UPFRONT RELATED DONOR TRANSPLANTATION IN PATIENTS WITH MYELODYSPLASTIC SYNDROME: A PHASE 2 TRIAL

FIRST ALLO MDS

INTERVENTIONAL RESEARCH PROTOCOL

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SIGNATURE page for a research PROTOCOL

Research code number:

Title: UPFRONT RELATED DONOR TRANSPLANTATION IN PATIENTS WITH MYELODYSPLASTIC SYNDROME: A PHASE 2 TRIAL

Version no.1.1 dated 07/12/2023

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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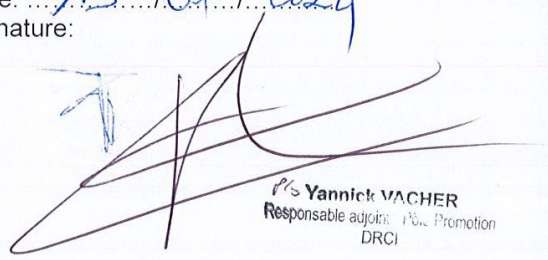

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1 SUMMARY

Full title	UPFRONT RELATED DONOR TRANSPLANTATION IN PATIENTS WITH MYELODYSPLASTIC SYNDROME: A PHASE 2 TRIAL
Acronym/reference	FIRST ALLO MDS
Coordinating investigator	Dr. Marie ROBIN Department of Hematology Hôpital Saint-Louis Paris
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Three recent prospective "transplant/no transplant" studies concluded to an advantage of OS with transplantation in patients with high or intermediate-2 IPSS risk (not significant in Kröger's study).[1–3] No prospective randomized trial has assessed the pre-transplant therapy in MDS patients yet but some information can be extracted from these 3 recent studies. In the French study (n=162), 72% patients with a donor received HSCT, previously treated by hypomethylating agent (HMA) in 71% of them.[3] There was a trend to a better survival in patients achieving a complete remission with pre-graft therapy (HR: 0.55, p=0.088) and higher risk of death in unresponsiveness patients transformed into AML (HR: 2.36, p=0.008). In Nakamura's study (n=384), 83% of patients with a donor were transplanted, previously treated by HMA in 68%[2]. The multivariable Cox model for Overall Survival (OS) and Leukemia-free survival showed an excess risk in patients treated by HMA. Moreover, responders still have a higher risk of mortality as compared to patients who did not receive any pre-graft therapy (HR: 2.417, p=0.0054). In the German study, the aim was to initiate azacytidine at inclusion and to transplant patients after 4 cycles if a donor was identified[1]. Among 170 registered patients, 162 initiated 5-aza but 36% of them were "lost during this pre-graft therapy" before allocation to "donor" or "no-donor" arm, for different reasons including death (n=12). After 4 cycles of 5-aza, 79/81 patients "donor arm" were transplanted. The multivariable analysis showed remission status did not influence OS. Those 3 previous clinical trials thus suggest that a substantial number of patients planned for transplantation are not transplanted nowadays while no evidence of HMA benefit before HSCT has been clearly identified. This phase 2 study aim to assess the feasibility of upfront HSCT in patients with high risk MDS in order to increase the probability to be transplanted and to achieve a subsequent remission and better survival.
Main objective and primary endpoint	**Primary Objective**: To demonstrate an improved disease-free survival (DFS) in patients undergoing upfront transplantation from a related donor as compared to 0.35 (historical prospective cohort). **Primary endpoint**: DFS 2 years after transplantation

Secondary objectives and endpoints	**Secondary Objectives**: Clinical and Biological outcomes: - Overall survival (OS) - Incidence of transplantation after donor identification - Incidence of transformation into AML - Relapse or progression - Engraftment - Acute and late rejection - Non-relapse mortality (NRM) - Acute GvHD - Chronic GvHD - Severe infections (CTAE grade 3-4) - Cardiac events grade 2-4 CTAE **Secondary Endpoints**: - OS, at 24 months after inclusion and after transplantation - NRM at 24 months after transplantation - Cumulative incidence of transformation into acute myeloid leukemia from inclusion at 24 months - Acute GvHD and grading at 100 days post HSCT - Chronic GvHD and grading at 2 years post HSCT - Engraftment at M3 (hematological recovery and donor chimerism > 95%) - Graft failure (acute or late rejection and non-engraftment) at 2 years post HSCT - Severe infections (CTAE grade 3-4) at M3, M6, M12 and M24 - Cardiac events grade 2-4 CTAE at M1 and M3
Design of the study	This study uses an uncontrolled phase 2 open-label design. To increase the level of incidence, external comparisons will be secondly performed to (i) demethylating agents using individual patient data from a prospective cohort (Robin 2015) or (ii) 5-Azacytidine, using aggregated data from a published randomized clinical trial (Kröger 2021).
Population of study participants	Adults (50 years and older) patients with MDS diagnosis for whom transplantation is indicated from a related donor identified.
Inclusion criteria	**Inclusion criteria** - Age ≥ 50 and ≤ 70 years - An HLA matched sibling donor or familial haplo-identical donor has been identified - The disease fulfills at least one of the following criteria: o Intermediate-2 or high risk according to classical IPSS o Intermediate-1 risk if marrow fibrosis > grade I or poor risk cytogenetics according to R IPSS or classified high or very high risk according to R IPSS or if the MDS is therapy-related neoplasm

	- Usual criteria for HSCT:
	  o ECOG ≤ 2
	  o No severe and uncontrolled infection
	  o Cardiac function compatible with high dose of cyclophosphamide LVF ≥ 50%
	  o Adequate organ function: ASAT and ALAT ≤ 2.5N, total bilirubin ≤ 2N, creatinine clearance ≥ 30 ml/min (according to Cockroft formula)
	
	- In case of transplantation with a haploidentical donor, absence of donor specific antibody (DSA) detected in the patient with *a* MFI >1000 *(antibodies directed towards the distinct* haplotype between donor and recipient) as recommended in EBMT guidelines.
	
	Contraception methods must be prescribed for women of childbearing age during all the study. If cyclophosphamide is used, effective contraceptive methods for men during ~~6~~ during all their participation in the study .
	- With health insurance coverage
	- With a written informed consent signed
	
	NB: The authorized contraceptive methods are:
	- For women of childbearing age and in absence of permanent sterilization: oral, intravaginal or transdermal combined hormonal contraception
	- oral, injectable or implantable progestogen-only hormonal contraception
	- intrauterine device (IUD)
	- intrauterine hormonal releasing system (IUS)
	- bilateral tubal occlusion
	- vasectomised partner
	- sexual abstinence (only if this the preferred and usual lifestyle of the participants)
	- For man in absence of permanent sterilization: sexual abstinence, condoms

Exclusion criteria	**Exclusion criteria** - Marrow blast > 15% at time of inclusion - MDS with excess blast >10% and NPM1 mutation or a recurrent genetic abnormality related to AML (WHO 2022) - Chemotherapy (AML like intensive chemotherapy or demethylating agent) to treat MDS at the current stage - Disponibility of an unrelated donor 10/10 (MUD) in absence of geno-identical donor - Patient with uncontrolled infection - Cancer in the last 5 years (except basal cell carcinoma of skin or “in situ” carcinoma of the cervix - Renal failure with creatinine clearance <30ml / min (according to Cockroft formula) - With contraindications to treatments used during the research - Uncontrolled coronary insufficiency, recent myocardial infarction <6 month, current manifestations of heart failure, uncontrolled cardiac rhythm disorders, ventricular ejection fraction <50% - With heart failure according to NYHA (II or more)

	- Patient with seropositivity for HIV or HTLV-1 or active hepatitis B or C defined by a positive PCR HBV or HCVYellow fever vaccine or any alive vaccine within 2 months before transplantation - Pregnancy (β-HCG positive) or breast-feeding - Who have any debilitating medical or psychiatric illness, which would preclude giving well understand informed consent or optimal treatment and follow-up - Under protection by law (tutorship or curatorship)
Intervention under investigation	Procedures of the study: 1. The indication of transplant is confirmed and the donor identified is a related donor . In cases, an haplo-identical donor has been chosen, the probability to identify an HLA 10/10 unrelated donor is nul or low (< 3 potential unrelated donor on the file or donor not well HLA typed). 2. The informed consent is signed in eligible patient and HSCT is planned as soon as possible 3. If the transplantation is scheduled more than 30 days after inclusion, a new disease assessment should be performed before transplantation to check that the disease has not transformed into AML, if yes, the patient cannot undergo upfront transplantation **Modalities transplants** **a) Conditionning regimen** 1) TBF RIC - fludarabine (4 days, 160 mg/m2 total) day-5 to day-2 - busulfan (2 days, 6.4 mg/kg) day-4 to day-3 - thiotepa (5mg/kg) day-6 2) TEC RIC - Thiotepa 5 mg/kg à D-13 - Cyclophosphamide 400 mg/m2/day de D-12 à D-10 - Etoposide 100 mg/m2/day day-12 to day-10 - Fludarabine (30 mg/m^2/day) , day-6 to day-2 - Busulfan (3.2 mg/Kg/Day) Day-5 to Day-4 In case of Body Mass Index (BMI) is > 25, chemotherapy (busulfan, thiotepa and cyclophosphamide should be adapted (Annexe 18.6) and for Fludarabine capped at 2 m^2. b) **Type of stem cell source** The stem cell source will be **in priority** peripheral blood stem cell (PBSC). The collection of PBSC is carried out according to the practice of each centre with the minimal target dose of 4.10^6 CD34+ cells/kg. Bone marrow is possible collected according to the practice of each centre

