hypogranulated myelocytes, Auer rods, increase of monocytes, pseudo-Pelger-cells, myeloperoxidase-defect, increase of promyelocytes
Dysmegakaryopoiesis:	Micromegakaryocyztes, mononuclear megakaryocytes, megakaryocytes with rounded, separate nucleus segments

24.9 *Appendix 9: Groups according to FAB-classification*

Subtype	**Percentage of blasts**		**Further changes**
	blood	**bone marrow**	
Refractory anemia (RA)	≤ 1 %	< 5 %	
Refractory anemia with ringed sideroblasts (RARS)	≤ 1 %	< 5 %	> 15 % ringed sideroblasts within erythropoiesis
Refractory anemia with excess of blasts (RAEB)	< 5 %	5-20 %	
RAEB in transformation (RAEB-T)	> 5 %	20-30 %	facultative Auer rods
Chronic myelomonocytic leukemia (CMML)	< 5 %	0-20 %	peripheral monocytosis (> 1000/µl)

24.10 *Appendix 10: Groups according to WHO-classification 2016*

Subtype	Dysplastic lines	Cyto-penias	Ring sideroblasts (% of erythroid cells)	Blasts in BM and PB	Karyotype (conventional banding)
MDS-SLD	1	1 or 2	<15% / <5 %[2]	BM <5%, PB <1% no Auer rods	All, except del(5q) ± 1 other non-chr 7 abnormality
MDS-MLD	2 or 3	1-3	<15% / <5 %[2]	BM <5%, PB <1% no Auer rods	All, except del(5q) ± 1 other non-chr 7 abnormality
MDS-RS					
MDS-RS-SLD	1	1 or 2	<15% / <5 %[2]	BM <5%, PB <1% no Auer rods	All, except del(5q) ± 1 other non-chr 7 abnormality
MDS-RS-MLD	2 or 3	1-3	<15% / <5 %[2]	BM <5%, PB <1% no Auer rods	All, except del(5q) ± 1 other non-chr 7 abnormality
MDS with del(5q)	1-3	1 or 2	not relevant	BM <5%, PB <1% no Auer rods	Isolated del(5q) or with 1 other non-chr 7 abnormality
MDS-EB					
MDS-EB1	0-3	1-3	not relevant	BM 5-9% or PB 2-4% no Auer rods	not relevant
MDS-EB2	0-3	1-3	not relevant	BM 10-19% or PB 5-19% or Auer rods	not relevant
MDS-U (unclassifiable)					
with 1% blood blasts	1-3	1-3	not relevant	BM <5%, PB =1% no Auer rods	not relevant
with single lineage dysplasia and pancytopenia	1	3	not relevant	BM <5%, PB <1% no Auer rods	not relevant
based on defining cytogenetic abnormality	0	1-3	<15%[4]	BM <5%, PB <1% no Auer rods	MDS-defining abnormality

1 cytopenias defined as hemoglobin < 100 g/L, Platelets < 100 x 10^9/L, ANC <1.8 x 10^9/L

2 if SF3B1 has a mutation

3 1 % peripheral blasts have to be judged at 2 different times

4 Cases with ≥ 15% of ring sideroblasts have (per definition) significant dyserythropoiesis and are therefore MDS-RS-SLD

24.11 *Appendix 11: MDS response criteria*

The following response criteria are based on the International MDS Working Group (IWG) 2006 Criteria for Measurement of Response/Treatment Effect in MDS by *Cheson et al.* [10].

24.11.1 Complete remission (CR)

Bone marrow evaluation: Bone marrow showing < 5% myeloblasts with normal maturation of all cell lines*. Persistent dysplasia will be noted*.
Peripheral blood‡ evaluation:

- Hemoglobin > 11 g/dL (untransfused, patient not on erythropoietin)
- Neutrophils ≥ 1.000/mm^3 (not on a myeloid growth factor)
- Platelets ≥ 100.000/mm^3 (untransfused, not on a thrombopoetic agent)
- Blasts – 0%

24.11.2 Partial remission (PR)

All of the CR criteria (if abnormal prior to treatment), except:
Bone marrow evaluation: Blasts decreased by ≥ 50% over pretreatment but still > 5%. Cellularity and morphology are not relevant.

24.11.3 Marrow CR

- Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment
- Peripheral blood: if HI responses, they will be noted in addition to marrow CR

24.11.4 Stable disease

Failure to achieve at least a PR, but with no evidence of progression for > 8 weeks.

24.11.5 Failure

Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment.

24.11.6 Relapse (following a CR or PR)

One or more of the following:

- Return to pretreatment bone marrow blast percentage.
- Decrement of ≥ 50% from maximum remission response levels in granulocytes or platelets.
- Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence.

