Protocol FLUCLORIC

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" Randomized multicentric Phase III study comparing the efficacy of two reduced intensity conditioning regimens (clofarabine/busulfan versus fludarabine/busulfan) in adults with acute myeloid leukemia and eligible to allogeneic stem cell transplantation: a SFGM-TC study. FLUCLORIC Study**"**

"Etude prospective de phase III randomisée multicentrique comparant 2 types de conditionnement d'intensité réduite (clofarabine/busulfan versus fludarabine/busulfan) chez des patients adultes éligibles à une allogreffe de cellules souches hématopoïétiques et porteurs d'une leucémie aigue myéloblastique : une étude SFGM-TC. Etude FLUCLORIC"

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SIGNATURE PAGE

SPONSOR SIGNATURE

The sponsor agrees to comply with the laws and regulations on clinical trials for the conduct of the above-mentioned study and agrees to abide by all provisions set forth therein.

Name and capacity of the signatory representative:	Date:	Signature:
For the Sponsor and by delegation of the Managing Director, the Director of Medical Affairs and Research	19/04/2023	La Responsable du Département Promotion Hélène AUBLE p/o

INVESTIGATOR'S SIGNATURE

I have read all the pages of the clinical trial protocol sponsored by Nantes University Hospital. I confirm that this protocol contains all the information necessary for the conduct of the trial. I agree to conduct the trial according to the protocol and to abide by all provisions set forth therein. I agree to conduct the trial in compliance with:

- the principles of the "Declaration of Helsinki",
- international (ICH) and French good clinical practice regulations and guidelines (Règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain (Décision du 24 novembre 2006))
- national laws and regulations relating to clinical trials,
- the current European Clinical Trials Directive

I also agree for the investigators and other qualified members of my staff to have access to the copies of this protocol and documents concerning the conduct of the study so that they abide by all provisions set forth therein.

	Name:	Date:	Signature:
Coordinating investigator	**Pr Patrice CHEVALLIER** Department of hematology CHU Hotel-Dieu, Place A. Ricordeau, 44093 Nantes Cedex	19/4/2023	
Principal investigator	**Name and institution:**	**Date:**	**Signature:**

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse events
allo-SCT	Allogeneic stem cell transplantation
AML	Acute Myeloid Leukemia
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
AR	Adverse reaction
ASR	Annual Safety Report
ATG	Anti-thymoglobuline
BMT	Bone marrow transplant
DSMC	Data and Safety Monitoring Committee
CEA	Cost-effectiveness analysis
CloB2A2 RIC	Conditionnement par Clorafabine/Busulfan/ATG
CNAMTS	Caisse Nationale d'Assurance Maladie des Travailleurs Salariés
CNIL	Commission Nationale de l'Informatique et des Libertés
CR	Complete remission
CRA	Clinical Research Associate (monitor)
eCRF	Electronic Case Report Form
CTFG	Clinical Trials Facilitation Group
CUA	Cost-utility analysis
DFS	Disease-free survival
DLCO	Diffucion capacity of carbon monoxide
DSMB	Data and Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ERB	Ethical Review Board
EvI	Adverse Event Intensity
FACT-BMT	Functional Assessment of Cancer Therapy - Bone Marrow Transplant
FB2A2 RIC	Conditionnement par Fludarabine/Busulfan/ATG
FLT3	Fms-like tyrosine kinase 3
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GRFS	GVHD free relapse free survival
GVHD	Acute and chronic graft-versus host-disease
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
ICER	incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
IMP	Investigational Medicinal Product
QALY	Quality Adjusted Life Year

QoL	Quality of Life
LFS	Leukemia-free survival
LH	Luteinizing hormone
MA	Marketing Authorisation
MDS	Myelodysplastic Syndrome
MMF	Mycophenolate mofetyl
MRD	Minimal residual disease
NHI	National Health Insurance
NRM	Non relapse mortality
NSAE	Non serious adverse event
OS	Overall survival
PBSC	Peripheral blood stem cells
PNN	Polynuclear neutrophils
QoL	Quality of Life
RIC	Reduced-intensity conditioning
RM	Reference Methodology
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SFGM-TC	Société Francophone de Greffe de Moelle et de Thérapie Cellulaire
SIP	Situation of special interest
SIRS	Systemic Inflammatory Response Syndrome
SMD	Syndrome myelodysplasique
SNDS	Système National des Données de Santé (SNDS)
SPmC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
USAR	Unexpected Serious Adverse Reaction

CONTENTS

INTRODUCTION

Relapse remains the main cause of death in patients with AML, especially after allo-SCT. Using drugs with higher anti-leukemic activity as part of the conditioning regimen is one of the strategies to decrease relapse incidence in this population. Retrospective studies have shown that clofarabine can achieve impressive results compared to the use of fludarabine in this setting. Confirming such results in a prospective manner would definitely establish the CloB2A2 RIC regimen as a superior RIC regimen compared to the FB2A2 for AML patients with a matched donor and in complete remission at transplant. For this purpose, we will conduct a prospective multicentric Phase 3 randomized study comparing 154 patients who will receive a CloB2A2 RIC regimen (experimental group) vs 154 who will receive a FB2A2 RIC regimen (standard group). Based on retrospective results, we wish to demonstrate a gain of 15% at 2 years in terms of overall survival in CloB2A2 cases.

The study will be promoted by Nantes University Hospital and conducted on behalf of the SFGM-TC. Clofarabine will be furnished by the protocol. We will also provide quality of life and economic analyses. The study will last 60 months, including 23 French centers.

1. JUSTIFICATION OF THE STUDY

1.1. POSITIONING OF THE STUDY

Recent advances in allogeneic stem cell transplantation (allo-SCT) have included the use of reduced-intensity conditioning regimens (RIC) to decrease the toxicity of myeloablative allo-SCT, allowing to perform allo-SCT in older patients and those with comorbidities.
FB2A2 is one of the standard of care RIC regimen in Europe, especially in France, for patients with matched related or unrelated donors. It combines fludarabine 30 mg/kg/day 5 days (d), busulfan 3.2 mg/kg/d iv 2 d, and rabbit anti-thymoglobuline (ATG) 2.5 mg/kg/d 2 d, while peripheral blood stem cells (PBSC) are used as source of graft. Large series have shown OS comprised between 37% and 76% and leukemia-free survival (LFS) between 37% and 68% at 2-3 years post-transplant.[1,2,3]

Clofarabine is a second generation purine analogue which has been already approved by authorities for the treatment of relapsed acute lymphoblastic leukemia. The toxicity profile of this drug is thus well known. Also, because of a higher anti-leukemic myeloid activity compared to fludarabine, clofarabine has been used as part of RIC regimen in order to improve outcomes of patients with myeloid malignancies. Thus, the CloB2A2 RIC regimen (clofarabine 30 mg/kg/d 5d, busulfan 3.2 mg/kg/day iv 2d, ATG 2.5 mg/kg/day 2d) has been validated in a prospective phase II study with encouraging results.[4]

Our group has shown in a retrospective study that clofarabine can achieve impressive results compared to the use of fludarabine in this setting, especially for AML patients in complete remission (CR) at transplant [5]. Thus, 2-year overall survival (OS) was 38%(14.5-61.6) using FB2A2 vs 79.2% (62.9-95.4) using CloB2A2, p=0.01 and 2-year leukemia-free survival (LFS) was: 38% (16-59.9) using FB2A2 vs 70.8% (52.6-89) using CloB2A2, p=0.03. The better survivals were due to the lower risk of relapse in the CloB2A2 AML sub-group (2-year relapse incidence (RI): FB2A2 41.2% (19-62.4) vs CloB2A2 16.7% (5-34.2), p=0.05). These results were confirmed later in a larger cohort of AML patients [6]. The benefit of clofarabine as part of the conditioning regimen in MDS remains more debated. There is no prospective data available currently confirming these results.

Therefore, the main objective of this prospective randomized trial will be to compare 2-year OS between AML patients in complete remission (CR) receiving either a CloB2A2 or a FB2A2 RIC regimen for allo-SCT in order to demonstrate the superiority of the CloB2A2 regimen. 2-year follow-up seems necessary as relapses can still occur after the first year post-transplant.

1.2. BENEFITS AND RISKS FOR SUBJECTS TAKING PART IN THE STUDY

1.2.1. Benefits

1.2.1.1. Individual benefit

We want to demonstrate that the CloB2A2 conditioning regimen will be associated with significant lower relapse and better overall survival. Thus, patients in this sub-group might expect an individual benefit, which remains however to demonstrate.

1.2.1.2. Collective benefit

By reducing the rate of relapse in the CloB2A2 sub-group, one can hypothesize collective economic benefit by reducing the number of hospitalizations/transfusions/treatments for patients.

1.2.2. Risks

1.2.2.1. Individual risk

- Physical risks and constraints

For both groups: The physical risks and constraints are represented by extra medical appointments and travels to the hospital but with no differences expected between the two groups of treatment. There will be also temporary extra blood and medullar and questionnaires to be completed.

- Disease-related risks

For both groups: This could be aplasia, infections, hemorrhage, metabolic disorders, compressive tumour, relapse and deaths.

- Test treatment risks including comparator if applicable (adverse reactions)

With Clofarabine, the reactions described as very frequent include: nausea, vomiting, febrile neutropénia, headache, diarrhea, pruritus, fever, palmoplantar erythrodysesthesia, fatigue, anxiety, mucosa inflammation and hot flashs.

Other possible reactions, and described as frequent, include: septis, anemia, thrombocytopenia and bruises, lymphopenia, increase of AST/ALT, total bilirubin, erythema, alopecia, renal dysfunction, hematuria, fatigue, weightloss, anorexia, bronchospasm, chest pain, dyspnea, cough, pneumonia, respiratory distress syndrome, myalgia, arthralgia, abdominal pain, cervical and back pain, tachycardia, hypotension, capillary leak syndrome, confusion, insomnia, depression, dizziness, headaches, paraesthesia, somnolence, hypoacousia, etc.

The same is expected with Fludarabine.

List of expected ADR of Clofarabine and Fludarabine are described in respective SmPC.

- Associated treatment-related risks

For both groups: This are the consequences of the transplant procedure: hospitalization in the sterile unit 4 to 6 weeks, risks related to clinical and biological exams, infections, acute and chronic GVHD, immunosuppressive drugs toxicities, catheter need with risks of pains and infections.

- Psychological risks and constraints

For both groups: These are the consequences of the transplant procedure and the disease. These can be stress, depression, or other mental disorders.

- Socio-economic risks

Not Applicable

1.2.2.2. Collective risk

Not Applicable

1.2.3. Benefit / risk balance

The patients receiving an allogeneic stem cell transplantation for acute myeloid leukemia (AML) in complete remission (CR) remain at risk of relapse after this procedure. One of the strategy to improve outcome of these patients is to strenghten the conditioning regimen by using drugs with higher anti-leukemic activity. Here we propose to compare two conditioning regimens: FB2A2 with fludarabine, which is one of the standard of care for matched allotransplant in adults with AML in CR at transplant; and CloB2A2, where fludarabine is replaced by clofarabine. Indeed, prospective and retrospective data showed a potential advantage of clofarabine over fludarabine in terms of decreasing relapse after allotransplant. Patients in the FB2A2 group will then receive the standard of care conditioning regimen while patients in the CloB2A2 have the potential to obtain a better control of the disease, which remains to be demonstrated. At least, it is expected that CloB2A2 will provide the same outcomes than FB2A2 (and not poorer outcome), then the patients in the experimental group do not have a disadvantage compared to the control group. Also the toxicity profile of the two drugs is quite similar, meaning that no higher toxicity is expected in the experimental group.

1.3. DESCRIPTION AND JUSTIFICATION OF THE TREATMENT PLAN

The FB2A2 (fludarabine 5 days/Busulfan 2 days /ATG 2 days) reduced-intensity conditioning regimen is a standard of care for AML patients in CR who receive an allotransplant. The CloB2A2 regimen is quite similar as the only difference is that only one drug is replaced (clofarabine instead of fludarabine) and at the same dose and for the same number of days of administration.