	with a target yield of 3× 10^8 nucleated cells/kg recipient ideal body weight , not exceeding the donor volume of 20ml /kg. c) **GvHD prophylaxis** will consisted : • In cases of HLA matched sibling donor:thymoglobulin on day-3 and day-2 (2 days, 5 mg/kg total dose), cyclosporine from day-1 IV (3 mg/kg/day) or day-3 per os (3 mg/kg x2 by day) to day 120 (in absence of GVHD) and mycophenolate mofétil (MMF) (15 mg/kg x2 by day) from day+1 to day +30 • In cases of HLA haplo-identical related donor: cyclophosphamide (2 days, 100 mg/kg) day +3 and day +4 (adapted if overweight) followed by cyclosporine (3 mg/kgx2 by day, by os) from day +5 to day 120 and MMF (15 mg/kg X2 by Day) from day +5 to day 30
Interventions added by the study	An additional sample will be collected during a routine blood sampling before HSCT and on day 60. Blood samples will be send to Lille CHRU laboratory There are no more exams or procedures added by the study. This is a standard of care procedure.
Expected benefits for the participants and for society	This study may reduce the “loss of patients” between diagnosis and transplantation and consequently increase the probability to be transplanted and to survive long-term. The role of pre-graft therapy (HMA) remains unclear and is able to induce complete remission (CR) only in few patients (25%), meaning that the majority of patients are not transplanted in CR. HMA or chemotherapy are usually started in high risk MDS in order to reduce the risk of disease progression or to decrease marrow blast percentage during transplantation organization. Our hypothesis is that we don’t need this treatment if the patient is transplanted in a short period of time.
Risks and burdens added by the study	There is no excess risks and burdens added by the study as compared to HLA matched sibling and haplo-identical routine transplantation. This is a standard of care transplantation. Risk level of the study: D
Number of participants included	55 patients
Number of centres	Multicenter national study: 16 Hematology departments in France (3 centres APHP).
Duration of the study	- *inclusion period: 24 months* - *participation period:24 months* - *total duration: 48 months*
Number of enrolments expected per site and per month	0,19 patient/site/month
Statistical analysis	A, two-sided, one-sample, logrank test calculated from a sample of 55 subjects achieves 90.36% power at a 0.050 significance level to detect a proportion surviving of 0.5500 in the new group when the proportion surviving in the historic control group is 0.3500. Such an historical proportion has been estimated from our previous French cohort study, as published in Leukemia where a 2-year DFS rate of 35% was

	observed in patients with a donor who were not transplanted upfront . By contrast, EBMT studies have reported that 2-year DFS in patients with MDS is expected to be 55%. These surviving proportions are for a period of 24.0 months. Subjects are accrued for a period of 24.0 months. Follow-up continues for a period of 24.0 months after the last subject is added. The probability that a subject experiences an event during the study is 0.5860. The expected number of events during the study is 24. It is assumed that the survival time distributions of both groups are approximated reasonably well by the Weibull distribution with a shape parameter of 1.00. To increase the level of evidence, external indirect comparisons will be secondly performed to (i) demethylating agents using individual patient data from a prospective cohort (Robin 2015) or (ii) 5-Azacytidine, using aggregated data from a published randomized clinical trial (Kröger 2021).
DSMB	YES
Funding sources	Fondation MSD Avenir

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

The hypothesis is that an upfront transplantation as soon as possible after donor identification increases the DFS at 2 years from 35% (historical cohorts) to 55%.

2.2 Description of knowledge relating to the condition in question

The role of pre-graft therapy in MDS patients has never been assessed by randomized trials and remains controversial. Marrow blast count has been previously reported to increase the relapse risk after HSCT including after adjustment on cytogenetics [4–6]. International recommendation published in 2013 and 2017 are favour chemotherapy before HSCT in patients with marrow blast > 10%, but that is a level D recommendation, which remains relatively weak[7,8]. Indeed, some reserves are put forward: this chemotherapy can be intensive or based on hypomethylating agents (HMA), it should preferably be done within prospective trials, and still discussed when patients have poor cytogenetic risk. Some studies analysed the role of the pre HSCT therapy in registries. The SFGM-TC has reported the outcome of 132 patients transplanted between 1999 and 2009 for MDS and either transplanted upfront or after hypomethylating agents[9]. Three-year OS and relapse incidence were superimposable. Another SFGM-TC has compared outcome after intensive chemotherapy (IC) or HMA[10]. Event-free survival was similar with IC or HMA, patients who received both IC and HMA had a significant worse outcome. An EBMT study also analysed the role of pre-HSCT therapy and reproduced same conclusions: HMA or IC were followed by same outcome, only refractory patients had worse outcome[11]. Furthermore, non-refractory patients who were in CR or not in CR (any response) had similar outcome. All these registry studies do not support a superiority of one of the 2 current therapies and do not give evidences that pre-graft therapy is beneficial for MDS patients. Three recent prospective “transplant/no transplant” studies concluded to an advantage of OS with transplantation in patients with high or intermediate-2 IPSS risk (not significant in Kröger’s study)[2,3,12]. Even if these prospective randomized trials were not designed to analyse pre-graft therapy, some information regarding the role of pre-graft therapy can be extracted from them. In the French study (n=162), 72% patients with a donor received HSCT, previously treated by hypomethylating agent (HMA) in 71% [3]. There was a trend to a better survival in patients achieving a complete remission with pre-graft therapy (HR: 0.55, p=0.088) and higher risk of death in unresponsiveness patients transformed into AML (HR: 2.36, p=0.008). In Nakamura’s study (n=384), 83% of patients with a donor were transplanted, previously treated by HMA in 68%[2]. The multivariable Cox model for OS and Leukemia-free survival showed an excess risk in patients treated by HMA. Moreover, responders still have a higher risk of mortality as compared to patients who did not receive any pre-graft therapy (HR: 2.417, p=0.0054). In the Kröger’s study, the aim was to initiate azacytidine at inclusion and to transplant patients after 4 cycles if a donor was identified[12]. Among 170 registered patients, 162 initiated 5-aza but 36% of them were “lost during this pre-graft therapy” before allocation to “donor” or “no-donor” arm, for different reasons including death (n=12). After 4 5-aza cycles, 79/81 patients “donor arm” were transplanted. The multivariable analysis showed remission status did not influence OS. Those 3 previous clinical trials thus suggest that a substantial number of patients planned for transplantation are not transplanted nowadays while no evidence of HMA benefit before HSCT has been clearly identified.
We propose here, a phase 2 study aimed to assess the feasibility of upfront HSCT in patients with high risk MDS in order to increase the probability to be transplanted and to achieve a subsequent remission and better survival.

Table 1. Summary of the 3 prospective trials

Donor / no donor	Percentage of patients who received a pre-graft treatment	Probability to receive HSCT in "donor arm"	Median time to transplant	OS Donor vs no donor	OS without disease Donor vs no donor
112 / 50[3]	89%	72%	8 months	37 vs 15% @4y	-
81 / 27[12]	100%	98%*	Not given	50 vs 32% @3y	34 vs 0% @3y
260 / 124 [2]	73%	83%	< 6 months	47vs 16% @3y	39 vs 11% @3y

*Among the 162 patients who received 5-azacytidine at inclusion, only 108 could be allocated to a specific arm (donor or no donor)

2.3 Description of the population to be studied and justification for the choice of participants

Patients with MDS and a transplantation indication can be included in the study.
MDS indication are based on classical IPSS, all patients intermediate 2 or high, as well as some intermediate 1 patients with poor prognostic feature (see inclusion criteria).
The inclusion of the later is justified by the poor prognostic value of marrow fibrosis in MDS patients, as exemplified by an increased risk of AML transformation reported in the literature[1]
.

Only patients with less than 15% marrow blast will be included.
Patients with more than 10% marrow blast and recurrent genetic mutation of AML including NPM1 will be excluded from the study (classified as AML according to ELN 2022 classification).[13]

As soon as a familial donor is chosen as the best option, the patient can be included.
Donor choice alorigthm is as follow:

1) Donor HLA matched among the sibling
2) If there is no HLA matched sibling, a search of 10/10 HLA matched donor in international registry should be done; if a 10/10 HLA matched donor is found, the patient cannot be included in the study
3) If there is no HLA matched sibling or HLA matched 10/10 unrelated donor, an haplo-identical donor should be searched, and the patient can be included if such a donor is identified

Only patients with an HLA matched sibling or an haplo-identical familial donor can be included.
As soon as the related donor is identified, the transplantation should be planified as soon as possible

[1] Lambertenghi-Deliliers G, Annaloro C, Oriani A, Solgio D, Pozzoli E, Polli E. Prognostic relevance of histological findings on bone marrow biopsy in myelodysplastic syndromes. Ann Hematol. 1993; 66(2):85-91. Verhoef GE, De Wolf-Peeters C, Ferrant A, Deprez S, Meeus P, Stuhl M. Myelodysplastic syndromes with bone marrow fibrosis: a myelodysplastic disorder with proliferative features. Ann Haematol. 1991; 63(5):235-41. Maschek H, Georgii A, Kaloutsi V, Bandecar K, Kressel MG, Choritz H. Myelofibrosis in primary myelodysplastic syndromes: a retrospective study of 352 patients. Eur J Haematol. 1992; 48(4):208-14. Buesche G, Teoman H, Wilczak W, Ganser A, Hecker H, Wilkens L. Marrow fibrosis predicts early fatal marrow failure in patients with myelodysplastic syndromes. Leukemia. 2008; 22(2):313-22.