24.11.7 Disease progression

For patients with:

- Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
- 5%-10% blasts: ≥ 50% increase to > 10% blasts
- 10%-20% blasts: ≥ 50% increase to > 20% blasts
- 20%-30% blasts: ≥ 50% increase to > 30% blasts

Any of the following:

- At least 50% decrement from maximum remission/response in granulocytes or platelets
- Reduction in Hgb by ≥ 2 g/dL
- Transfusion dependence

24.11.8 Cytogenetic response

Requires 20 analyzable metaphases when using conventional cytogenetic techniques.

- Complete Cytogenetic Response: Disappearance of the chromosomal abnormality without appearance of new ones.
- Partial Cytogenetic Response: At least 50% reduction of the chromosomal abnormality.

24.11.9 Survival

Endpoints:

Overall: death from any cause

Event free: failure or death from any cause

PFS: disease progression or death from MDS

DFS: time to relapse

Cause-specific death: death related to MDS

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.
*Dysplastic changes should consider the normal range of dysplastic changes.
‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

24.11.10 MDS - Hematologic improvement

Hematologic Improvement (HI)*	Response Criteria (Responses must last at least 8 weeks)
Erythroid response (HI-E) (pretreatment Hgb < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (HI-P) (pretreatment, < 100 x 10^9/L)	Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L platelets Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
Neutrophil response (HI-N) (pretreatment, < 1.0 x 10^9/L)	At least 100% increase and an absolute increase > 0.5 x 10^9/L
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence

To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.

*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart.

‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

24.11.11 MDS - Duration of response

Defined as time to disease progression (as per bone marrow response see 24.11.1) or progression/relapse following hematologic improvement (as per hematologic improvement see 24.11.10).

24.12 *Appendix 12: AML Classification and response criteria*

24.12.1 AML classification

Subgroup	Specification
Acute Myeloid Leukemia with recurrent genetic aberrations	AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	APL with t(15;17)(q22;q12); PML-RARA
	AML with t(9;11)(p22;q23); MLLT3-KMT2A
	AML with t(6;9)(p23;q34); DEK-NUP214
	AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2, MECOM
	AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
	Provisional entity: AML with BCR-ABL1
	AML with mutated NPM1
	AML with biallelic mutations of CEBPA
	Provisional entity: AML with mutated RUNX1
Acute myeloid leukemia with myelodysplasia-related changes	
Therapy-related myeloid neoplasms	
Acute myeloid leukemia, not otherwise specified (NOS)	Acute myeloid leukemia with minimal differentiation
	Acute myeloid leukemia without maturation
	Acute myeloid leukemia with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/monocytic leukemia
	Pure erythroid leukemia
	Erythroleukemia, erythroid/myeloid
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute myelosclerosis)
Myeloid sarcoma	
Myeloid proliferations related to Down-syndrome	Myeloid leukemia associated with Down syndrome
	Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder)
Acute leukemias of ambiguous lineage	Acute undifferentiated leukemia

	Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1
	Mixed phenotype acute leukemia with t(v;11q23); MLL rearranged/KMT2A
	Mixed phenotype acute leukemia, B/myeloid, NOS
	Mixed phenotype acute leukemia, T/myeloid, NOS

24.12.2 AML response criteria

The following response criteria are based on the criteria of European LeukemiaNet (*Döhner et al)*[11].

CATEGORY	DEFINITION	COMMENT
Response		
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥ 1.0 x 10^9/L (1000/µL); platelet count ≥ 100 x 10^9/L (100 000/µL)	MRD^+ or unknown
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (< 1.0 x 10^9/L [1000/µL]) or thrombocytopenia (< 100 x 10^9/L [100 000/µL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be “aplastic”; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	
Treatment failure		
Primary refractory disease	No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine (see Table 8 in [11]) are generally considered as the best option for patients not responding to a first

CATEGORY	DEFINITION	COMMENT
		cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring ≥ 7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 d following its completion; or deaths occurring ≥ 7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	
Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mon
Progressive disease (PD)*,†	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (> 0.5 x 10^9/L [500/µL], and/or platelet count to > 50 x 10^9/L [50 000/µL] non-transfused); or • 50% increase in peripheral blasts (WBC x % blasts) to > 25 x 10^9/L (> 25 000/µL) (in the absence of differentiation syndrome)†; or • New extramedullary disease	Category mainly applies for older patient given low-intensity or single-agent "targeted therapies" in clinical trials In general, at least 2 cycles of a novel agent should be administered Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date Some protocols may allow transient addition of hydroxyurea to lower blast counts

CATEGORY	DEFINITION	COMMENT
		"Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
Hematologic relapse ¶ (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.
*The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.
†Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm reapse. 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 MDS/AML.

24.13 *Appendix 13: 2017 ELN Risk Stratification by Genetics*

Risk category*	**Genetic abnormality**
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}‡
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}‡
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}‡ (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}‡
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

*Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

* Prognostic impact of a marker is treatment-dependent and may change with new therapies.

† Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic hematocrit (HCT).[57⇓-59,77]

‡ The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§ Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

‖ Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).116

¶ These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

TP53 mutations are significantly associated with AML with complex and monosomal karyotype.37,66⇓⇓-69

Reference: Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum F, B¨uchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424-447.