Both conditionings are used routinely nowadays in France but no prospective comparison are available. Also, this comparison will inform us specifically on the effects of clofarabine vs fludarabine in this particular situation.

The bibliographical references are appended to the document.

2. OBJECTIVES AND ENDPOINTS

2.1. PRIMARY OBJECTIVE AND ENDPOINT

2.1.1. Primary objective

To compare 2-year OS between patients with AML in complete remission receiving either a CloB2A2 or a FB2A2 RIC regimen for allo-SCT.

2.1.2. Primary endpoint

OS is defined as the time from day 1 of conditioning to death or last follow-up for survivors.

2.2. SECONDARY OBJECTIVES AND ENDPOINTS

2.2.1. Secondary objective(s)

To compare between AML patients in complete remission receiving either a CloB2A2 or a FB2A2 RIC regimen for allo-SCT:
-Engraftment, primary and secondary graft failure
-Neutrophils and platelet recoveries
-2-year DFS
-2-year relapse incidence,
-2-year NRM,
-Incidence of acute and chronic graft versus host disease (GVHD),
-Incidence of GVHD free relapse free survival (GRFS).
-Chimerism
-Immune reconstitution
-Minimal residual disease (MRD)
-Veno-occlusive disease
- Outcomes according to FB2 vs CloB2, to ELN classification: good, intermediate, high-risk sub-groups; to molecular markers: FLT3-ITD+ vs -, NPM1+ vs –, and to minimal residual disease by flow cytometry: + vs – before transplant
-Comparison of infections after FB2A2 vs CloB2A2: bacterial, viral, parasitic and fungal
-Quality of Life (QoL) in both treatment arms
-Graft hospitalization: Comparison between both groups in terms of length of stay, use of antibiotics and blood products
- General Health State in both treatment arms
- Safety assessment
- Health Economic study: Evaluation of economic efficiency of a CloB2A2 compared to a FB2A2 RIC regimen for allo-SCT in patients with AML, from a collective perspective (considering costs to the National Health Insurance (NHI) system, hospital and patients) and with a 24-month time horizon. Two analyses will be performed: a cost-utility analysis (CUA) and a cost-effectiveness analysis (CEA). The effectiveness of the two compared strategies will

be assessed in terms of potential changes in survival weighted by quality of life (CUA) and in terms of survival (CEA), respectively
-Comparison of outcomes between patients in first vs second line therapy and impact of clofarabine vs fludarabine in each sub-group.
-Comparison of outcomes between patients receiving a first vs a second allograft and impact of clofarabine vs fludarabine in each sub-group.

2.2.2. Secondary endpoint(s)

-Engraftment: PNN >500/mm3 + donor chimerism >=5% (day +30/42)
-Primary and secondary graft failure: donor chimerism <5% at day +30/42 post-transplant (primary) or at distance of transplant after achieving engraftment (secondary)
-Neutrophils recovery: the first of three consecutive days with neutrophils ≥500/mm3 after aplasia from day 0 of the graft
-Platelets recovery: the first of three consecutive days with platelets ≥20000/mm3 without transfusion after aplasia from day 0 of the graft
-DFS: time from day 1 of the conditioning to time without death or evidence of relapse or disease progression censored at the date of last follow-up.
-Relapse: any event related to progression or re-occurrence of the disease from day 1 of the conditioning
-NRM: death from any cause without previous relapse or progression from day 1 of the conditioning .
-Acute GVHD: NIH criteria
-Chronic GVHD: NIH criteria
-GRFS: alive with no previous grade III-IV acute GvHD, no moderate or severe chronic GvHD and no relapse from day 1 of the conditioning
-Chimerism: peripheral blood and CD3 T cells by molecular markers at days +30, +60, +90/100
-Immune reconstitution: Immunophenotype of PB lymphocytes and EPP: CD4, CD8, B, NK, EPP at 3, 6, 9 and 12 months
-Minimal residual disease (MRD): before transplant, at day +30 and dayd+90/100 by flow cytometry, molecular biology and NGS (if available) (ELN 2022 recommendation, Dohner et al Blood 2022)
- Comparison of occurrence of veno-occlusive disease (Mohty et al, BMT 2016) between day 0 and day+90/100
- Comparison of infections after FB2A2 vs CloB2A2: bacterial, viral, parasitic and fungal between day 0 and day+90/100
-Quality of life: EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30) and FACT-BMT (Functional Assessment of Cancer Therapy - Bone Marrow Transplant). at D-7, D30, D90, D180 and D360
-Graft hospitalization: Comparison between both groups in terms of length of stay (in days), use of antibiotics (type and length in days) and blood products (numbers)
- General Health State with Euroqol EQ-5D-5L questionnaire at D-7, D30, D90, D180, D360 and D720.
-Safety assessment: the safety assessment shall be done by collecting all adverse events that occur during the research. All adverse event (except GvHD) shall be graded according to CTC-AE Toxicity Grading Scale (version 5).
-Health Economic study: Incremental cost-utility ratio (ICUR, cost per quality-adjusted life year [QALY] gained) and incremental cost-effectiveness ratio (ICER, cost per life year gained), from a collective perspective and with a 24-month time horizon
-Comparison of outcomes betwwen patients in first vs second line therapy and impact of clofarabine vs fludaribine in each sub-group: OS, DFS, RI, NRM
-Comparison of outcomes between patients receiving a first vs a second allograft and impact of clofarabine vs fludarabine in each sub-group: OS, DFS, RI, NRM

2.3. OBJECTIVE AND ENDPOINTS FOR ANCILLARY STUDIES

A biological monocentric study (patients included at the CHU of Nantes only) should be conducted (when a financial support has been found) to better understand the superiority of clofarabine vs fludarabine in terms of relapse decrease after allotransplant in AML. To address this issue we will perform a biological study as part of an ancillary study using leukemics blasts from patients participating to the study (30 in the CloB2A2 arm and 30 in the FB2A2 arm) and frozen at diagnosis (routine) or at relapse (routine) in the Hematology Department of Nantes University Hospital. A second analysis will be performed in the same patients regarding the particular immune sub-population reconstitution post allograft (at inclusion, months 3, 6 and 12).
This ancillary study will be conducted by Dr Beatrice Clemenceau (Equipe 1 INSERM UMR1232, CRCINA IRS-UN, University of Nantes, University Hospital)

3. STUDY DESIGN

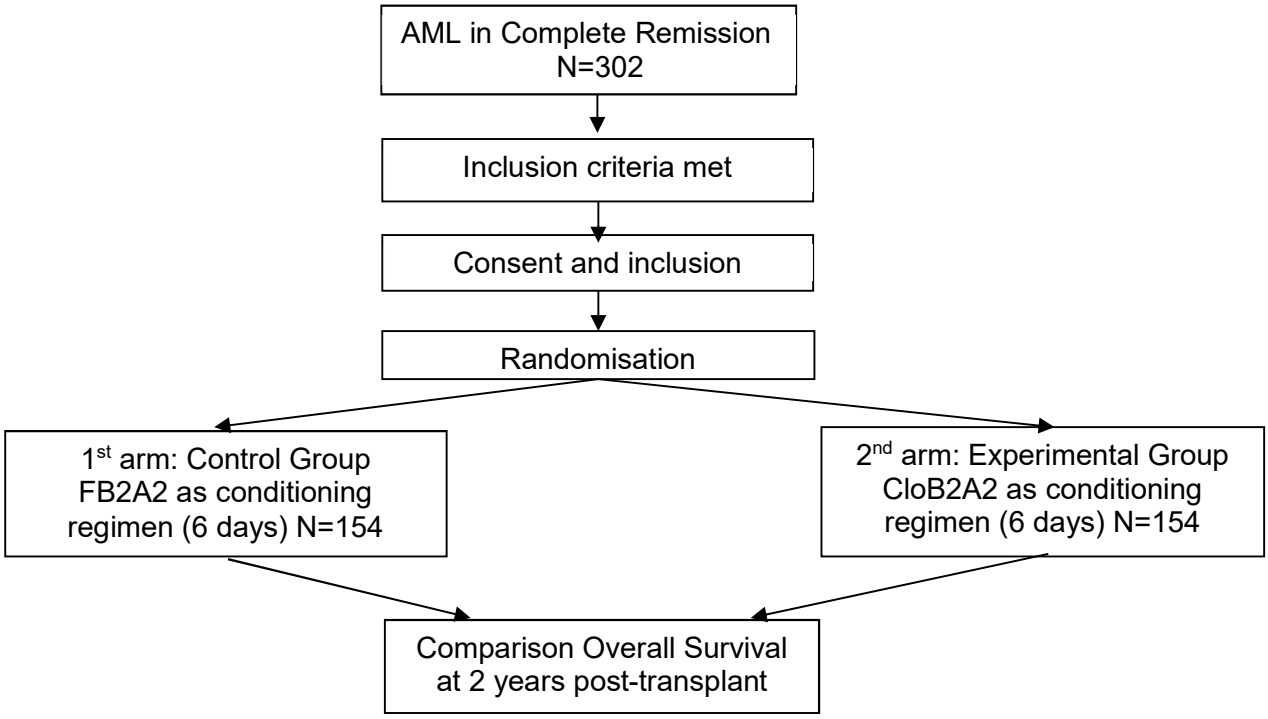
3.1. GENERAL STUDY METHODOLOGY

The study presents the following characteristics:

- **Type of study**: Phase III
- **Multi-centre** (national study),
- **Controlled** (2 groups)
- **Randomised** (stratified)
- **Open label**,
- **Prospective**

3.2. STUDY DIAGRAM

Period of Inclusion: 3 years
Period of follow-up: 2 years
Duration of the study: 5 years



4. STUDY POPULATION

4.1. DESCRIPTION OF THE POPULATION

The total of patients to be included is 302 including 151 patients in both group. Only adult patients with an AML in complete remission are eligible to the protocol.

4.2. PRE-INCLUSION CRITERIA

Not Applicable

4.3. INCLUSION CRITERIA

- Age ≥ 18 years' old
- De novo or secondary AML (according to ELN 2022 classification) in complete cytological remission at time of transplant (bone marrow blast count < 5%) or MDS with bone marrow blast count ≤ 10% and intermediate-2 or high-risk IPSS score
- Patients in first or second line therapy are allowed
- Patient eligible to a RIC regimen: patients aged ≥ 60 year old or <60 year old with co-morbidity(ies).
- Patient with a related or an unrelated matched donor
- Graft using only peripheral blood stem cells
- Performance status ECOG 0 - 2
- Who provide their written informed consent
- Previous allograft allowed
- Affiliated with French social security system or beneficiary from such system
- Women must meet one of the following criteria at the time of inclusion:

- use adequate contraceptive measures as recommended by the CTFG (Recommendations related to contraception and pregnancy testing in clinical trials v1.1; includes injectable implants, dual hormone birth control pills, intrauterine devices, abstinence from sex, or a sterilized partner), and have a negative pregnancy test (urine or serum pregnancy test) prior to receiving the first dose of study drug;
- or be post-menopausal (over 50 years of age with amenorrhea for at least 12 months after discontinuation of all exogenous hormonal therapy)
- or (if under 50 years of age) have been amenorrheic for at least 12 months after discontinuation of exogenous hormonal therapy and with luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels corresponding to post-menopausal levels
- or have undergone irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy (this operation must be documented).
- Contraception methods must be prescribed using effective contraceptive methods during treatment and within 6 months for women of childbearing age (WOCB) and 6 months for men in case they have sexual relations with WOCB after the last dose of Fludarabine/Clofarabine.

4.4. NON-INCLUSION CRITERIA

- Pro-myelocytic leukemia
- Patient eligible to a myeloablative conditioning regimen
- Patient with haploidentical, mismatched unrelated donor or umbilical cord blood
- Pregnant or breastfeeding woman or patient refusing contraceptive mesures
- HIV positive
- Active Hepatitis B or C
- Left ventricular ejection fraction < 50%.
- DLCO <40%
- Uncontrolled infection
- Uncontrolled haemolytic anaemia
- Creatinine clearance < 50 ml/min (evaluated by MDRD or CKDEPI).
- Serum bilirubine < 30 mmol/l, Cytolysis >5 the upper limit range
- Previous or concurrent second malignancy except for adequately treated basal cell carcinoma of the skin, curatively treated in situ carcinoma of the cervix, curatively treated solid cancer, with no evidence of disease for at least 2 years
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Participation to another interventional study during the last month or expected participation to another interventional study during participation to the FLUCLORIC study.