If the screening is more than 30 days before transplantation, a new disease assessment should be performed less than 30 days before transplantation to check that the disease has not transformed into AML.
If marrow blast > 20%, the patient cannot undergo upfront transplantation and this will be a screening failure.

2.4 Succinct description of the investigational product(s) or intervention(s)

There is no investigational product. The intervention is allogeneic transplantation in patients with an indication if transplantion. The procedure is performed according to French centers policy. The aim of the study is to transplant patients as soon as possible, without any previous therapy to improved 2-year DFS.

2.5 Summary of the known and foreseeable benefits and risks for the research participants

The hypothesis of the protocol is that the probability to be transplanted, to achieve a remission and so to be alive without the disease is higher with upfront transplantation.
The risks are related to complications related to the transplantation including GVHD, organ toxicity, immune defect and poor graft function.

3 OBJECTIVES

3.1 Primary objective

To demonstrate an improved disease-free survival (DFS) in patients undergoing upfront transplantation from a related donor as compared to 0.35 (historical prospective cohort).

3.2 Secondary objectives

Clinical and Biological outcomes:

- Overall survival (OS)
- Incidence of transplantation after donor identification
- Incidence of transformation into AML
- Relapse or progression
- Engraftment
- Acute and late rejection
- Non-relapse mortality (NRM)
- Acute GvHD
- Chronic GvHD
- Severe infections (CTAE grade 3-4)
- Cardiac events grade 2-4 CTAE

4 STUDY DESIGN

4.1 4.1 Study endpoints.

4.1.1 Primary endpoint

DFS 2 years after transplantation

4.1.2 Secondary endpoints

- OS, at 24 months after inclusion and after transplantation
- NRM at 24 months after transplantation
- Cumulative incidence of transformation into acute myeloid leukemia from inclusion at 24 months
- Acute GvHD and grading at 100 days post HSCT
- Chronic GvHD and grading at 2 years post HSCT
- Graft failure (Acute and late rejection and non engraftment at M24)
- Engraftment at M3 (hematological recovery and donor chimerism > 95%)
- Severe infections (CTAE grade 3-4)at M3, M6, M12 and M24
- Cardiac AE grade 2-4 CTAE at M1 and M3

4.2 4.2 Description of research methodology

4.2.1 Design of the study

This study uses an uncontrolled phase 2 open-label design. To increase the level of incidence, external comparisons wil be secondly performed to (i) demethylating agents using individual patient data from a prospective cohort (Robin 2015)[3] or (ii) 5-Azacytidine, using aggregated data from a published randomized clinical trial (Kröger 2021).[12]

4.2.2 Number of participating sites

This is a national multi-center study, 15 centers will participate and enrole patients during the study. Patients will be recruited in the hematology departments and referred to the transplant team for the pre-transplant assessment.

4.2.3 Recruitment centers

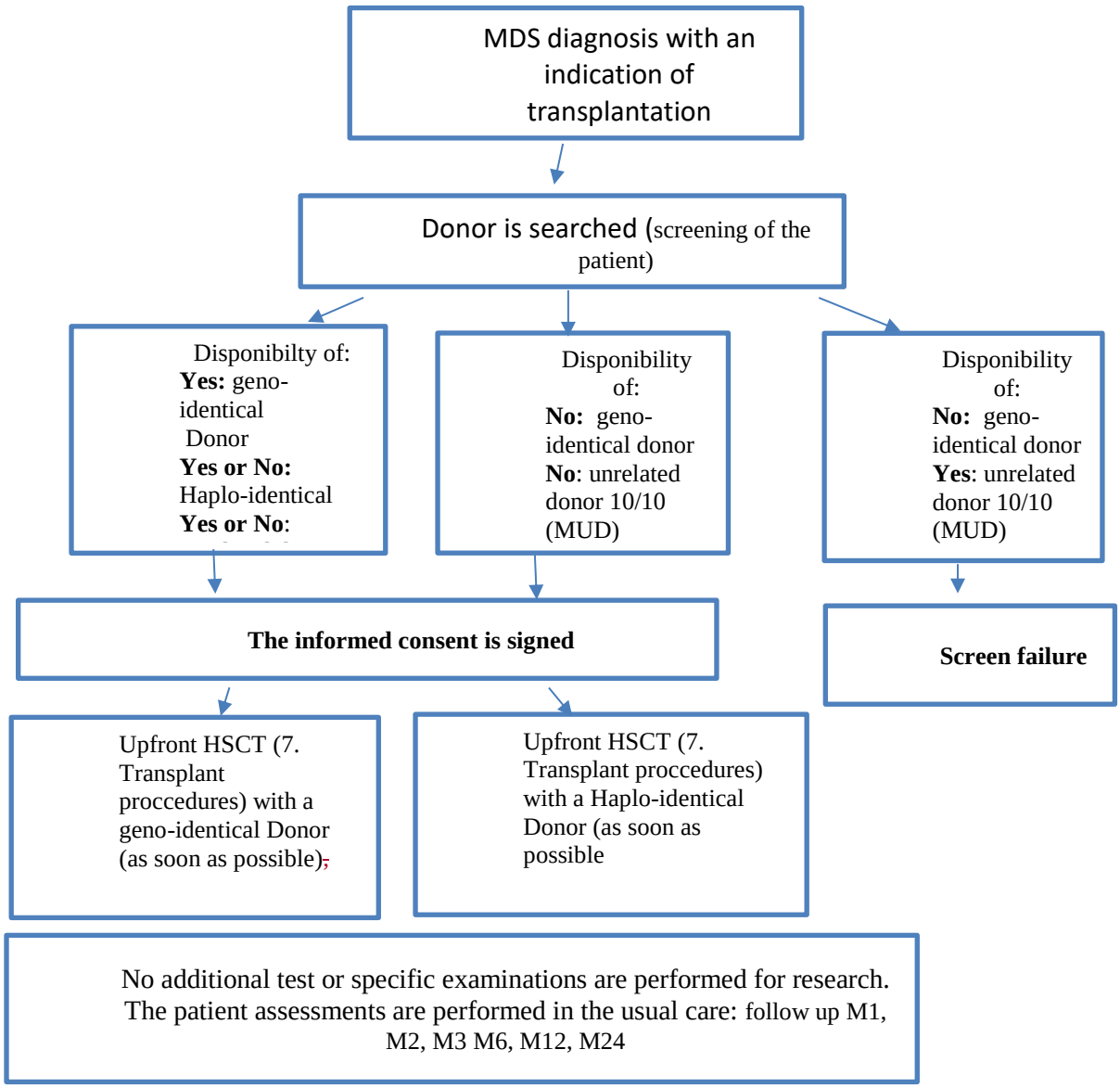
The Study is conducted with the French society of cellular therapy (SFGM-TC) and the french group of myelodysplastic syndrome (GFM).

4.2.4 Identification of participants

The participants in this research will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

5 IMPLEMENTATION OF THE STUDY

5.1 Study Scheme



5.2 Screening visit

The indication of transplant is confirmed and a donor has beensearched (as described & 2.3). If the patient is planned to receive a transplantation from related donor, the investigator will check the eligibility criteria and will propose the study to the patient. Donor has not to be definitively validated at time of screening visit. Information about the protocol is delivered by the transplant physician in charge of the patient. Information and consent forms will be given to the patient by the investigator.

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
the individual participating in the study	The transplant physician (investigator of research)	Screening visit	At the inclusion visit, when the patient is planned to receive a transplantation from related donor

5.3 Inclusion visit

If the patient is planned to receive a transplantation from related donor, the informed consent is signed in eligible patient and HSCT is planned; a matched sibling donor would be preferred to an haplo-identical if no donor MUD 10/10 (cf &5.1).

At this visit, the consent of the patient will be collected. A Patient triplicated Information Sheet and consent form are given to the patient by the investigator: one for the investigator one for the sponsor and one for the patient.
This visit is performed according to the practice of the investigator The patient assessment is performed in the usual care of allogeneic transplant.

Data collected for the research :

- Physical examination
  - Reports of patient and disease history
  - Weight and height
  - ECOG performans status assessment
  - Sorror score of comorbidities
  - Complete physical examination with evaluation of tumor localization
  - Electrocardiogram done at screening visit or no less than 2 months before inclusion
  - Echocardiogram with evaluation of left ventricular ejection done at screening visit or no less than 2 months before inclusion
  - Evaluation of the cardiovascular risk factors (dyslipidemia, obesity, smoking, diabetes requiring a therapy, previous cardiac disease including coronaropathy & hypertension) done at screening visit.
  - Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1), Diffusing Capacity of Carbon Monoxide (DCCM) , residual volume (RV) and Forced vital capacity (FVC) done at screening visit or no less than 2 months before inclusion

-

- SMD assessment: Pre-transplant bone marrow aspiration for smear and cytogenetics, blood cell count for disease evaluation (revised IPSS) at local laboratory should be performed maximum 30 days before transplantation
  - At 2 months, if the patient is not in remission, no other marrow analysis will be required in the protocol.
  - At 2 months if the patient is in complete remission, additional marrow analysis will be performed if a relapse is suspected meaning that blood cell count change or chimerism becomes mixed, as measured at M3, M6, M12 and M24 and systematic marrow analysis at M24.
- Results of the most recent NGS if done (ASXL1; SF3B1; TP53; RUNX1 mutated with %VAF> lower threshold)
- One blood sample with 2 tubes 5 mL with EDTA (volume in accordance with the decree of February 17, 2021, Annexe 18.7) to send to Lille CHRU hematological laboratory (Pr. Claude Preudhomme) collected at the same time of pre-transplant evaluation:

If the transplantation is scheduled more than 30 days after inclusion, marrow and blood assessment should be redone to check that the patient has not transformed into AML. If the patient has transformed into AML, he should receive a therapy before subsequent transplantation (not upfront transplantation).