5. STUDY TREATMENTS

The investigational product for this study is clofarabine, a second-generation purine analogue already approved by French authorities for acute lymphoblastic leukemia. Clofarabine will be taken from the stock of each pharmacy site and reimbursed by the sponsor. Clofarabine will be compared to fludarabine (a first-generation purine analogue) as part of the conditioning regimen for allotransplant.

5.1. DESCRIPTION AND MODE OF ADMINISTRATION

5.1.1. IMP: Clofarabine

5.1.1.1. Treatment authorised

CLOFARABINE 1MG/ML sol diluer p perf (FL 20 ML)
Dose: 30 mg/m²/day days-6 to -2

5.1.1.2. Administration

IV by central venous catheter in 30 minutes

5.1.1.3. Dose adjustment

None

5.1.1.4. Reference documents

The reference document for the study is the SPmC in his current version (Annexe 9).

5.1.2. Study comparator: Fludarabine

The comparator product for this study is Fludarabine, used as reference treatment. Since Fludarabine is used in routine practice, it will be supplied by each site from commercial sources.

5.1.2.1. Treatment authorised

FLUDARABINE 25MG/ML sol dilute p perf (FL 2 ML
Dose: 30 mg/m²/day days-6 to -2

5.1.2.2. Administration

IV by central venous catheter in 30 minutes

5.1.2.3. Dose adjustment

None

5.1.2.4. Reference documents

The reference document for the study is the SPmC in his current version (Annexe 10).

5.1.3. Other treatments

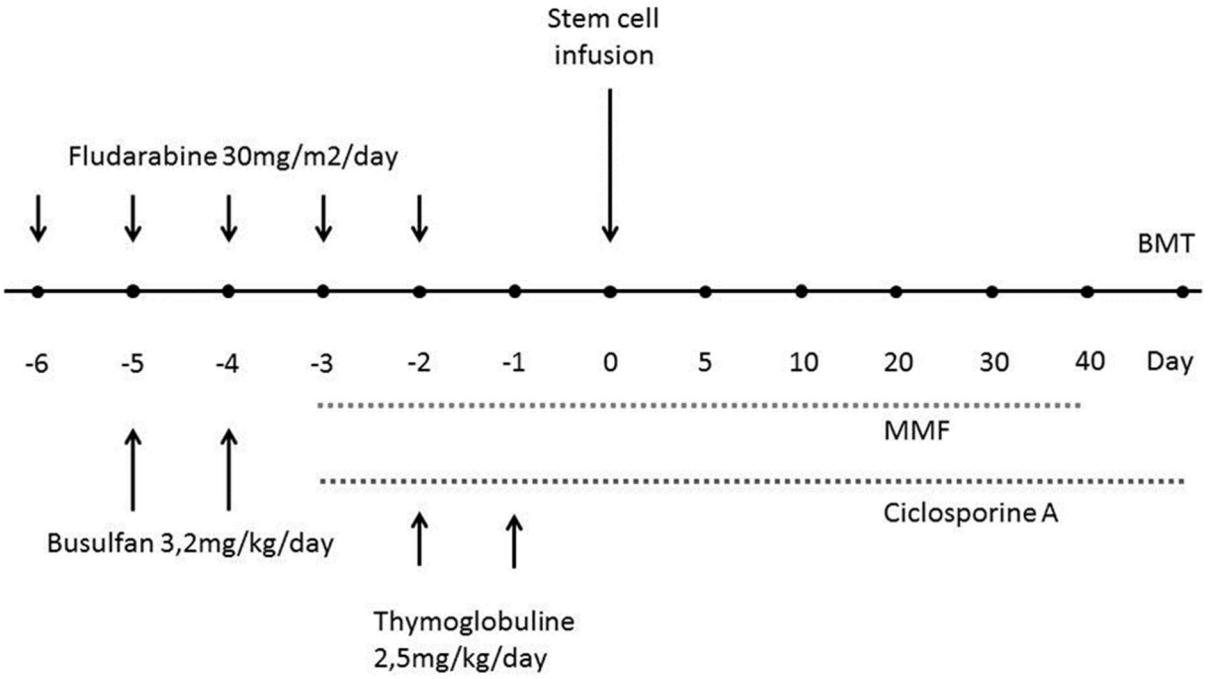
5.1.3.1. Auxiliary treatment

Prophylaxis may be used in preventing signs or symptoms of Systemic Inflammatory Response Syndrome (SIRS) or capillary leak inducted by Clofarabine:

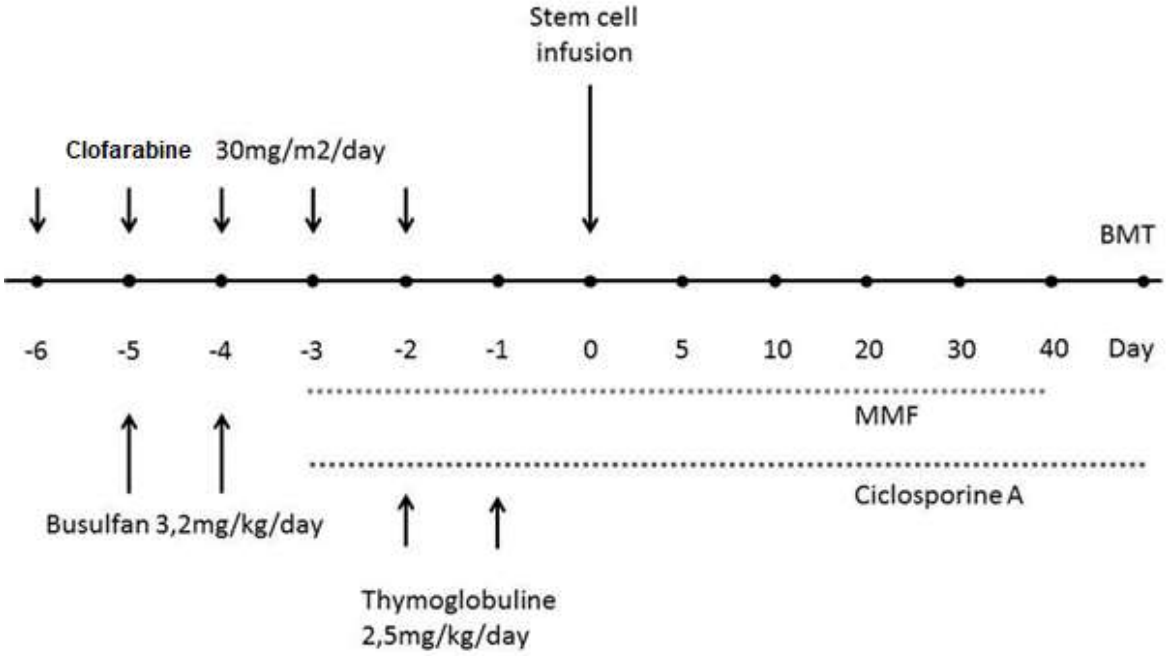
Corticosteroids, 0.5mg/Kg x 2/day days-6 to -2.
Administration: oral twice a day
Dose adjustment: none
Corticosteroids will be taken from the stock of each site pharmacy and reimbursed to the sites by the sponsor.

5.1.3.2. Associated treatments

Two reduced conditioning regimens will be performed in patients and are represented below:
Control group: FB2A2



Experimental Group: CloB2A2



The graft is performed the next day after the end of the conditioning regimen at day 0 by definition. Peripheral blood stem cells will be used as source of graft with at least >=4 106 CD34+ stem cells/kg of recipient body weight. Only HLA matched related or unrelated are allowed in this study.

As GVHD prophylaxis, we recommend to use ciclosporine A alone in case of sibling donor and in combination with mycophenolate mofetyl (MMF) in case of matched unrelated donor.

Supportive care will be at the discretion of each center. Also, donor lymphocyte infusion is allowed after transplant according to each center procedure.

5.1.3.3. Administration and dose adjustment

Each site will be responsible for providing the drugs below and ancillary supplies needed for chemotherapy administration.

Busulfan (Busilvex®)
Treatment: 3,2 mg/Kg/day day -5 and -4
Administration: IV by central venous catheter in 3 hours once daily or in 2 hours fourth a day
Dose adjustment: none

Anti-lymphocyte globulin ATG (Thymoglobuline®)
Treatment: 2,5mg/Kg/day day -2 and -1
Administration: IV
Dose adjustment: none

Ciclosporine (Neoral®)
Treatment: 3 mg/kg/day from day-3 until day+90/100 post-transplant with tapering from day+45
Administration: IV then PO
Dose adjustment: according to blood concentration (target dose: 200 to 300 ng/mL)

Mycophenolate mofetyl (Cell-Cept®)
Treatment: 1 g/12 hours from day-3 until day +40/45 post-transplant with tapering from day +30
Administration: IV or PO
Dose adjustment: none

5.2. AUTHORISED AND UNAUTHORISED TREATMENTS

5.2.1. Authorised treatments

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except those listed at 5.2.2
Also maintenance treatment in order to prevent relapse (5' azacytidine, DLI, anti-FLT3 or other targeted therapy) after transplant is authorized at the discretion of the investigator. However, the decision to perform such post-transplant strategy must be specified at the time of inclusion.

5.2.2. Unauthorised treatments

The following treatments are not permitted:
-Any anti-tumor therapy other than the protocol specified therapy (ie conditioning regimen, graft and GVHD prophylaxis)
-P-GP substrate treatments and Hyperircum perforatum (St. John's wort) when cyclosporine is administered
-Investigators have to be careful about prescribing CYP3A4 inducers and inhibitors as there are interactions with cyclosporine (see VIDAL)
-Any other investigational agent

5.2.3. Emergency treatments (if applicable)

In case of anaphylactic reaction, adrenaline, antihistaminic, paracetamol/acetaminophen or corticosteroid should be immediately available.

5.3. TREATMENT COMPLIANCE FOLLOW-UP

Not applicable as conditioning regimen will be administered by nurses or doctors only at the hospital.

5.4. EXPERIMENTAL DRUG CIRCUIT

5.4.1. General circuit

Vials of clofarabine will be taken from commercial sources of each pharmacy site and reimbursed to the sites by the sponsor. Labels for secondary packaging will be provided by the sponsor to the pharmacy of the associed sites to identify clofarabine vials as an experimental drug used for the protocol.

5.4.2. Experimental drug storage conditions

5.4.2.1. Description of dispensary storage

No particular condition of storage

5.4.2.2. Description of storage at patient's home

Not applicable

6. CONDUCT OF THE STUDY

6.1. TESTS AND ANALYSIS

6.1.1. Detailed description of the parameters for evaluating efficacy

See primary and secondary objectives and endpoints.

6.1.2. Description of tests and analysis

All screening and on-study laboratory samples and tests will be collected and processed at the investigators local laboratory or specific department and analyzed locally.

Local laboratory assessments:
Chemistry: Sodium, Potassium, chloride, total protein, albumin, calcium, magnesium, phosphorus, glucose, urea, creatinine, phosphatase, AST (SGOT), ALT (SGPT), bilirubin (total and indirect) GGT, LDH
Hematology: hemoglobin, hematocrit, platelets, white blood counts and differential, TP, TCA, fibrinogen
Others: serology for Hepatitis B or C, HIV, urine or serum pregnancy tests, ferritinemia, cholesterolemia, triglyceridemia, uricemia, TSH, COVID PCR and serology
Immunophenotype of peripheral blood lymphocytes (CD4, CD8, B, NK) and EPP

Other assessments:
Bone marrow aspirate/biopsy if indicated with histochemical, immunophenotypic, cytogenetic analysis.
Chimerism

Left ventricular ejection fraction, lung function test (DLCO)
All exams when clinically indicated: CTscan of thorax, abdomen and pelvis, 18F-FDG PETscan, lumbar puncture, ect.

6.2. STUDY SCHEDULE

6.2.1. Pre-Inclusion/Inclusion visits (day-30/day-7 from the graft)

Medical history
Demographic data: sex, age (date of birth)
Report on associated concomitant medications
ECOG performance status assessment (Appendix 5)

Sorror score (Annexe 7)
DRI score (Annexe 6)
Physical examination, including weight, height, vital signs (systolic/diastolic blood pressure, pulse rate, respirations and temperature), cardiopulmonary examination, neurological examination, search of signs of infection.
AE related to the protocole-induced procedures will be collected.

Laboratory assessments:
•Standard hematology tests including CBC (hemoglobin, hematocrit, RBC count, WBC count, differential leukocyte count, platelets count, TP TCA fibrinogen), white cell morphology
•Blood chemistry: including total bilirubin, AST, ALT, alkaline phosphatase, serum creatinine, clearance of creatinine evaluated by MDRD or CKDEPI, urea, glucose, sodium, potassium, calcium, phosphate, total protein.
•Serology for Hepatitis B or C, HIV
• Ferritinemia, cholesterolemia, triglyceridemia, uricemia, TSH,
• COVID PCR and serology 48/72h before admission and COVID serology
•Urine or serum pregnancy tests
Immune status at transplant: CD3, CD4, CD8, B, NK, EPP
Bone marrow aspiration to confirm complete remission and MRD evaluation
Left ventricular ejection fraction (LVEF), lung function test (DLCO)
All exams needed to document extramedullary relapse: scan, pet-scan, biopsy, ect…
Quality of life: EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30) and FACT-BMT (Functional Assessment of Cancer Therapy - Bone Marrow Transplant)
General Health State with Euroqol EQ-5D-5L questionnaire
Signature of informed consent

6.2.2. Assessment during Hospitalisation in Sterile Unit (day-7 until day 30/42):

Randomization
Infusion of CloB2A2 or FB2A2 according to randomization.
Infusion of the graft at day 0 (D0).
Every day until patient has recovered >0.5 G/L polynuclears neutrophils:
Physical examination, including weight, height, vital signs (systolic/diastolic blood pressure, pulse rate, respirations and temperature), cardiopulmonary examination, neurological examination, search of signs of infection
AE related to the protocole-induced procedures will be collected.
-Complete (full) blood cell counts
At least twice a week:
-Blood chemistry: including total bilirubin, AST, ALT, alkaline phosphatase, serum creatinine, clearance of creatinine evaluated by MDRD or CKDEPI, urea, glucose, sodium, potassium, calcium, phosphate, total protein.
- TP TCA fibrinogen,
- Daily medical examination.
- Documentation of toxicities and adverse events whenever it appears
- Health resources consumption

6.2.3. Assessment at D30, D60, D90, 6, 12 and 24 months:

- Physical examination, including weight, height, vital signs (systolic/diastolic blood pressure, pulse rate, respirations and temperature), cardiopulmonary examination, neurological examination, search of signs of infection

• Laboratory assessments:
Standard hematology tests including CBC (hemoglobin, hematocrit, RBC count, WBC count, differential leukocyte count, platelets count), white cell morphology , TP TCA fibrinigen
Blood chemistry: including total bilirubin, AST, ALT, alkaline phosphatase, serum creatinine, clearance of creatinine evaluated by MDRD or CKDEPI, urea, glucose, sodium, potassium, calcium, phosphate, total protein.
Ferritinemia, cholesterolemia, triglyceridemia, uricemia, TSH at D90, 6, 12 and 24 months
Urine or serum pregnancy tests (if applicable) at D30, D60 and monthly thereafter, until 6 months after the last dose of Clofarabine/Fludarabine.

- Response assessment with Bone marrow aspiration, with cytology, immunophenotype caryotype and molecular analysis for MRD at D30 and D90/100
- Chimerism at days +30, +90/100
- Documentation of acute and chronic GVHD
- Documentation of toxicities and adverse events
- Documentation of relapse if suspicion of relapse
- Documentation of infections after transplant: bacterial, viral, parasitic and fungal
- Immune reconstitution: CD3, CD4, CD8, B, NK, EPP at 3, 6 and 12 months
- Left ventricular ejection fraction (LVEF), lung function test (DLCO) at 12 months
- Quality of Life (QoL) at D30, D90, D180, D365 and Day 720: EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30) and FACT-BMT (Functional Assessment of Cancer Therapy - Bone Marrow Transplant)
- Registration of maintenance treatment and donor lymphocyte infusion after transplant
- Number of readmission days after transplant
- General Health State with Euroqol EQ-5D-5L questionnaire at D30, D90, D180,D365 and D720.
- AE related to the protocole-induced procedures will be collected.
- Health resources consumption from the beginning of conditioning (D-6) regimen to Month 24

STUDY SCHEDULE

Activities	Between D-30 and D-7 Inclusion visit	D-6 (beginning of the conditioning regimen)	Daily from D-6 until PNN>0.5G/L	D 30	D 60	D 90	M 6	M 12	M 24	Withdrawal from the study
Patient information and consent	X									
Eligibility criteria	X									
Randomisation	X									
Previous medical history	X									
Clinical examination	X	X	X	X	X	X	X	X	X	X
Para-clinical examinations	X	X	X	X	X	X	X	X	X	X
Response assessment (blood and / or marrow)[1]	X			X		X		X	X	X
Biocollection (Bone marrow)	X					X				
Biocollection (blood sample)	X					X	X	X		
pulmonary function test with measure of the DLCO	X							X		
ECG	X			X	X	X	X	X	X	
ventricular function assessed by multigated acquisition (MUGA) scan or echocardiogram	X							X		
Analysis (biochemistry, haematology, etc.)	X	X	X	X	X	X	X	X	X	X

Urine or serum pregnancy tests (if applicable)	X		X	X	X	X	X			
Quality of life assessment : EORTC QLQ-C30 and FACT-BMT	X			X		X	X	X	X	
General Health State (Euroqol EQ-5D-5L)	X			X		X	X	X	X	
Health Resource Consumption : (a) help by relatives in eCRF and (b) Query in SNDS Database						X(a)		X(a)	X(a) X(b)	
Adverse events	X°	X	X	X	X	X	X	X	X	X
Concomitants treatments	X	X	X	X	X	X	X	X	X	X

1: Response assessment with Bone marrow aspiration, with cytology, caryotype and molecular analysis if evaluable at D60
° Before randomization, only AE related to the protocole-induced procedures will be collected.

6.2.4. Economic evaluation: cost-effectiveness and cost-utility analyses

The economic efficiency of a CloB2A2 compared to a FB2A2 RIC regimen for allo-SCT in patients with AML in complete remission will be evaluated, from a collective perspective (considering costs to the National Health Insurance (NHI) system, hospital and patients) and with a 24-month time horizon. Two analyses will be performed: a cost-utility analysis (CUA) estimating an incremental cost per Quality Adjusted Life Year (QALY) gained, and a cost-effectiveness analysis (CEA) estimating an incremental cost per life year gained. The effectiveness of the two compared strategies will be assessed in terms of potential changes in survival weighted by quality of life (CUA) and in terms of survival (CEA), respectively. Economic evaluations will comply with the HAS Methodological Guide (2020). QALYs will be calculated from utility scores obtained from patients' answers to the EQ-5D-5L (EuroQol) health-related quality of life questionnaire at D-7, D30, D90, D180, D365 and Day 730. Costs and results will be discounted. Costs will be estimated in 3 steps: (1) identification and quantification of healthcare resources consumed, (2) monetary valuation of unit resources (using NHI official tariffs), and (3) multiplication of quantities of resources by unit costs. The estimated costs will include costs related to hospitalizations (diagnosis-related groups (DRG), hospital stay length), medication, transportation, home help (by a housekeeper and by relatives), work stoppage, blood products, medical visits, nursing care, biological exams. Healthcare resources consumed will be collected thanks to a query into the French National Health Database (Système National des Données de Santé, SNDS) at the end of the study, and thanks to the eCRF to collect the home help by relatives at M3, M12 and M24. The data from eCRF (survival, EQ-5D-5L answers, patient characteristics) and from the SNDS Database will be matched thanks to a probabilistic matching method, with the NHI team's (CNAMTS) cooperation. Variables such as patients' date of birth, gender, codes of clofarabine and fludarabine and date of patients' enrolment will be used to achieve the pairing. Then, a query will be carried out in the DCIR and PMSI, to collect outpatient and inpatient data over the 2-year follow-up period. Analyses will be performed directly on the CNAMTS platform by identified health economists. Missing data in eCRF will be processed with multiple imputation methods.
Mean effectiveness and costs per patient will be reported for each group with their 95% confidence intervals estimated using the non-parametric bootstrap resampling method. The ICUR and ICER will be presented. The probability that the CloB2A2 RIC regimen strategy is cost-effective compared to FB2A2 will be estimated for different thresholds of Society's willingness to pay a QALY and a life year. Sensitivity analyses will be carried out to evaluate the robustness of the results.

6.3. IDENTIFICATION OF ALL DATA SOURCES NOT INCLUDED IN THE MEDICAL RECORD

Not applicable. Data required for follow-up outside the study will be compiled in medical records.

6.4. RULES FOR DISCONTINUING SUBJECT PARTICIPATION

6.4.1. Criteria in respect of early withdrawal of a subject from the study

The criteria when a subject should be discontinued from the study treatment are:

- Occurence of an adverse event which makes discontinuation from treatment necessary due to protocol specified safety criteria or desirable in the investigator's and/or the patient's opinion.
- Investigator's decision that a change of therapy is in the patient's best interest
- Administration of relevant non-permitted concomitant medications
- Intercurrent medical condition, which in the opinion of the investigator or the patient precludes further treatment of the patient with experimental tested drugs
- Withdrawal of patient's consent to study treatment
- Death of patient

The criteria when a subject should be discontinued from the study are:

- No administration of the conditioning regimen (because for example hematological or extramedullary relapse before starting the study treatment or because other complications).
- Withdrawal of patient's consent to study treatment
- Failure of the patient or investigator to comply with the study protocol
- Death of patient

6.4.2. Procedures in respect of early withdrawal of a subject from the study

Discontinuing from the study or the study treatment can only be effective after confirmation by the investigator and the sponsor. These discontinuing are always definitive. All reasons for treatment or study or study treatment discontinuation will be documented in the CRFs. The sponsor and the principal investigator need to be notified immediately if a patient discontinues from treatment or from study.

In case of premature treatment discontinuation, the assessment planned at month +24 should be performed immediately. The patient should continue to come to all relevant follow-up visits. If a patient fails to keep the appointments for study visits, the investigator will document the reason and circumstances as completely and accurately as possible.

The reason for early withdrawal will be collected.

In case of death of the patient, the date and reason of death will be collected by contacting a clinician in charge of the patient's care, the family, or the person identified as contact person by the patient.

In case of withdrawal of consent, an end-of-study visit will be organised in order to collect the end-of-study visit.

6.4.3. Criteria in respect of discontinuation of all or part of the study (excluding biostatistical considerations)

The end of the study corresponds to the date of the 2-year follow-up for the last patients included in the study.

A definitive or temporary discontinuation of all or part of the study may be decided by ANSM, the ERB, Sponsor or Data and Safety Monitoring Committee (DSMC).
In case of early discontinuation of the study decided by the Sponsor or DSMC (if applicable), ANSM and the ERB shall be informed within less than 15 days by mail.

In any case:
- A written confirmation of this early discontinuation of the study shall be sent to the coordinating investigator of the study (specifying the reasons for the early discontinuation) and to the principal investigator of each centre (if applicable),
- All the patients included in the study shall be informed and should attend their early withdrawal visit.

6.5. PATIENT MEDICAL CARE AT THE END OF THE STUDY

After the study is closed or after the 2-year follow-up (from day+0 post graft), medical care for patients is at the discretion of the investigators.