- Biological tests
  - Complete Blood count: neutrophil, monocyte, peripheral blood blast%, lymphocyte, haemoglobin, platelet (screening and inclusion visit)
  - ABO and Rh typing Blood cell
  - Chemistry panel (creatinine, ferritin, CRP)
  - HDL, LDL cholesterol, triglyceride
  - Pro BNP
  - Liver function tests (transaminases, alkaline phosphatase, gamma-GT and bilirubine)
  - Date of HLA typing of donor
  - Search of donor specific anti-HLA antibodies with LUMINEX technology if the donor is haplo-identical (DSA)
  - Viral serologies: Serology for hepatitis B (Antigen HBs, Ig antiHBc) and C, EBV (IgG and M), CMV (IgG and M), HIV (2 Elisa tests), HTLV-1 and 2 (IgG)
  - PCR: HIV, B and C hepatitis

5.4 Follow-up visits (M1, M2, M3, M6, M12, M24)

Patients are monitored daily during initial hospitalization to detect possible complications of procedure or GvHD occurrence. Once patients get out from the hospital, the follow-up will be done according to each center policy and protocol requirement but at least once a week until Months 3 and then in consultation on a regular basis lifelong.
The minimum expected length of hospitalization is 21 days.

Data will be collected in the eCRF as follow :

☛At M1, M2, M3, M6, M12 and M24 after transplantation:

- Clinical examination, blood cell count (M1, M2, M3, M6, M12, M24), creatinine and liver test (M24) will be performed at each visit.
- Acute GVHD: date of apparition, maximal grade, steroid response,
- Chronic GVH date of apparition, maximal grade, steroid response, treatment(s)
- Cardiologic monitoring: before cyclophosphamide use, as well as clinical assessement
- Engraftment and acute rejection at M1, M2, M3
- Late rejection

-

- Disease evaluation in blood and marrow will be performed preferentially at M2 and no later than D100 with smear (blood and marrow), chimerism (blood and marrow) and cytogenetics (marrow)
- Chimerism at M6, M12, M24
- Bone marrow aspiration at M24
- Date(s) of DLI if done and reason(s) (prophylaxis, relapse and mixed chimerism)
- The same day than marrow evaluation (between M2 & M3), blood samples with 2 tubes 5 mL with EDTA (volume in accordance with the decree of February 17, 2021, Annexe 18.7) will be sent to Lille CHRU hematological laboratory (Pr. Claude Preudhomme) (centralized shipment) (MRD) :

Additionnal marrow analysis and/or chimerism can be performed guided by clinical or biological abnormalities, especially if progression, relapse or rejection are suspected according to center policy

- Safety assessment by collection of all adverse events grade ≥3 /serious adverse events at each visit and Cardiac grade 2-4 AE at M1 and M3.

5.5 Early termination visit

Subjects may exit the study at any time and for any reason.

The investigator must make every effort to contact subjects lost to follow-up. Attempts to contact such subjects must be documented in the subject's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

If a subject exits the trial prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
The case report form must list the various reasons why the subject exited from the study

In case of premature termination of study procedure, the subject remains enrolled in the study until the end of the subject's participation:
The investigator must:
- Document the reason(s)
- Schedule further follow-up visits, especially in case of a serious adverse event.

5.6 Expected length of participation and description of the chronology and duration of the study.

Duration of enrolment period	24 months
The length of participation for participants, of which: Duration of follow-up period after transplantation : Maximum duration between inclusion and transplatation	 24 months 3 months
Total study duration:	51 months
End of trial	Last visit of last patient

5.7 Table or diagram summarising the chronology of the study

	Screening visit	*Inclusion visit*	*D0 = Graft*	*M1*	*M2*	*M3 +- 10j*	*M6*	*M12*	*M24*
Information	X	X							
Verification of inclusion and exclusion criteria	X	X							
Informed consent signed		X							
STANDARD OF CARE									
Related donor is searched	X								
Planned transplantation with related donor		X							
Disease history	X								
(1)(2) Pre-graft organ assessment	X								
(3) Pre-graft blood tests	X		X						
Physical examination	X		X	X	X	X	X	X	X
βHCG test for women of childbearing ~~age~~ potential)(before start treatment for conditioning regiment)		X	X						
(4) Blood cell count,	X	X	X	X	X	X	X	X	X
(5) Disease evaluation	X	X			X				
Chimerism					X	X			
Grading of acute and chronic GvHD				X	X	x	X	X	X
DFS, OS, NRM, Cumulative incidence of transformation into acute myeloid leukemia, Graft failure									X
Engraftment (hematological recovery and donor chimerism > 95%)						X			
Adverse events.serious adverse events *All toxicity not attributed to GvHD will be classified according to CTC-AE toxicity, v5.0*			X	X	X	X	X	X	X
ADDITIONAL FOR STUDY									
Centrailized blood sample		X			X				
Chimerism							X	X	X
bone marrow aspiration									X

(1) Lung function test at screening visit: Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1), Diffusing Capacity of Carbon Monoxide (DCCM) , residual volume (RV) and Forced vital capacity (FVC). (2) Cardiac monitoring: Electrocardiogram and echocardiogram with evaluation of left ventricular ejection and Evaluation of the cardiovascular risk factors (dyslipidemia, HBP, obesity, smoking). (3) Biological tests: Complete Blood count, creatinine, ferritin, CRP, Liver function tests (transaminases, alkaline phosphatase, gamma-GT and bilirubine), HDL, LDL cholecterol, triglyceridemia, (and for Pre-graft: HLA compatibility check between recipient and donor, DSA, Chimerism markers' identification. serology for hepatitis B and C, EBV (IgG and M), CMV (IgG and M), HSV (IgG and M), HIV (2 Elisa tests), HTL V-1 and 2, TPHA and VDRL. HIV, B and C hepatitis PCR). (4) *haemoglobin level, platelet count, white blood cells, neutrophil cout, monocyte, lymphocyte count, peripheral blood % (5) Disease evaluation by blood cell count, marrow analysis including cytogenetics, (6) Additional for study : blood should be collected before HSCT and between day 60 and D+100, the same time than the pre-graft and post-graft marrow analysis , send to Lille CHRU hematological laboratory (Pr Claude Preudhomme): centralized shipment for morphological analysis (Blood 2 tubes 5 mL with EDTA). (a) Marrow aspiration will be redone : If the transplantation is scheduled more than 30 days after inclusion with blood (in the care)*

Infectious markers will be performed according to center policy (at least once a week for CMV and EBV PCR in patient/donor seropositive; aspergillus fumigatus at least once a week until day 100 or at physician discretion)

5.8 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with standard care**	**Interventions, procedures and**

		treatments added for <u>research purposes</u>
Treatments	Allogenic transplantation, conditioning regimen, GVHD prophylaxis as well as infection prophylaxis HSCT overall follow-up	No
Hospitalizations - Consultations	Patients will be monitored daily during the hospitalization duration, the minimum expected length of hospitalization is 21 days up to 60 days . Patients will be assessed (routine follow up) weekly after hospitalization until D+100 or later until the patient has no requirement for intraveinous treatment or transfusion, minimally then at M6, M12 and M24 (usually monthly the first year and every 3 months the second ~~month~~year)	No
Imaging	All exams related to tranplant procedure	No
Blood samples	At each visit	Additional Blood : 2 tubes 5 mL with EDTA for disease evaluation before HSCT and between M2 & M3
Chimerism		Additional Chimerism at M6, M12, M24
Bone marrow aspiration	Pre-transplant including the new marrow aspiration if transplantation is scheduled more than 30 days after inclusion Post-transplant between J60 and M3	Additional Bone marrow aspiration at M24

5.9 Centralization of sample for desease evalutation

Additional blood before HSCT and on day 60 or the day of post-transplantation evaluation (between M2 & M3 (2 tubes 5 mL with EDTA (volume in accordance with the decree of February 17, 2021, Annexe 18.7) taken as part of the study will be send for molecular analysis to Lille CHRU hematological laboratory (Pr. Claude Preudhomme).

At the end of the study, the blood samples will be destroyed.