6.6. FINAL STUDY REPORT

The final study report includes the full written description of the study. This report should be sent to the competent authorities and the ethical review board less than one year after the end of the study. This final report is written in collaboration between Sponsor and study Coordinator.

7. DATA MANAGEMENT AND STATISTICS

7.1. STUDY DATA COLLECTION AND PROCESSING

7.1.1. Data collection

An electronic Case Report Form (eCRF) will be drawn up for each subject. All information required by the protocol should be provided in the CRF/eCRF. It should include data required to confirm compliance with the protocol and all data necessary for statistical analysis, and identify major deviations from the protocol.

Each person responsible for the filling of the eCRF (investigator, ARC ...):
- will have to be identified in the table of delegations of responsibilities of each center (see investigator's file).
- Will have a "user" account with specific computer rights linked to his role (right to enter or modify a data, right to lock, monitor or sign a page of eCRF ...)

Entering, viewing or modifying data will only be possible via the eCRF pages (input masks), on https://nantes-lrsy.hugo-online.fr/CSonline

As for the health economic analysis, a query in the NHI Database (SNDS) will be carried out to collect health resources consumed.

7.1.2. Data encoding

By signing this protocol, the principal investigator and all co-investigators agree to keep the identities of the patients participating in the study confidential by assigning them a code.
This code will be the only information featuring in the eCRF enabling a retrospective link with the patient.
The investigator shall also encode patient data on any documents liable to be in its possession (reports of imaging studies, biology, etc.) which are attached to the eCRF and SAE report. All the documents attached to the SAE report should remain anonymous.
The coding rule is the following: 1ère lettre du prénom + 1ère lettre du nom ; mois et année de naissance, N°centre_N° d'inclusion

7.1.3. Data processing

Clinical data collection shall be based on a database and creating input templates similar to the CRF in compliance with the protocol and applicable regulations.
The structure of the database and data input screens shall be approved by the trial sponsor.
At the end of the study, database reconciliation is carried out between the CRF database and safety database. This reconciliation is performed before database locking. Similarly, an annual reconciliation is carried out when updating the Annual Safety Report (ASR).

7.2. STATISTICS

The total number of patients to be included is 302 including 151 in both groups.

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7.2.1. Description of planned statistical methods, including planned intermediate analysis schedule

All analyses will be performed using SAS software (version 9.4, NC, USA). Continuous variables will be described with minimum, maximum, quartiles, mean and standard deviation. Categorical variables will be described with numbers and percentages.

No baseline comparisons will be done.

Primary endpoint: OS is defined as the time from day 1 of the conditioning to death or last follow-up for survivors. The Kaplan-Meier estimator will be used to estimate overall survival at 2 years in the 2 groups. Estimates of overall survival at 2 years and median will be presented with 95% confidence interval. Log-rank test will be used to compare the 2 groups and a Cox proportional hazards model will be performed to estimate hazard ratio adjusted for stratification factors.

Secondary endpoints:

- Probabilities of PNN > 500/mm3, neutrophilis recovery (the first of three consecutive days with neutrophils ≥500/mm3 after aplasia) and platelets recovery (the first of three consecutive days with platelets ≥20000/mm3 without transfusion after aplasia) will be estimated using cumulative incidence estimates. Relapse and death will be considered competing risks for these events. Subdistribution hazard models will be fit to take into account stratification factors.

- Engraftment donor chimerism >=5% at days +30/42, primary graft failure (donor chimerism <5% at day +30/42 post-transplant) and secondary graft failure will be estimated and compared between groups with Mantel-Haenzel stratified Chi-square tests.

- Probabilities of 2-year DFS will be estimated using the Kaplan-Meier method. Cox proportional hazards model will be performed to estimate hazard ratio adjusted for stratification factors.

- Probabilities of 2-year GRFS will be estimated using the Kaplan-Meier method. Cox proportional hazards model will be performed to estimate hazard ratio adjusted for stratification factors.

- Probabilities of 2-year relapse incidence, 2-year NRM, aGVHD and cGVHD will be estimated using cumulative incidence estimates. Relapse and death will be considered competing risks for aGVHD and cGVHD. Death will be competing risks for Relapse-Incidence. Relapse will be competing risks for NRM. Subdistribution hazard models will be fit to take into account stratification factors.

- Evolution of the chimerism (percentage of patients with > 95% cells donor) will be estimated and compared between groups with generalized logistic models taking into account repeated measures for the patients.

- Evolution of the immune reconstitution will be estimated and compared between groups with linear mixed model taking into account repeated measures from patients.

- Percentage of MRD at days +30 and +90/100 will be estimated and compared between groups with Mantel-Haenzel stratified Chi-square tests.

- The presence of signs of veno-occlusive disease will be described in the 2 groups.

- Infections (bacterial, viral, parasitic and fungal) will be described in the 2 groups.

- Evolution of the scores of quality of life (from EORTC QLQ-C30 and FACT-BMT) will be estimated and compared between the 2 groups with linear mixed models taking into account repeated measures from patients.

- Safety assessment will be evaluated and compared between the 2 groups in terms of type, frequency, severity, and relationship of adverse events to study treatment with Chi-square test (for AE more frequent)

- Graft hospitalization: comparison between both groups in terms of length of stay, use of antibiotics and blood products will be performed with Student or Chi-square tests.

Subgroups analysis: comparisons of OS, DFS, GRFS, Relapse-Incidence and NRM between FB2A2 and CloB2 will be performed in different subgroups ELN classification: good, intermediate and high risk subgroups

- FLT3-ITD + and –
- NPM1 + vs –
- MRD before transplant + vs -
- First and second line therapy
- First and second allograft

Interim analysis:
One intermediate analysis is planned when 50% of events will be observed (79 events).

Table 1: Boundary Information for efficacy at interim and final analysis according to the O'Brien-Fleming with Lan-Demets alpha spending function

Boundary Information (p-Value Scale) Null Reference = 0							
				Alternative		Boundary Values	
	Information Level			Reference		Lower	Upper
Stage	Proportion	Actual	Events	Lower	Upper	Alpha	Alpha
1	0.5000	19.75355	79.01419	-2.29601	2.29601	0.00153	0.99847
2	1.0000	39.50709	158.0284	-3.24705	3.24705	0.02450	0.97550

One interim analysis will be conducted. The objective will be to evaluate early the efficacy of CloB2A2 vs FB2A2. The analysis will be performed when 50% of the events will be observed, i.e 79 events. Stopping rules are determined according to the O'Brien and Fleming type of boundary with Lan-DeMets alpha spending function. At the interim analysis, the study will be discontinued for early efficacy if the p-value for difference between the 2 groups is below 0.00306 (cf. Table 1).

Safety analysis:

Safety analyses will be conducted on all subjects receiving at least one dose of study treatment. Analyses will consist of data summaries (type, frequency, severity, and relationship of adverse events to study treatment) for reported AEs.

7.2.2. Statistical justification of the number of inclusions

Our hypothesis is to obtain a 2-year OS of 70% for patients receiving CloB2A2 compared to a 2-year OS of 55% for patients receiving FB2A2 (HR = 0.60). With a randomization 1:1, an alpha-risk of 5% (two-sided test), a beta-risk of 10% and a 5% drop-out rate, the number of patients required is 302 (151 patients in each group).

7.2.3. Expected level of statistical significance

All the tests will be realized with a statistical significance of 5%.

7.2.4. Statistical criteria for discontinuation of study

Stopping rule is determined by using a truncated O'Brien-Fleming stopping rule, implemented via a Lan-DeMets alpha-spending function.
A definitive discontinuation of the study may be decided by DSMB in case of a a difference >20% of serious adverse events (grade 3+grade 4+grade 5) with clofarabine compared to fludarabine.
A comparison of related-fludarabine/clofarabine toxicitieswill be performed every 50 patients included until the end of the protocol and presented to the DSMC.

7.2.5. Consideration method for missing, unused or invalid data

All randomised patients regardless of the medical device/treatment received or not are considered for analysis. If the conditioning is not received after randomisation, the patient is not replaced and he/she will still be evaluated for primary and secondary objectives, then up to 2 years from the randomisation. When a patient is released from the study (e.g. in the event of ARs preventing the continuation of the study), his/her data should then be collected, except for safety data (follow-up of AR or onset of AR associated with the experimental treatment).
The recommended procedure for analysing incomplete observations, in case of lost to follow-up, early withdrawals, non-compliance with the protocol, missing data, is to collect the maximum data up to 2 years from the randomisation or to the last follow-up (if the event occurred <2 years from randomisation).

Primary endpoint: no missing data are expected for death status at the end of the study. However, in case of lost to follow-up or consent withdrawals, patient will be censored at the date of last follow-up.

Secondary endpoints: for survival endpoints, patients with missing data will be censored at the date of last follow-up. None imputation will be done for other endpoints.

As for health economic study, See Chapter 6.2.4.

7.2.6. Management of changes made to the initial analytical strategy

Not applicable

7.2.7. Choice of subjects to be included in analysis

Three populations will be considered:

The Intention to treat population
This is a Phase III randomised trial. The analysis will focus on the "intention to treat population" (= all randomised patients in the group in which they were randomised, regardless of the medical device/treatment received and breaches of the protocol, etc.).

The Per-protocol population
A sensitivity analysis will be performed on per-protocol population (= all randomised patients except those with one or more major protocol violations).

The safety set population
Safety analyses will be conducted on all subjects receiving at least one dose of study treatment.

7.2.8. Randomisation

.
The patients will be randomized between the two treatment arms with a ratio 1 : 1. Randomisation will be centralised at the CHU of Nantes and performed after inclusion. Blocked randomisation will be used with random block sizes.
Randomization will be stratified according to ELN 2022 classification (good, intermediate or high risk), age (<60 or >=60 years) and type of donor (sibling or matched unrelated).

Randomization will be conducted via eCRF by connecting to the web site: https://nantes-lrsy.ennov.com/EnnovClinical/login. The connection will be made with a login and a password given by a data manager from the CHU de Nantes Research Department. The following information should be provided:

- The first letter of the first name
- The first letter of the surname
- Date of birth
- Compliance with inclusion criteria and exclusion criteria (yes/no)
- Stratification factors.

The number and the randomization arm will be assigned automatically at the time of the randomization. The randomization list will be prepared by a statistician from the CHU de Nantes Research Department

8. PHARMACOVIGILANCE AND ADVERSE EVENT MANAGEMENT

8.1. DEFINITIONS

Vigilance	Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.
Adverse events (AE)	Any untoward medical occurrence in a person participating in a research on human being whether or not considered related to the product or the research.
Adverse Event Intensity (EvI)	Rated according to the CTCAE v.5.0 (Annexe 11). Any event not rated in the selected classification should be rated as follows: Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE. Activities of Daily Living (ADL) *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Adverse reactions (AR)	All untoward medical occurrences in a person participating in a research on human being, when this response is related to the research or the investigational medicinal product (IMP).
Adverse reaction of an experimental medicinal product – Adverse Drug Reaction (ADR)	All untoward and unintended responses to an investigational medicinal product related to any dose administered.
Serious adverse events (SAE)	Any untoward medical occurrence or effect that: - results in death, - is life-threatening, - results in persistent or significant disability or incapacity, - requires hospitalisation or prolongation of existing hospitalisation, - is a congenital anomaly or birth defect. - is medically significant (the list of medically significant events/reactions is defined by the EMA)

Unexpected adverse reactions	An adverse reaction, the nature or severity of which is not consistent with the applicable product information.
Suspected Unexpected Serious Adverse Reactions (SUSAR)	An untoward and unintended response to an investigational medicinal product, which is not listed is the applicable product information, and meets one of the serious criteria.
New safety information	Any new data which could: ➢ Induce new evaluation of benefit/ risk ratio of the study or of the product object of the study, ➢ modify product utilization, the conduct of the study or documents related to the study ➢ Suspend or terminate the protocol under research or similar researches. For trials on first administration or non-health product with person without any affection: all adverse effect.
Abuse	This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
Overdose	This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied. (Real overdose: due to a brut excessive amount / relative overdose: due to patient predisposal factors as renal insufficiency, hypo-albuminuria…)
Misuse or use outside marketing authorisation	This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.
Quality defect	Non conformity to the specifications described in the marketing authorisation file / CE marking / technical documentation or deviation against good manufacturing practices / good distribution/storage/labelling practices.
Medication Error	Medication errors are unintended mistakes (proved or potential) during the care process, in the circuit (from manufacturing to administration) implying a product that can lead to a risk or an adverse event for the patient. The risk of error or potential error concerns situations where the error did not happen, was intercepted but could have happen.

8.2. SAFETY EVALUATION PARAMETERS

There will be no additional parameters other than the toxicity evaluation parameters described above.

8.3. LIST OF EXPECTED ARS

Within the scope of this protocol, the expected ARs are associated with drugs under study (CLOFARABINE®), his comparator (FLUDARABINE®), auxiliary treatments (Corticosteroids), associated treatments (BUSUFLAN®, ATG®, etc.), the disease and the transplant procedure.
The Reference Safety Informations (RSI), containing the exhaustive expected ARs, are listed in the current version of treatment SmPC (section 4.8)

For Clofarabine, the reactions described as very frequent include: nausea, vomiting, febrile neutropénia, headache, diarrhea, pruritus, fever, palmoplantar erythrodysesthesia, fatigue, anxiety, mucosa inflammation and hot flashs.

For Fludarabine, the reactions described as very frequent include: nausea, vomiting, diarrhea, cough, fever, fatigue, weakness, neutropenia, anemia, thrombopenia, Opportunistic infections and pneumonia

Concerning the transplant procedure, the consequences are: hospitalization in sterile unit 4 to 6 weeks, risks related to clinical and biological exams, infections, acute and chronic GVHD, immunosuppressive drugs toxicities, catheter need with risks of pains, infections.

Concerning the disease, the most expected AEs in patients are aplasia, infections, haemorrhage, metabolic disorders, compressive tumour, relapse and deaths (non-exhaustive list).

For auxiliary and associated treatments, expected ADRs are listed in their respective SmPCs.

8.4. ADVERSE EVENT MANAGEMENT

8.4.1. Serious AE/AR (SAE/SAR) and non-serious (NSAE/NSAR) collection

Any AR/AE (unless specify otherwise in 8.3), whether expected or unexpected, serious or not, must be real-time collected in the study eCRF whether noted by the investigator or reported spontaneously by the patient.

8.4.2. Abnormal test results

An abnormal laboratory value/test result is considered as an AE if the abnormality:
- occurs in discontinuation of the study
- requires the introduction of treatment, modification or discontinuation of study treatment or other therapeutic intervention.
- is considered clinically significant (i.e., indicative of a new disease process and/or organ toxicity, or indicative of the onset of a disease or an exacerbation/aggravation of an existing disease).

If a laboratory abnormality or abnormal test result is a component of a diagnosis or syndrome, only the diagnosis or syndrome should be recorded as an AE.

8.4.3. SAR/SAE reporting

All SAEs (except grade 1/2), whether expected or unexpected, must be reported immediately (from the day the of the investigator becoming aware of the event) and in the same terms in the eCRF. (electronic notification via the eCRF which automatically triggers an email to **recherche-pv@chu-nantes.fr**). In case of eCRF unavailability, the SAE/SAR notification should be sent to the sponsor by e-mail to recherche-pv@chu-nantes.fr.

The investigator should verify that all the information noted in the SAE report and the documents attached to this report must be completed, specified, cleared (no abbreviation, etc.) and coded.
The investigator should establish the causality assessment for the adverse events.
The occurrence of a new safety issue must be reported to the sponsor.
According to the protocol, some not serious AE can be declared to the Sponsor.

Pregnancy

If pregnancy begins during the clinical trial or if her partner take part in the clinical trial (drug that can affect the male seminal line), the pregnancy must be notified immediately to the sponsor.
The investigator informs, with the pregnancy form, the sponsor's vigilance.
The investigator should monitor the patient until the end of the pregnancy (or until the child reaches the age of majority) or its termination and notify the sponsor of the outcome using the pregnancy form.
In the case of paternal exposure, the investigator should obtain the consent of the parturient to collect information about the pregnancy.

Situations of Special Interest (SIP)

Overdose, misuse, medical errors or potential medication errors, quality defects should be notified by Investigator to Sponsor even if there is no AE associated using the SIP form.

8.4.4. Exclusion from reporting/notification

Regarding the nature of the study, some adverse events have not to be collected in safety section of the eCRF:

- Events and medical complications not related to the study but related to the usual management of the patient;
- Events and medical complications that have occurred before the first administration of the study treatment will be considered as adverse events only if they have worsened (according to the intensity or frequency) after the start of the IMPs;
- Hospitalization for social or administrative reasons;
- Hospitalization for technical problems not related to the study (e.g. change of catheter, accommodation and logistic organization...);
- Hospitalization scheduled before inclusion for a pre-existing condition that has not worsened (e.g. regular follow-up of a chronic disease).

8.4.5. Reporting period

All AE/AR/SAE/SAR must be reported to the sponsor if it happens for a research participant:

- Since the consent signature date,
- During all the participant follow up period scheduled by the study
- Until 28 days after the end of the study for the research participant
- After the end of the patient follow-up and without any time limit if the investigator becomes aware of a SAR possibly linked to the experimental treatment.

8.4.6. Sponsor's responsibilities

The sponsor is responsible for the continuous evaluation of the safety of the clinical trial, both in terms of the procedures performed and the products used.

In accordance with the regulations, the sponsor will report any suspicion of SUSAR to the regulatory authorities according to the regulatory deadlines under the European and French regulations.

The sponsor must also notify without delay to the ANSM and the CPP any new safety information with or without urgent safety measures.

Because the sponsor is a non-commercial sponsor, he's not the owner of the marketing authorization of the IMPs. Therefore, only one annual safety report will be established for the trial, based only on the data of this clinical trial and including the evaluation of all IMPs of the trial.

8.4.7. Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee is a consultative committee responsible for reviewing the safety of a study on behalf of the sponsor and the coordinator of the study. The competent members in the field of clinical trials (disease and methodology) are not involved in the study. They are appointed for the period of the study and undertake to participate and to respect the data confidentiality. The members are selected by the sponsor and the coordinator.
The annual safety report is sent to the Data and Safety Monitoring Committee. The committee may be requested for a review by the person in charge of safety pharmacology if a SUSAR or a SAE presents a particular analytical problem or if a doubt in respect benefit/risk arises during the study.
The list of members of the Data and Safety Monitoring Committee is attached in appendix 04.
A review of the toxicity data of every 50 patients included will be carried out by the DSMB.

8.5. FOLLOW-UP PROCEDURE AND PERIOD FOR SUBJECTS FOLLOWING THE ONSET OF ADVERSE EVENTS

All events, serious or non-serious, expected or not expected, must be followed until the cure, healing or death.
When a patient died, the outcome of the ongoing AE is not necessarily "death": only an AE that contributed to the patient's death can have a "fatal" outcome.

In case of premature treatment discontinuation, the patient should continue to come to all relevant follow-up visits. If a patient fails to keep the appointments for study visits, the investigator will document the reason and circumstances as completely and accurately as possible.

9. ADMINISTRATIVE AND REGULATORY ASPECTS

9.1. SOURCE DATA AND DOCUMENT ACCESS RIGHTS

Each patient's medical data shall only be provided to the sponsor or any person duly authorised by the sponsor, and, where applicable, to authorised health authorities, in confidential conditions. The sponsor and the supervisory authorities may request direct access to medical records for the purposes of verification of the procedures and/or data in respect of the clinical trial, within the limits authorised by the legislation and regulations.
The data compiled during the trial may be processed electronically in compliance with CNIL requirements (compliance with French Reference Methodology MR001).

The SNDS query will require a CNIL and a CESREES authorization, to perform the health economic analysis.

9.2. TRIAL MONITORING

Monitoring shall be carried out by the Research Division Promotion Department. A Clinical Research Associate (CRA) shall visit each site (investigator and dispensary) regularly to conduct quality control on the data reported in the case report forms.

The protocol has been classified according to the estimated level of risk for the patient taking part in the study. It shall be monitored as follows:

Risk B: foreseeable risk similar to that of standard care

The on-site monitoring visits shall be organised after making arrangements with the investigator. The CRAs should be able to consult on each site:
- the enrolled patients' data compilation records,
- the patients' medical and nursing files,
- the investigator file.
- the treatment storage and dispensation place

9.3. INSPECTION / AUDIT

As part of this study, an inspection or audit may take place. Sponsor and study centers must give an access to the data to inspectors or auditors.

9.4. ETHICAL CONSIDERATIONS

9.4.1. Written informed consent

The investigator agrees to provide the subject with clear and precise information about the protocol and request him/her for written informed consent. The investigator will give the subject a copy of the information form and consent form. The subject can only be enrolled in the study after reading the information form and signing and dating the consent form, after taking time to reflect on the matter.
The investigator should also sign and date the consent form. Both documents should be issued at least in duplicate hard copy format so that the patient and the investigator can each keep a copy. The investigator's original will be placed in the investigator's file gives the copy to the subject.

9.4.2. Ethical Review Board

The sponsor agrees to submit the study to an Ethical Review Board for prior approval. The information disclosed relates to the procedure and nature of the study and the guarantees provided for subjects participating in the study.

9.4.3. Registration with the competent authorities

This protocol shall be the subject of an ANSM authorisation application.

9.5. AMENDMENTS TO THE PROTOCOL

Requests for substantial modifications should be addressed by the sponsor for approval or notification to ANSM and/or the Ethical Review Board concerned in compliance with the law and its implementing decrees.

The amended protocol should be a dated updated version. If necessary, the information form and consent form should be amended.

9.6. STUDY FUNDING AND INSURANCE

The sponsor shall fund the study and take out an insurance policy covering the financial consequences of its civil liability in compliance with the regulations.

9.7. PUBLICATION RULES

A copy of the publication will be delivered to the CHU de Nantes, the study sponsor, which will necessarily be mentioned. The authors will be determined in proportion to the number of subjects enrolled. The coordinator shall draw up the list of authors.
Publications regarding projects financed by the French Ministry of Health must have the mention: "This study was supported by a grant from the French Ministry of Health (programme acronym, year and registered number: ex PHRC 2022 XXXX)".
The sponsor will enter the study results in the European Union database as soon as the main publication from the research is released, in order to preserve intellectual property.

9.8. OUTCOME OF BIOLOGICAL SAMPLES

At the end of the study, biological samples resulting from sampling (See Ancillary study) will be kept (in the case of further scientific benefit). The subject's written consent will be collected and the samples stored in a biocollection under the responsibility of Dr Beatrice Clemenceau (Equipe 1 INSERM UMR1232, CRCINA IRS-UN, University of Nantes, University Hospital).

9.9. SOURCE DATA ARCHIVING

The investigator should archive all study data for at least 25 years after the end of the study.
At the end of the study, Investigator will receive by Sponsor a copy of patient(s) data in his center.