Type of sample	Quantity	Storage location (name and entity)	Supervisor of the sample collection (name and entity)	Purpose of the sample collection	Storage duration	End use/Future (destruction, etc.)
Blood	10ml (2 tubes 5 mL with EDTA)	Lille CHRU hematological laboratory	Pr. Claude Preudhomme	Centralized disease evaluation to assess the impact of	48 months maximum	Destruction at the end of the study

				minimal residual disease		

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Age ≥ 50 and ≤ 70 years
- A matched sibling donor or an haplo-identical related donor has been identified
- The disease fulfills at least one of the following criteria:
  - Intermediate-2 or high risk according to classical IPSS
  - Intermediate-1 risk if marrow fibrosis > grade I or poor risk cytogenetics according to R IPSS or classified high or very high risk according to R IPSS or if the MDS is therapy-related neoplasm
- With usual criteria for HSCT:
  - ECOG ≤ 2
  - No severe and uncontrolled infection
  - Cardiac function compatible with high dose of cyclophosphamide LVF ≥ 50%
  - Adequate organ function: ASAT and ALAT ≤ 2.5N, total bilirubin ≤ 2N, creatinine clearance ≥ 30 ml/min (according to Cockroft formula)
- In case of transplantation with a haploidentical donor, absence of donor specific antibody (DSA) detected in the patient with *a* MFI >1000 *(antibodies directed towards the distinct* haplotype between donor and recipient) as recommended in EBMT guidelines[2]
-
- Contraception methods must be prescribed for women of childbearing age during all their participation in the study. If cyclophosphamide is used, effective contraceptive methods for men during all their participation in the study.
- With health insurance coverage
- With a written informed consent signed

NB: The authorized contraceptive methods are:
- For women of childbearing age and in absence of permanent sterilization: oral, intravaginal or transdermal combined hormonal contraception
- oral, injectable or implantable progestogen-only hormonal contraception
- intrauterine device (IUD)
- intrauterine hormonal releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence (only if this the preferred and usual lifestyle of the participants)
- For man in absence of permanent sterilization:
sexual abstinence, condoms

6.2 Exclusion criteria

- Marrow blast > 15% at time of inclusion
- MDS with excess blast >10% and NPM1 mutation or a recurrent genetic abnormality related to AML (WHO 2022)
- Chemotherapy (AML like intensive chemotherapy or demethylating agent) to treat MDS at the current stage

[2] O. Ciurea S, Cao K, Fernadez-Vina M, Kongtim P, Al Malki M et al. The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor Specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation. Bone Marrow Transplant. 2018 May; 53(5): 521–534.

-
- Disponibility of an unrelated donor 10/10 (MUD) in absence of geno-identical donor
- Patient with uncontrolled infection
- Cancer in the last 5 years (except basal cell carcinoma of the skin or “in situ” carcinoma of the cervix
- Renal failure with creatinine clearance <30ml / min (according to Cockroft formula)
- With contraindications to treatments used during the research
- Uncontrolled coronary insufficiency, recent myocardial infarction <6 month, current manifestations of heart failure, uncontrolled cardiac rhythm disorders, ventricular ejection fraction <50%
- With heart failure according to NYHA (II or more)Patient with seropositivity for HIV or HTLV-1 or active hepatitis B or C defined by a positive PCR HBV or HCV
- Yellow fever vaccine or any alive vaccine within 2 months before transplantation
- Pregnancy (β-HCG positive) or breast-feeding
- Who have any debilitating medical or psychiatric illness, which would preclude giving well understand informed consent or optimal treatment and follow-up.
- Under protection by law (tutorship or curatorship)

6.3 Birth control

6.3.1 Birth control methods

As part of standard of care, a progestative-based contraception will be used at hospital discharge for all females.

• For women of childbearing potential:

A highly effective birth control method must be used from baseline until the end of the participation period.

Women of childbearing potential are defined as fertile women until post-menopausal state unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause

Highly effective birth control method accepted in this study are:

- oral, intravaginal or transdermal combined hormonal contraception
- oral, injectable or implantable progestogen-only hormonal contraception
- intrauterine device (IUD)
- intrauterine hormonal releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence (only if this the preferred and usual lifestyle of the participants)

• For men, in absence of permanent sterilization:
The methods accepted in this study are listed below and must be used from baseline until the end of the participation period:

- condoms
- sexual abstinence (only if this the preferred and usual lifestyle of the participants)

For women of childbearing potential partner of a male participant, contraception should be considered.

6.3.2 Preservation of the fertility for men

It is mandatory to propose a consultation at the CECOS (Centre for the Study and Conservation of Sperm) for the collection and cryopreservation of sperm prior to treatment..

6.4 Donor Selection

A matched sibling donor would be preferred to an haplo-identical donor

6.5 Recruitment procedure

In France, between 2017 and 2019, 793 patients have been transplanted for MDS (372 (47%) from a related donor including 171 matched and 201 haplo-identical). In case no HLA matched unrealated donor is identified, haplo-identical donor is a valuable source of donor. Indeed, one large EBMT (n=833) haplo transplantation was followed by a better DFS and OS than mismatched unrealated or coord blood (5).

	Number of subjects
Total number of subjects to be included	55
Number of sites	16
Enrolment period (months)	24
Number of subjects/site	3,66
Number of subjects/site/month	0.15

6.6 Termination rules

6.6.1 Criteria and methods for premature discontinuation of study procedures

The transplant procedure started cannot be interrupted unless the patient dies.
The investigator must:

- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

6.6.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- If a participant exits the study prematurely, and if the participant agrees, the investigator will make every effort to obtain the primary endpoint.
- If a subject exits the trial before the end of study (even in case of relapse or progression of underlying disease), this will in no way affect the standard care received for his/her condition.

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.6.3 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed or if there is a discrepancy in the serious adverse reactions, requiring a reassessment of the benefit-risk ratio for the study

Similarly, AP-HP as the sponsor or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the intervention performed or the product used, in light of which the objectives of the study or clinical programme are unlikely to be achieved**.**

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

In case of early trial termination, patients enrolled in the study will be follow in accordance with standard of care received for his/her medical condition.

7 TRANSPLANT PROCEDURE

7.1 Conditionning regimen

In case of Body Mass Index (BMI) is > 25, chemotherapy (busulfan, thiotepa and cyclophosphamid should be adapted (Annexe 18.6)
The use of a myeloablative conditioning regimen in patients with myelodysplastic syndrome is often associated with an unacceptable rate of treatment related mortality. Kroger et al published in 2017 a randomized clinical trial in MDS (not including AML) with no advantage of

MAC over RIC[3]. A similar result has been published in 2020 again in a phase 3 trial showing that the intensification of the conditioning regimen did not improve the results[4]. Finally, the MDS subgroup of the phase 3 trial ran in the USA comparing RIC and MAC regimen (majority of AML in this trial), did not show any advantage in term of OS with MAC. Because of those 3 recent prospective phase 3 clinical trials, we decided to use a reduced intensity conditioning regimen in our patients with MDS to avoid an excess rate of treatment related mortality (associated with MAC).

Therefore, two main reduced conditioning regimens will be allowed:
1) TBF RIC
- fludarabine (4 days, 160 mg/m2) day-5 to day-2 (capped at 2 m²)
- busulfan (2 days, 6.4 mg/kg) day-4 to day-3
- +thiotepa (5mg/kg) day-6
2) TEC RIC
- Thiotepa 5 mg/kg à D-13
- Cyclophosphamide 400 mg/m2/j par jour de D-12 à D-10
- Etoposide 100 mg/m2/j de D-12 à D-10
- Fludarabine (30 mg/m^2/day) , day-6 to day-2
- Busulfan (3.2 mg/Kg/Day) Day-5 to Day-4

7.2 Stem Cell source

The Stem cell source will be in priority peripheral blood stem cell (PBSC). The collection of PBSC is carried out according to the practice of each centre with the minimal target dose of 4.10^6 CD34+ cells/kg. Bone marrow is possible collected according to the practice of each centre with a target yield of 3 × 10^8 nucleated cells/kg recipient ideal body weight , not exceeding the donor volume of 20ml / kg.

7.3 GVHD Prophylaxis

- In cases of HLA matched sibling donor: thymoglobulin on day-3 and day-2 (2 days, 5 mg/kg total dose), (5mg/kg total dose), cyclosporine from day-1 IV (3 mg/kg/day) or day-3 per os (3 mg/kg x2 by day) to day 120 (in absence of GVHD) and mycophenolate mofétil (MMF) (15 mg/kg x2 by day) from day+1 to day 30.
- In cases of HLA haplo-identical related donor: cyclophosphamide (2 days, 100 mg/kg) day +3 and day +4 adapted to BMI (Annexe 18.6), followed by cyclosporine (3 mg/kgx2 by day, by os) from day +5 to day 120 and MMF(15 mg/kg X2 by Day) from day +5 to day 30.

[3] *Kröger N, Iacobelli S, Franke GN, Platzbecker U, Uddin R, Hübel K, Scheid C, Weber T, Robin M, Stelljes M, Afanasyev B, Heim D, Deliliers GL, Onida F, Dreger P, Pini M, Guidi S, Volin L, Günther A, Bethge W, Poiré X, Kobbe G, van Os M, Brand R, de Witte T. Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem-Cell Transplantation for Patients With Myelodysplastic Syndrome: A Prospective Randomized Phase III Study of the EBMT (RICMAC Trial). J Clin Oncol. 2017 Jul 1;35(19):2157-2164. doi: 10.1200/JCO.2016.70.7349. Epub 2017 May 2. PMID: 28463633.*

[4] *Craddock C, Jackson A, Loke J, Siddique S, Hodgkinson A, Mason J, Andrew G, Nagra S, Malladi R, Peniket A, Gilleece M, Salim R, Tholouli E, Potter V, Crawley C, Wheatley K, Protheroe R, Vyas P, Hunter A, Parker A, Wilson K, Pavlu J, Byrne J, Dillon R, Khan N, McCarthy N, Freeman SD. Augmented Reduced-Intensity Regimen Does Not Improve Postallogeneic Transplant Outcomes in Acute Myeloid Leukemia. J Clin Oncol. 2021 Mar 1;39(7):768-778. doi: 10.1200/JCO.20.02308. Epub 2020 Dec 29. PMID: 33373276; PMCID: PMC8078252.*

7.4 Infection Prophylaxis

Prophylactic and curative anti-infectious treatments (antibiotics, antivirals, antifungals) will be administered according to the ECIL recommendations *(link: www.kobe.fr/ecil workshops, recommendations).*
In brief, patients will receive anti-herpes simplex prophylaxis (acyclovir or valacyclovir).
Letermovir is recommended in patients with a positive CMV serology[14].
Antifungal therapy (fluconazole or posaconazole) is recommended in the early phase after transplantation (during neutropenia) according to center policy.

■ Management of toxicities

Management of toxicities (in particular renal, hepatic, ..) will be managed by each center according to usual practice (according to JACIE standard).

7.5 Post transplant monitoring

Patients are monitored according to transplant center policy to detect possible complications of procedure or GvHD occurrence. Once patients get out from the hospital, the follow-up will be done according to each center policy but at least once a week until months 3 and then in consultation on a regular basis lifelong adapted to each patient evolution.
All adverse events (AEs) grade ≥ 3 will be recorded . All AEs (except GvHD) shall be graded according to CTC-AE Toxicity Grading Scale.
GVHD occurrence and disease progression will be monitored.

7.6 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including emergency medications

The investigator should verified that patients have no contraindication of treatments use in the study.

- **Authorized treatments**

Anti-infectious treatments (antibiotics, antivirals, antifungals), transfusions, growth factors according to usual practice of each centres are authorized.

- **Treatments forbidden**

All vaccine with alive germ are contraindicated before transplantation. .

- **Treatments not recommended**

For cyclophosphamide
- Attenuated vaccine (except yellow fever who is forbidden during 6 months after treatment discontinuation)
- Phenytoin
- Pentostatin

For Fludarabine
- Pentostatin
- Dipyridamole or other inhibitor of adenoside captation

For Thiotepa
- Phenytoin, Fosphénytoïne

For Busulfan
- Phenytoin

-

For Thymoglobulin
- Attenuated vaccine

Patients receiving, Benzodiazepines, Carbamazepine, Corticosteroids, Chloral hydrate, Phenobarbital Rifampicin, traconazol, métronidazol, kétobemidone, déférasirox should be closely monitored for signs of toxicity
With the exception of the drugs listed above the other drugs in reference with their SPC and "associations to be considered" will be administered according to the usual practice of the centre and at the discretion of the investigator.

8 EFFICACY ASSESSMENT

8.1 Description of efficacy endpoint assessment parameters

8.1.1 Upfront related donor HSCT

An upfront related donor HSCT is defined by an HSCT effectively performed without pre-graft therapy aimed to decrease marrow blast percentage as soon as possible

8.1.2 Disease-free survival (DFS)

Disease-free survival (DFS) is defined as the time from HSCT until the occurrence of any of the following events that all define disease persistance, namely : transformation into acute myeloid leukemia, disease detectable after transplantation in blood or in marrow (morphological) (Bone marrow evaluation will be done preferably on day 60 or not later than D100), death from any cause within 24 months after transplantation.
Patients who are not in complete response (CR) according to IWG2023 will be considered as having detectable disease. CR will be defined according to IWG 2023, as reported below:[5]
- BM < 5% myeloblasts; dysplasia may persist
- Peripheral blood: Hb ≥ 10 g/dL, platelets ≥ 100 Giga/L, neutrophils ≥ 1 Giga/L, blasts 0%
- Full cytogenetic: clearance of baseline abnormalities (complete cytogenetic response)

8.1.3 Cumulative incidence of relapse

Relapse will be considered only in patients in remission at 2 months after transplantation and defined according to IWG2023[3]
- either by an absolute and relative increase in BM blasts by at least 5% and ≥ 50%, from prior assessments, or development of extramedullary disease
- or by the worsening of cytopenias: decrement in at least one blood count cell lineage by ≥ 50% from maximum response levels for platelets, or absolute neutrophil count or a reduction of Hb by 1.5 g/dL, combined with an absolute reduction in the same lineage as follows: hb<10 g/dL, platelets < 100 Giga/L, or absolute neutrophils < 1 Giga/L, or repeated (more than once and separated by ≥ 7 days) need for red blood cells or platelets tranfusions whichj are not related to acute intercurrent illness or treatment effect; in the absence of HI of at least one other blood lineage as defined above.

[5] *Zeidan AM, Platzbecker U, Bewersdorf JP, Stahl M, Adès L, Borate U, Bowen D, Buckstein R, Brunner A, Carraway HE, Daver N, Díez-Campelo M, de Witte T, DeZern AE, Efficace F, Garcia-Manero G, Garcia JS, Germing U, Giagounidis A, Griffiths EA, Hasserjian RP, Hellström-Lindberg E, Iastrebner M, Komrokji R, Kulasekararaj AG, Malcovati L, Miyazaki Y, Odenike O, Santini V, Sanz G, Scheinberg P, Stauder R, van de Loosdrecht AA, Wei AH, Sekeres MA, Fenaux P. Consensus proposal for revised International Working Group 2023 response criteria for higher-risk myelodysplastic syndromes. Blood. 2023 Apr 27;141(17):2047-2061. doi: 10.1182/blood.2022018604. PMID: 36724453..*

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8.1.4 Overall survival

Overall survival (OS) is defined as the time from graft until death from any cause within 24 months after transplantation.

8.1.5 Non-relapse mortality

Non-relapse mortality (NRM) is defined as the time from transplantation to death in patients who have no relapse nor progression (ie, lack of complete remission) after HSCT.

8.1.6 Chronic GvHD

Chronic GvHD is defined according to the NIH classification published in 2005 (Annexe 18.5). The diagnosis of chronic GvHD is made if there is a distinctive sign (1 alone is sufficient) or evocative signs associated with a supplementary examination in favor (biopsy, for example). The date of chronic GvHD is the date of first symptoms of GvHD required local or systemic therapy. We then define:

A- Classical chronic GvHD in patients with only evidence of chronic GvHD

B- The overlap syndrome when a patient presents both signs of acute GvHD and chronic GvHD

C- Late acute GvHD, which corresponds to exclusive signs of acute GvHD without signs of chronic GvHD occurring after J100.

The severity of chronic GvHD is defined by the number of affected organs.

Affected organ	**Mild**	**Moderate**					**Severe**		
Number of organ affected	1 or 2 without significant dysfunction	≥3	**or**	≥ 1	**or**	lung	≥ 1	Or	lung
Score of the achievement of each organ	1 (except lung)	1		2		1	3		≥2

8.1.7 Acute GvHD

Acute GvHD is defined according to MAGIC consortium 2016. Each organ is rated with the diagnosis in stage, which allows to define a grade. Similarly, the clinician is asked to rate the maximum grade of acute GvHD over the period and maximum grade date. The date of acute GvHD is the date of first occurrence of symptoms required a systemic therapy (annexe 18.5)

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy assessment parameters

The parameters for assessing efficacy were collected according to the schedule in table paragraph 5.7.

9 SPECIFIC STUDY COMMITTEES

9.1.1 Scientific Steering Committee

The scientific steering committee provides overall supervision for the research. It will take decisions about continuation or termination of the trial or substantial amendments to the protocol and will propose procedures to be followed during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.
Members: Dr. Marie Robin, Pr. Régis Peffault de Latour, Dr Marie Sébert, Pr Matthieu Resche-Rigon and for the DRCD: Project manager and Clinical Research Assistant, Pr Sylvie Chevret statistician.

9.1.2 Data Safety Monitoring Board (DSMB)

See paragraph 10.3.4

10 SAFETY ASSESSMENT - RISKS AND BURDENS ADDED BY THE STUDY

10.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

Adverse event occurring in a person enrolled in a study involving human participants, when this event is related to the study or to the product being studied.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the research participant, requires hospitalisation or prolongs hospitalisation, causes a serious or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction**

Any adverse reaction for which the nature, severity or progression are not consistent with information pertaining to the products, acts practiced and methods used during the study.

Pursuant to article R. 1123-46 of the Code de la Santé Publique and the opinion of the clinical trial sponsor not relating to a health product (ANSM):

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the study or the product under investigation, modifications to the use of the product, the conduct of the clinical trial, or the clinical trial documents, or to a suspension, interruption or modification of the clinical trial or of similar studies.

For example, this concerns:

- any clinically significant increase in the frequency of an expected serious adverse reaction;
- early termination or a temporary halt for safety reasons for a trial carried out in another country with the same product (act or method) as the one being studied in France;
- recommendations from the Data Monitoring Committee, if applicable, if they are relevant to the safety of the participants;

-

- suspected unexpected serious adverse reactions in participants who have terminated the trial and of which the sponsor has been notified by the investigator, in addition to any possible follow-up reports.

10.2 The role of the investigator

For each adverse event, the investigator must assess its severity and report all serious and non-serious adverse events in the case report form (e-CRF Cleanweb).