LIST OF APPENDICES

- *Investigator listing*
- *Summary of protocol*
- *Bibliographic references*
- *Composition and charter of the Data and Safety Monitoring Committee*
- *Performance status*
- *Sorros score*
- *ELN 2022 classification*
- *Summary of Product Characteristics for Clorafabine end Flodarabine*
- *CTCAE Version 5.0*

APPENDIX 1: INVESTIGATOR LIST

FIRST NAME SURNAME	Area of medicine	Title	Name of institution	Name of affiliated department	Telephone and e-mail	RPPS No.	Expected number of patients
CHEVALLIER Patrice	Hematology	Pr	Chu de Nantes	Service d'hématologie clinique	0240083271 patrice.chevallier@chu-nantes.fr	10002583754	24
NGUYEN Stéphanie	Hematology	Pr	Pitie-Salpetriere, APHP	Service d'hématologie clinique	(33)142162823 stephanie.nguyen-quoc@aphp.fr	10004599980	24
FRANCOIS Sylvie	Hematology	Dr	CHU Angers	Service d'hématologie - Maladies du Sang	(33)241354472 Syfrancois@chu.angers.fr	10002546637	14
MOHTY Mohamad	Hematology	Pr	St-Antoine, APHP	Service d'hématologie Clinique et thérapie cellulaire	(33)149282620 Mohamad.mohty@inserm.fr	10003429817	12
BERCEANU Ana	Hematology	Dr	CHU Besançon	Unité de Soins Intensifs et Greffe Service d'hématologie	(33)381668232 aberceanu@chu-besancon.fr	100055171441	12
CHANTEPIE Sylvain	Hematology	Dr	CRLC Caen	Service d'hématologie clinique	(33)231272073 chantepie-s@chu-caen.fr	10005187314	12
GUILLERM Gaelle	Hematology	Dr	CHU Brest	Service d'hématologie clinique	(33)298223395 Gaelle.guillerm@chu-brest.fr	10002676509	12
CHARBONNIER Amandine	Hematology	Dr	CHU Amiens	Service d'hématologie clinique, soins intensifs et greffe	(33)322455606 Charbonnier.amandine@chu-amiens.fr	10100316578	12
HUYNH Anne	Hematology	Dr	CRLC Toulouse	Service d'hématologie	(33)531155527 huynh.anne@iuct-oncopole.fr	10002873411	12
BAY Jacques-Olivier	Hematology	Pr	CHU Clermont-Ferrand	Service de Thérapie Cellulaire et d'Hématologie Clinique Adulte	(33)473750750 jobay@chu-clermontferrand.fr	10003167912	12
TURLURE Pascal	Hematology	Dr	CHU Limoges	Service d'hématologie Clinique et Thérapie Cellulaire	(33)555056642 Pascal.turlure@chu-limoges.fr	10002939329	12
ROBIN Marie	Hematology	Dr	CHU Paris St-Louis	Service d'hématologie Greffe	(33) 142499639 marie.robin@aphp.fr	10001569044	12

MEAR Jean-Baptiste	Hematology	Dr	CHU Rennes	Service d'hématologie clinique	(33) 299284291 jeanbaptiste.mear@chu-rennes.fr	10100809077	12
MAURY Sebastien	Hematology	Pr	Creteil	Service d'hématologie clinique	(33) 149812059 sebastien.maury@aphp.fr	10001482594	12
COITEUX Valérie	Hematology	Dr	CHRU Lille	Service des maladies du sang	(33) 320445551 Valerie.coiteux@chu-lille.fr	10002310414	12
RUBIO Marie-Therese	Hematology	Pr	CHRU Nancy	Service d'hématologie	(33) 383153030 M.RUBIO@chru-nancy.fr	10001591311	12
CEBALLOS Patrice	Hematology	Dr	CHU Montpellier	Service d'hématologie clinique	(33) 467338079 p-ceballos@chu-montpellier.fr	10003241980	12
LABUSSIERE-WALLET Helene	Hematology	Dr	CHU Lyon	Service d'hématologie	(33) 472117402 helene.labussiere-wallet@chu-lyon.fr	10005187314	12
CARRE Martin	Hematology	Dr	CHU Grenoble	Service d'hématologie	(33) 476769445 MCarre@chu-grenoble.fr	10100684538	12
CORNILLON Jerome	Hematology	Dr	CHU St-Etienne	Service d'hématologie clinique et thérapie cellulaire	(33) 477917000 Jerome.Cornillon@icloire.fr	10003118451	12
MAILLARD Natacha	Hematology	Dr	CHU Poitiers	Service d'ocologie hématologie et thérapie cellulaire	(33) 549444472 natacha.maillard@chu-poitiers.fr	10001567436	12
FORCADE Edouard	Hematology	Dr	CHU Bordeaux	Service d'hématologie clinique	(33) 557656511 Edouard.forcade@chu-bordeaux.fr	101000787018	12
DEVILLIER Raynier	Hematology	Dr	Institut Paoli Calmettes, Marseille	Département d'hématologie Programme de transplantation et de thérapie Cellulaire	(33) 491223868 DEVILLIER@ipc.unicancer.fr	10100721504	22

APPENDIX 2: SUMMARY OF PROTOCOL

Title of study	**FLUCLORIC** ***Randomized multicentric Phase III study comparing the efficacy of two reduced intensity conditioning regimens (clofarabine/busulfan versus fludarabine/busulfan) in adults with acute myeloid leukemia and eligible to allogeneic stem cell transplantation: a SFGM-TC study.***
Keywords	-clofarabine -fludarabine -reduced intensity conditioning regimen -allogeneic stem cells transplantation -acute myeloid leukemia
Sponsor of study	**NANTES University Hospital**
Coordinator (if multi-centre)	Pr Patrice CHEVALLIER
Number of centres envisaged	23
Study Type	Drug
Study duration	❖ Total duration: *60 months* ❖ Enrolment period: *36 months* ❖ Patient treatment period: *5 days* ❖ Patient follow-up period: 2 years of follow-up from day 0 of the graft (survival status until the end of the study)
Study design	❖multi-centre ❖3 ❖Controlled ❖Randomised ❖Open ❖Prospective
Study objectives	Primary objective: To compare 2-year overall survival (OS) between patients with AML in complete remission receiving either a CloB2A2 or a FB2A2 RIC regimen for allo-SCT. Secondary objective(s): To compare between AML patients receiving either a CloB2A2 or a FB2A2 RIC regimen for allo-SCT: -Engraftment, primary and secondary graft failure -Neutrophils and platelet recoveries -2-year DFS -2-year relapse incidence, -2-year NRM, -Incidence of acute and chronic graft versus host disease (GVHD), -Incidence of GVHD free relapse free survival (GRFS). -Chimerism -Immune reconstitution -Veno-occlusive disease -Outcomes according to FB2 vs CloB2, to ELN classification: good, intermediate, high-risk sub-groups; to molecular markers: FLT3-ITD vs -, NPM1+ vs –, and to minimal residual disease by flow cytometry: + vs – before transplant

Study objectives	-Comparison of infections after FB2A2 vs CloB2A2: bacterial, viral, parasitic and fungal -Quality of Life (QoL) in both treatment arms -Graft hospitalization: Comparison between both groups in terms of length of stay, use of antibiotics and blood products - General Health State in both treatment arms - Safety assessment - Health Economic study: Evaluation of economic efficiency of a CloB2A2 compared to a FB2A2 RIC regimen for allo-SCT in patients with AML or MDS, from a collective perspective (considering costs to the National Health Insurance (NHI) system, hospital and patients) and with a 24-months time horizon. Two analyses will be performed: a cost-utility analysis (CUA) and a cost-effectiveness analysis (CEA). The effectiveness of the two compared strategies will be assessed in terms of potential changes in survival weighted by quality of life (CUA) and in terms of survival (CEA), respectively - Comparison of outcomes betwwen patients in first vs second line therapy and impact of clofarabine vs fludaribine in each sub-group: OS, DFS, RI, NRM
Projected number of subjects	*302*
Schedule of visits and tests	-1/J-7 before graft: Patient should be included. Hospitalisation for conditionning regimen and graft: After registration for the study, the following treatment plan is to be followed: FB2A2 arm or CloB2A2 arm. Graft infusion on Day 0: only peripheral blood stem cells will be accepted; CD34 target dose is 4 × 10^6 per Kg body weight, with a minimum of 2 × 10^6 per Kg body weight. <u>GVHD prophylaxis</u> In case of sibling donor: Cyclosporine A (CsA) 3mg/kg/day IV from day -3 In case of unrelated donor: Cyclosporine A (CsA) 3mg/kg/day IV from day -3+Mycophenolate Mofetil (MMF) oral; 500mg x 4/d from day -3 Follow up visits: Graft+30 days, Graft+60 days, Graft+90/100 days, 6, 9, 12 months and 24 months
Main inclusion criteria	**Main inclusion criteria** • Age ≥ 18 years old • De novo or secondary AML (according to ELN 2022 classification) in complete cytological remission at time of transplant (bone marrow blast count < 5%) • Patients in first or second line therapy are allowed • Patient eligible to a RIC regimen: patients aged ≥ 60 year old or <60 year old with co-morbidity(ies). • Patient with a related or an unrelated matched donor 10/10 • Graft using peripheral blood stem cells • Performance status ECOG 0 - 2 • Written informed consent • Previous allograft allowed
Main exclusion criteria	**Main exclusion criteria** • Pro-myelocytic leukemia • Patient eligible to a myeloablative conditioning regimen • Patient with haploidentical, mismatched unrelated donor or umbilical cord blood • Pregnant or breastfeeding woman or patient refusing contraceptive mesures

	• HIV positive • Active Hepatitis B or C • Left ventricular ejection fraction < 50%. • DLCO <40% • Uncontrolled infection • Uncontrolled haemolytic anaemia • Creatinine clearance < 50 ml/min (evaluated by MDRD or CKDEPI). • Serum bilirubine < 30 mmol/l, Cytolysis >5 the upper limit range • Previous or concurrent second malignancy except for adequately treated basal cell carcinoma of the skin, curatively treated in situ carcinoma of the cervix, curatively treated solid cancer, with no evidence of disease for at least 2 years • Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule • Absence of written informed consent
Experimental treatment	The CloB2 arm: -30 mg/m2/day IV clofarabine for 5 days (day-6 to day-2) -130 mg/m2/day IV busulfan once daily for 2 days (day -4 and -3) - ATG (Thymoglobuline®) 2.5 mg/Kg/day IV for 2 consecutive days (day -2 and -1) Corticosteroids may be used in profilaxis
Comparator	FB2A2 arm: -30 mg/m2/day IV fludarabine for 5 days (day-6 to day-2) -130 mg/m2/day IV busulfan once daily for 2 days (day -4 and -3) - ATG (Thymoglobuline®) 2.5 mg/Kg/day IV for 2 consecutive days (day -2 and -1)
Primary endpoint	OS is defined as the time from day 1 of conditioning to death or last follow-up for survivors.
Secondary endpoints	-Engraftment: PNN >500/mm3 + donor chimerism >=5% -Primary and secondary graft failure: donor chimerism <5% at day +30/42 post-transplant (primary) or at distance of transplant after achieving engraftment (secondary) -Neutrophils recovery: the first of three consecutive days with neutrophils ≥500/mm3 after aplasia from day 0 of the graft -Platelets recovery: the first of three consecutive days with platelets ≥20000/mm3 without transfusion after aplasia from day 0 of the graft -DFS: time from day 1 of the conditioning to time without death, evidence of relapse or disease progression censored at the date of last follow-up. -Relapse: any event related to progression or re-occurrence of the disease from day 1 of the conditioning. -NRM: death from any cause without previous relapse or progression from day 1 of the conditioning. -Acute GVHD: grade 0, 1, 2 3 4 NIH criteria between day 0 and day +90/100 -Chronic GVHD: mild moderate severe NIH criteria up to 2 years post-transplant -GRFS: alive with no previous grade III-IV acute GvHD, no moderate or severe chronic GvHD and no relapse from day 1 of the conditioning. -Chimerism: peripheral blood and CD3 T cells by molecular markers at days +30, +60, +90/100 -Immune reconstitution: Immunophenotype of PB lymphocytes and EPP at 3, 6, 9 and 12 months -veno-occlusive disease: Mohty BMT 2016
Secondary endpoints	- Comparison of infections after FB2A2 vs CloB2A2: bacterial, viral, parasitic and fungal between day 0 and day+90/100