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events using CTA-AE Toxicity Grading Scale v5.0.

The investigator must **assess the causal relationship between** a serious and none seriouse adverse events and the procedures added by the study.

The method used by the investigator is based on binary method: related, not related.

10.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per Article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies informs the sponsor without delay on the day he become aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the *Code de la Santé Publique*, with the exception except any event which is listed in the protocol (see section 10.2.2) and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

10.2.2 Specific features of the protocol

Other events that require the investigator to notify the sponsor without delay

- Adverse events judged as being **"medically significant"** (i.e. considered as "serious")
  - All adverse event not listed as expected graft complication (refere to the RSI in the IB.
  - Non engraftment or acute rejection of the transplant
  - Secondary neoplasia (excepted basal cell carcinoma of the skin or "in situ" carcinoma of the cervix).

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- In utero exposure

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.
The events are reported using a special form, appended to the protocol.

10.2.3 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the eCRF. An eCRF extraction of all the SAE listed below will be sent to the DRCI Safety department every 6 month by the Clinical trial Unit. This extraction should mentioned : investigation number, inclusion date, sex, date of birth, reaction event as reported by the investigator, AE seriousness criteria, outcome of reaction, date of start/date of end, investigator assessment.

- *Normal and natural course of the condition*:

- Scheduled inpatient hospitalization for monitoring the condition under investigation [with no deterioration in the subject's medical condition compared to baseline]
- Inpatient hospitalization for routine treatment or monitoring the condition under investigation, not associated with a deterioration in the subject's medical condition
- Emergency inpatient hospitalization upon enrollment or prolongation of hospitalization upon enrollment for monitoring the condition under investigation
- Worsening of the condition under investigation before the start of the study procedure (including conditioning regimen) excluding those leading to death

- Other condition:

- In case of disturbance of biological values corresponding to an adverse event of grade 3 and no other symptoms (fever, etc.) associated with this adverse event, this event will not required the investigator to notify the sponsor as a serious adverse event but only in the case report form.
- Grade 3 or 4 hematological toxicity without clinical complication after conditioning regimen (expected in all patients)
- All expected post graft complication (including conditioning regimen and graft prophylaxis) listed in the Reference Safety Information in the IB (according to the grade reported in the IB).
- Special circumstances

  - Hospitalisation for a pre-existing illness or condition
  - Hospitalisation for a medical or surgical treatment scheduled prior to the study
  - Admission for social or administrative reasons
  - Emergency care (< 12 hours)

- Serious Adverse events during the trial possibly related to the graft procedure realized as part of the patient's standard care.

  The investigator as health care professional must notify these events to the appropriate health surveillance institution according to the situation. Examples: Agence Régionale

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de Santé, quality department of your hospital, Centre Régional de Pharmacovigilance, local correspondent of the materiovigilance unit (ANSM), etc.

10.2.4 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the date on wich the participant begins the procedure of transplant including conditioning regimen
- throughout the whole follow-up period required for the trial
- Indefinitely, if the SAE is likely to be due to the procedures of transplant including conditioning regimen and GVHD prophylaxis

10.2.4.1 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99, only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies using e-CRFs:

- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr

For cases of *in utero* exposure, the investigator will complete the "report and follow-up form for pregnancy during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.

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If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.

10.2.5 Role of the sponsor

The sponsor, represented by its Safety Department, continuously, throughout the trial, assesses participant safety throughout the study.

10.2.5.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** with the transplant procedure
  All serious adverse events which the investigator and/or the sponsor believe could have a causal relationship with the transplant procedures that could reasonably be considered as having suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction is considered to be unexpected when the nature, severity or progression are not consistent with information pertaining to the interventions/procedures/practiced acts and/or administered products over the course of the study.
  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the study procedures (conditioning regimen, HSCT graft, GVHD prophylaxis) : refer to the IB in force

refer to the appendix.

Serious adverse events likely to be related to the study procedures :
The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency):
• The sponsor must send the initial report immediately upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;
• All additional, relevant information must be declared by the sponsor in the form of monitoring reports within a period of 8 calendar days starting from when the sponsor had this information.

Any suspected unexpected serious adverse reaction related to a drug must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

10.2.5.2 Analysis and declaration of other safety data

Pursuant to article 1123-46 of the Code de la Santé Publique, a new development is defined by any new data that may lead to a reassessment of the study's risk-benefits ratio or studied product, to modifications in the use of this product, in the conduct of the study, or documents pertaining to the study, or to suspend or halt or modify the study protocol or similar studies.

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The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issues and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issues, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 7 days from learning of the information.

10.2.5.3 Annual safety report

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (ASR or annual safety report), which includes, in particular:
- a safety analysis for the research participants,
- a list of all the suspected serious adverse reactions that occurred in France in the concerned study during the period covered by the report,
- summary tables including all of the SAEs that have occurred since the start of the study.

The annual safety report must be sent no later than 60 days after the anniversary of the date on which the first participant was included in the study.

10.2.6 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) can be set up by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of a DSMB to the Competent Authority (ANSM) and to the Ethics committee.
A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first subject is enrolled. The DSMB's preliminary meeting should take place before the protocol submission to competent health authority (ANSM) and Ethics committee.

The members of the DSMB are: Dr Etienne Daguidau, etienne.daguindau@gmail.com
Dr Mitja Nabergoj, mitja.nabergoj@gmail.com
Dr Myriam Labopin, myriam.labopin@upmc.fr)

11 DATA MANAGEMENT

11.1 Right to access data and source documents

11.1.1 Data access

In accordance with GCPs:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority

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- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.1.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

11.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.2 Data processing and storage of research documents and data

11.2.1 Identification of the data processing manager and location(s)

Data Management and statistical analysis will be managed and carried out at the URC of GH Lariboisière Saint-Louis, Saint-Louis site, Pr Matthieu Resche-Rigon.

11.2.2 Data entry

e-CRF CLeanweb: Non-identifying data will be entered electronically via a web browser.

11.3 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Description of statistical methods

The estimation of the DFS will use the Kaplan Meier method, with point estimations and 95% Confidence Intervals (95%CI).
To increase the level of incidence, external comparisons wil lbe secondly performed to (i) demethylating agents using individual patient data from a prospective cohort (Robin 2015) or (ii) 5-Azacytidine, using aggregated data from a published randomized clinical trial (Kröger 2021). Such comparison to external data will use an unanchored matching-adjusted indirect

comparison (MAIC), unless survival curves with number of exposed patients over time are not available.
This will allow to adjust treatment comparison for baseline differences in samples in terms of prognostic and effect modifiers across the groups.

The Kaplan Meier method, with point estimations and 95% CI, will be applied to the analysis of DFS. Cumulative incidence of transplantation, of relapse and of non relapse mortality, and of GvHD will use competing risks methods, given deaths that possibly occur before the evnt of interest. Cumulative hazards of infection will be plotted, allowing to account for all infectious episodes observed in the patients.

All analyses will use the intention-to-treat (ITT) population, that is, all patients enrolled in the trial, whichever they received the scheduled intervention or not. No replacement will be allowed.

12.2 Calculation hypotheses for the number of participants required and the result

A, two-sided, one-sample, logrank test calculated from a sample of 55 subjects achieves 90.36% power at a 0.050 significance level to detect a proportion surviving of 0.5500 in the new group when the proportion surviving in the historic control group is 0.3500. Such an historical proportion has been estimated from our previous French cohort study, as published in Leukemia where a 2-year DFS rate of 35% was observed in patients with a donor who were not transplanted upfront[6]. By contrast, EBMT studies have reported that 2-year DFS in patients with MDS is expected to be 55%[7].
These surviving proportions are for a period of 24.0 months. Subjects are accrued for a period of 24.0 months. Follow-up continues for a period of 24.0 months after the last subject is added.

The probability that a subject experiences an event during the study is 0.5860. The expected number of events during the study is 24.

It is assumed that the survival time distributions of both groups are approximated reasonably well by the Weibull distribution with a shape parameter of 1.00.

Reference:
Wu, Jianrong. 2015. 'Sample size calculation for the one-sample log-rank test', Pharmaceutical Statistics,
Volume 14, pages 26-33

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[7] *Dietrich W. Beelen, Matthias Stelljes, Péter Reményi, Eva-Maria Wagner-Drouet, Peter Dreger, Wolfgang Bethge, Fabio Ciceri, Friedrich Stölzel, Christian Junghanß, Hélène Labussiere-Wallet, Kerstin Schaefer-Eckart, Goetz U. Grigoleit, Christof Scheid, Francesca Patriarca,| Alessandro Rambaldi, Dietger Niederwieser, Inken Hilgendorf, Domenico Russo, Gérard Socié, Ernst Holler, Bertram Glass, Jochen Casper, Gerald Wulf, Nadezda Basara, Maria Bieniaszewska, Gernot Stuhler, Mareike Verbeek, Ursula La Rocca, Jürgen Finke, Fabio Benedetti, Uwe Pichlmeier, Anja Klein, Joachim Baumgart, Miroslaw Markiewicz.T reosulfan compared with reduced-intensity busulfan improves allogeneic hematopoietic cell transplantation outcomes of older acute myeloid leukemia and myelodysplastic syndrome patients: Final analysis of a prospective randomized trial. Am J Hematol. 2022 Aug;97(8):1023-1034. doi: 10.1002/ajh.26620. Epub 2022 Jun 8.. PMID: 35617104*

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13 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

13.1.1 Strategy for centre opening

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan. Centers will be opened with a priority for the centers that will have an eligible patient or within 3 months of the start of the research.

13.1.2 Scope of centre monitoring

In the case of this D risk study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level high.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the products used.

13.3 Case report forms

Electronic CRF Cleanweb:

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

13.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research.. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

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The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

In accordance with Article L1122-1-1 of the *Code de la Santé Publique* (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period of **30 days** is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

14.2 Prohibition from participating in another clinical study or exclusion period set after the study, if applicable

No exclusion period of participation after the participant has finished this study is defined in the context of this research.

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies or in minimal risk and constraint study that does not involve therapeutic strategies, but this should be reported to the physician who follows it in the present research.

14.3 Authorisation for the research location

The study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialised and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorisation.

14.4 Legal obligations

14.4.1 Role of the sponsor

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique* (French Public Health Code). Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.4.2 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants not concerning a health product mentioned in Article L5311-1, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory provisions in force.

14.4.3 Request for authorisation from ANSM

Proit to starting the study, AP-HP, as sponsor, must obtain authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants not concerning a health product,, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

14.4.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.
Commitment to comply with "Reference Methodology" MR-001
This research is governed by the CNIL (French Data Protection Agency) "Reference Methodology for processing personal data used within the scope of health research" (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this "Reference Methodology"

14.4.5 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.4.6 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

14.4.7 Archiving

Specific documents for an interventional study involving human participants not concerning a health product will be archived by the investigator and the sponsor for 15 years after the end of the research.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the investigator and the sponsor, including (non-exhaustive list):
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the ANSM authorisations and CPP (Research Ethics Committee) decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- the data collection documents

15 FUNDING AND INSURANCE

15.1 Funding sources

This study is performed by funding a donation of fondation MSD Avenir.

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI - GLOBAL SE through BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

16 PUBLICATION RULES

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be “AP-HP”
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym “**AP-HP**” first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- “The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation)”

16.3 Mention of the financial backer in the acknowledgements of the text

- funding by donation of fondation MSD Avenir

This study has been registered on the website http://clinicaltrials.gov/ under number

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18 LIST OF ADDENDA

18.1 List of investigators

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18.2 Serious Adverse Events notification form (Separate document)

18.3 Pregnancy notification form (Separate document)

18.4 SCP must have been obtained from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php) or EMEA webite; otherwise, use the SCP from Vidal

18.5 GVHD classification

Rating of acute GVH :

Acute GvHD is defined according to MAGIC CONSORTIUM 2016 criteria (14). Each organ is rated with the diagnosis in stage, which allows to define a grade. Similarly, the clinician is asked to rate the maximum grade of acute GvHD over the period and maximum grade date. Histological documentation is recommended for GI GVHD.

1. Stage by organ

Stade	Peau	Foie (bilirubine)	Tube digestif haut	Tube digestif bas (quantification des selles/jour)
0	Absence d'érythème cutané actif	< 2 mg/dl	Absence ou présence de manière intermittente de nausée, vomissement ou anorexie	< 500 ml/jour ou<3 selles/jour
1	Erythème maculopapulaire <25% SC	2–3 mg/dl	Présence de manière persistante de nausée, vomissement ou anorexie	500–999 ml/jour ou 3–4 selles/jour
2	Erythème maculopapulaire 25 – 50% SC	3.1–6 mg/dl	-	1000–1500 ml/jour ou 5–7 selles/jour
3	Erythème maculopapulaire > 50% SC	6.1–15 mg/dl	-	>1500 ml/jour Ou >7 selles/jour
4	Erythème généralisé (>50% SC) avec décollement (bulles) et desquamation > 5% SC	>15 mg/dl	-	Douleur abdominale importante avec ou sans ileus ou hémorragie digestive indépendamment du volume de selles

SC= surface corporelle

2. Overall grade of acute GVH (according to the most severe organ stage affected):

- Grade 0: Pas de stade 1-4 dans aucun des organes
- Grade I: Stade 1–2 cutané sans atteinte hépatique, ni digestive haute et basse
- Grade II: Stade 3 cutané et/ou stade 1 hépatique et/ou stade 1 digestif haut ou bas
- Grade III: Stade 2–3 hépatique et/ou stade 2–3 digestif bas + stade 0-3 cutané et/ou stade 0-1 digestif haut
- Grade IV: Stade 4 cutané, hépatique ou digestif bas avec stade 0-1 digestif haut

Rating of chronic GVH

Chronic GvHD is defined according to the NIH classification. The diagnosis of chronic GVHD is retained if there is a distinctive sign (1 alone is sufficient) or evocative signs associated with a supplementary examination in favor (biopsy, for example). We then define:
A- Classical chronic GvHD in patients with only evidence of chronic GvHD
B- The overlap syndrome when a patient presents both signs of acute GvHD and chronic GvHD
C- Late acute GvHD which corresponds to exclusive signs of acute GvHD without signs of chronic GvHD occurring after J100.
The severity of chronic GvHD is defined by the number of affected organ.

Overall grade of chronic GVH

Affected organ	Mild	Moderate					Severe		
Number of organ affected	1 or 2 without significant dysfunction	≥3	or	≥ 1	or	lung	≥ 1	or	lung
Score of the achievement of each organ	1 (except lung)	1		2		1	3		≥2

Manifestation of chronic GVHD

Dans le cas de manifestations cliniques parallèles comme un épisode infectieux ou une réaction médicamenteuse, cette évaluation ne sera pas prise en compte.
Un Karnofsky < 60% avec une perte de poids > 15% et des infections récurrentes sont en général des signes de GVHD chronique extensive.
Les anomalies cliniques selon les organes touchés permettant d'évaluer la GVHD chronique sont les suivantes :
Peau Erythème, sécheresse, prurit, changement de pigmentation (vitiligo, hyperpigmentation) plaques papulosquameuses, nodules, exfoliation, rash maculo-papulaire ou urticaire, sclérodermie, morphée (une ou plusieurs lésions lisses indurées et circonscrites)
Ongles Onychodystrophie, onycholyse, striés, fendus.
Cheveux Canitie prématurée (cuir chevelu, cils, sourcils), alopécie, amincissement du cuir chevelu, raréfaction de la pilosité corporelle.
Bouche Sécheresse, brûlures, gingivite, mucite, atrophie gingivale, érythème, lichen, ulcères, atrophie labiale, changement de pigmentation, contracture de la bouche, caries dentaires.
Yeux Sécheresse, brûlures, photophobie, douleur, larmoiement, sensation de grain de sable
Organes génitale, lichen Sécheresse, sténose vaginale, dyspareunie, érythème vulvaire, atrophie génitaux
Foie Élévation du bilan hépatique sanguin sans autre cause connue. En l'absence d'une autre atteinte organique, une biopsie est nécessaire pour confirmer le diagnostic.

Poumons	Bronchiolite oblitérante, toux, sifflements, dyspnée d'effort, bronchites chroniques ou sinusites.
Tube digestif	Anorexie, nausées, vomissements, perte de poids, diarrhées, dysphagie, malabsorption.
Fasciite	Ankylose et réduction des mouvements, avec occasionnellement gonflement, douleurs, crampes, érythème et induration, atteignant le plus fréquemment les avant- bras les poignets et les mains, les chevilles, les jambes et les pieds, incapacité d'étendre les poignets sans fléchir les doigts ou les coudes, contractures.
Muscles	Faiblesse proximale, crampes.
Squelette	Arthralgies proximales des articulations des os du bassin, et parfois d'articulation moins importantes
Séreuses	Douleurs pulmonaires ou cardiaques secondaires à une pleurésie ou une péricardite.

Chronic GVHD gradation

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS† FEV1 ☐ DLCO ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

18.6 Adaptation dose for conditioning regimen :

In patients with BMI > 25, table 1 and 2 should be used to adapted chemotherapy.
For fludarabine, maximal dose will be caped at 2 m^2 maximal in patient with body surface greater than 2

Table 1 ; Calculation of Ideal Body Weight (IBW) and adapted body weight (ABW)

Weight	Formula
IBW male	50 + 0,91 x (height in cm - 152)
IBW female	45 + 0,91 x (height in cm - 152)
ABW_{25}	IBW + 0,25 x (Body Weight – IBW)
ABW_{40}	IBW + 0,40 x (Body Weight – IBW)

Table 2. Adjustment according to chemotherapy

Chemotherapy	Dose
Busulfan	**ABW_{25}.**
Thiotepa	**ABW_{40}**
Endoxan ≤ 120mg/kg	**ABW_{25}**

18.7 Volume of blood sample according to personn's weight

Body weight (kg)	**Circulating total blood volume (ml)**	**Maximum allowable sample volume over 4 weeks (ml) - 3% of total blood volume**	**Maximum allowable sample volume at single time (ml) - 1% of total blood volume**
0.5 - 1.5	50 - 150	1.5 -4.5	0.5 – 1.5
2.5 - 5	250 - 500	7.5 – 15	2.5 – 5
5 - 12	480 - 960	14.4 – 28.8	4.8 - 9.6
12 - 20	960 - 1600	28.8 – 48	9.6 -16
20 - 30	1600 - 2400	48 – 72	16 – 24
30 - ≥ 70	2400 - ≥ 5600	48 – 168	24 – 56