	-Quality of life: EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30) and FACT-BMT (Functional Assessment of Cancer Therapy - Bone Marrow Transplant) at D-7, D30, D90, D180 and D360 -Graft hospitalization: Comparison between both groups in terms of length of stay (in days), use of antibiotics (type and length in days) and blood products (numbers) - General Health State with Euroqol EQ-5D-5L questionnaire at D-7, D30, D90, D180, D360 and D720. -Safety assessment: the safety assessment shall be done by collecting all adverse events that occur during the research. All adverse event (except GvHD) shall be graded according to CTC-AE Toxicity Grading Scale (version 5). - Health Economic study: Incremental cost-utility ratio (ICUR, cost per quality-adjusted life year [QALY] gained) and incremental cost-effectiveness ratio (ICER, cost per life year gained), from a collective perspective and with a 24-months time horizon -Comparison of outcomes betwwen patients in first vs second line therapy and impact of clofarabine vs fludaribine in each sub-group: OS, DFS, RI, NRM
Ancillary study: A biological monocentric study (patients included at the CHU of Nantes only) should be conducted (when a financial support has been found) to better understand the superiority of clofarabine vs fludarabine in terms of relapse decrease after allotransplant in AML. To address this issue we will perform a biological study as part of an ancillary study using leukemics blasts from patients participating to the study (30 in the CloB2A2 arm and 30 in the FB2A2 arm) and frozen at diagnosis (routine) or at relapse (routine) in the Hematology Department of Nantes University Hospital. A second analysis will be performed in the same patients regarding the particular immune sub-population reconstitution post allograft.	
Statistical analysis	Our hypothesis is to obtain a 2-year OS of 70% for patients receiving CloB2A2 compared to a 2-year OS of 55% for patients receiving FB2A2 (HR = 0.60). With a randomization 1:1, an alpha-risk of 5% (two-sided test), a beta-risk of 10% and a 5% drop-out rate, the number of patients required is 302 (151 patients in each group). All the tests will be realized with a statistical significance of 5%. One intermediate analysis is planned when 50% of events will be observed (79 events). Stopping rule is determined by using a truncated O'Brien-Fleming stopping rule, implemented via a Lan-DeMets alpha-spending function. Randomization will be stratified according to ELN 2022 classification (good, intermediate or high risk), age (<60 or >=60 years) and type of donor (sibling or matched unrelated). A Safety Analysis Set (SAS) that includes all randomised patients who were treated at least once will be conducted by the DSMC (see 8.4.7). A comparison of related-fludarabine/clofarabine toxicities will be performed every 50 patients included until the end of the protocol. A difference >20% of serious adverse events (grade 3+grade 4+grade 5) with clofarabine compared to fludarabine will conduct to the arrest of the trial for excessive toxicity.

APPENDIX 3: BIBLIOGRAPHIC REFERENCES

1. 1. Lioure B, Béné MC, Pigneux A, Huynh A, Chevallier P, Fegueux N, et al. Early matched sibling hematopoietic cell transplantation for adult AML in first remission using an age-adapted strategy: long-term results of a prospective GOELAMS study. Blood. 2012; 119:2943-2498.

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3. Rubio MT, Labopin M, Blaise D, Socié G, Contreras RR, Chevallier P, et al. The impact of graft-versus-host disease prophylaxis in reduced-intensity conditioning allogeneic stem cell transplant in acute myeloid leukemia: a study from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Haematologica. 2015; 100:683-689.

4. Chevallier P, Labopin M, Socié G et al. Result from clofarabine-busulfan-containing, reduced-toxicity conditioning regimen prior to allogeneic stem cell transplantation: the phase 2 prospective CLORIC trial. Haematologica 2014; 99(9): 1486-91.

5. Chevallier P, Labopin M, Peffault De Latour R et al. Clofarabine versus Fludarabine-based reduced-intensity conditioning regimen prior allogeneic transplantation in adult with AML/MDS. Cancer Medecine 2016; 5(11): 3068-3076.

6. Le Bourgeois A, Labopin M, Leclerc M, de Latour RP, Bourhis JH, Ceballos P, Orvain C, Wallet HL, Bilger K, Blaise D, Rubio MT, Guillaume T, Mohty M, Chevallier P; Société Francophone de Greffe de Moelle et de Thérapie Cellulaire. Clofarabine/busulfan-based reduced intensity conditioning regimens provides very good survivals in acute myeloid leukemia patients in complete remission at transplant: a retrospective study on behalf of the SFGM-TC. Oncotarget. 2018 Nov 27;9(93):36603-36612.

APPENDIX 4: DATA AND SAFETY MONITORING COMMITTEE COMPOSITION

Name	**Area of medicine**	**Name and address of institution**
Zinaida PERIC	hematologist	University Hospital Centre Zagreb, Zagreb, Croatia
Xavier POIRE	hematologist	Cliniques universitaires Saint Luc, Bruxelle, Belgique
Aline SCHMIDT	hematologist	CHU Angers, Angers, France

DSMB OPERATING CHARTER

1. DESCRIPTION – MISSIONS

Le Comité Indépendant de Surveillance (*Data and Safety Monitoring Board – DSMB*) est un comité consultatif composé de personnes compétentes dans le domaine des essais cliniques (pathologie, méthodologie, sécurité et éthique), et non impliquées dans l'étude. Ce comité est chargé d'analyser les données de l'étude et de fournir au promoteur et à l'investigateur coordinateur de l'étude un avis sur le rapport risque-bénéfice de l'essai clinique, notamment en ce qui concerne sa sécurité. Il peut proposer au promoteur des recommandations sur l'avenir de l'étude (poursuite, modification, arrêt, etc.)

La participation au DSMB se fait sur une base volontaire après signature d'un accord de confidentialité et absence de conflit d'intérêt.

2. NOMINATION - MODIFICATION - DISSOLUTION DU DSMB

Les membres du DSMB sont nommés pour toute la durée de l'étude. En cas d'indisponibilité, ils désignent un suppléant qui est soumis au même accord de participation. Le quorum requis pour chaque réunion est de 3 membres minimum.
La composition du comité ne sera pas modifiée pendant toute la durée de l'essai clinique, sauf demande expresse du DSMB lui-même ou en cas de force majeure.
Le DSMB sera dissous après la fin de l'essai clinique par le promoteur. Chaque membre sera informé individuellement par le promoteur des principaux résultats de l'étude.

3. ORGANISATION

3.1 *CALENDRIER*

La première réunion sera une réunion de lancement et doit être programmée dans la mesure du possible avant l'obtention des autorisations de l'étude, et en tout état de cause avant la première inclusion. Au cours de cette réunion de lancement, les membres du comité, avec le soutien de l'équipe de projet du promoteur :

- désigneront un président-animateur et un secrétaire de séance
- valideront les modalités des réunions définies avec le promoteur, le type de réunions et la logistique nécessaire (téléphone, salle, etc.), et la fréquence des futures réunions (par ex. tous les X patients inclus, changement de doses tous les X événements observés),
- devront définir/valider les données de l'étude requises et nécessaires qui devront être mises à disposition avant les réunions et qui serviront de bases à l'évaluation faite par le DSMB.

Le promoteur de l'étude peut demander des réunions extraordinaires en cas d'effet indésirable grave ou de faits nouveaux de sécurité. Les membres du DSMB peuvent aussi demander une réunion exceptionnelle en cas d'information d'intérêt majeur dont ils auraient connaissance.

Le calendrier prévisionnel des réunions défini est le suivant : une réunion à 25%, 50%, 75% des patients inclus et en fin d'étude.

3.2 *DÉROULEMENT DES RÉUNIONS*

L'ordre du jour contient la liste des questions pour lesquelles le promoteur et/ou le coordinateur demandent une aide à la décision ; le président-animateur, désigné lors de la première réunion, peut également ajouter toute question pertinente à l'ordre du jour; les membres du DSMB peuvent, quant à eux, aborder toute question qui leur semble importante et pertinente. Un avis de concertation finale du DSMB sous forme de compte-rendu formalisé (*0062-IM-031 trame de compte-rendu de réunion de concertation des membres du DSMB*), pré-rédigé par le chef de projet, est rédigé par un membre désigné, et validé par l'ensemble du DSMB.

Environ 7 jours avant chaque réunion, le chef de projet enverra aux membres du DSMB toutes les informations pertinentes disponibles (le cas échéant) :

- Mise à jour de la version du protocole actuelle
- Etat des inclusions (entrées et sorties d'étude)
- Bilan des monitorings (déviation, etc.)
- Données statistiques disponibles
- Liste SAE / AE
- Point spécifique selon les besoins
- Informations complémentaires (alertes, bibliographie, autres études, etc.)

Pour chaque réunion, le chef de projet remplira une liste de présence et devra s'assurer du quorum.

Chaque réunion se déroulera en deux temps : une session ouverte et une session fermée. Lors de la session ouverte, discussion sur le déroulement de l'étude, l'avancement des inclusions, le respect du protocole, les déviations et les problèmes rencontrés ; les représentants du promoteur, les investigateurs (en particulier le coordinateur) peuvent assister à cette session ouverte afin de répondre aux questions, de fournir tout document annexe si besoin.
Seuls les membres du DSMB peuvent assister à la session fermée : les données de l'étude, et en particulier les données de sécurité, y seront discutées et analysées.
La réunion de lancement de l'étude peut ne comporter qu'une session ouverte.

3.3 *DÉCISION DU DSMB*

Les recommandations du DSMB peuvent être (mais ne sont pas limitées à) :

- Poursuite de l'étude sans modification
- Poursuite de l'étude avec amendement
- Suspension des inclusions
- Arrêt de l'étude

Les délibérations du DSMB sont confidentielles, seules leurs conclusions et l'avis final du DSMB seront diffusés ; le président-animateur sera responsable de la transmission de cet avis final au promoteur (*0062-IM-031 trame de compte-rendu de réunion de concertation des membres du DSMB*). Cet avis final doit être transmis dès la fin de la réunion.

3.4 *PRISE EN COMPTE DE LA DECISION DU DSMB*

L'avis du DSMB est consultatif. Le promoteur n'est pas tenu de suivre cet avis ; cependant, une forte divergence d'appréciation nécessite de justifier les raisons par écrit auprès du DSMB et, le cas échéant, de l'autorité compétente et du comité d'éthique.

3.5 *DIFFUSION DE LA DECISION DU DSMB*

Tous les rapports d'avis du DSMB seront archivés dans le dossier principal de l'essai du promoteur ; ils peuvent être consultés à tout moment par les autorités compétentes.
Si la décision entraîne une modification de l'étude, l'avis du DSMB sera transmis à l'autorité compétente, au comité d'éthique dans le rapport annuel de sécurité et, si nécessaire, aux investigateurs de l'étude.

Si des mesures de sécurité urgentes doivent être mises en place, y compris l'arrêt temporaire ou permanent de l'essai, l'autorité compétente et le comité d'éthique seront informés dans les délais réglementaires.

APPENDIX 5 : PERFORMANCE STATUS - OMS

0	Capacité d'une activité identique à celle précédant la maladie sans aucune restriction
1	Activité physique diminuée mais ambulatoire et capable de mener un travail
2	Ambulatoire et capable de prendre soin de soi; incapable de travailler ; alité moins de 50 % de son temps
3	Nécessitant seulement quelques soins; alité ou en chaise plus de 50 % du temps
4	Incapable de prendre soin de lui-même; alité ou en chaise en permanence

APPENDIX 6 : DISEASE RISK INDEX (DRI) FROM ARMAND ET AL, BLOOD 2014.

Table 4. Refinement of the DRI

Disease	Stage	No. of patients	HR*	Original DRI	Percentage of patients	New DRI Group	2-y OS (%)	95% C
Hodgkin lymphoma CR		126	0.36	Int	14	Low	66	63-68
CLL CR		81	0.47	Low		Low		
Mantle cell lymphoma CR		160	0.51	Int		Low		
Indolent NHL CR		183	0.53	Low		Low		
AML favorable cytogenetics CR		190	0.64	Low		Low		
Indolent NHL PR		276	0.71	Low		Low		
CLL PR		400	0.78	Low		Low		
CML chronic phase 1/2		390	0.82	Low		Low		
CML advanced phase		69	0.92	Int	63	Int	51	50-52
Mantle cell lymphoma PR		149	0.95	Int		Int		
Myeloproliferative neoplasm	Any	426	0.98	Int		Int		
AML intermediate cytogenetics CR		3611	Ref	Int		Int		
ALL CR1		1023	1.00	Int		Int		
T-cell NHL CR		171	1.00	Int		Int		
Multiple myeloma CR/VGPR/PR		339	1.03	Int		Int		
Aggressive NHL CR		181	1.05	Int		Int		
Low-risk MDS adverse cytogenetics	Early†	103	1.06	High		Int		
T-cell NHL PR		164	1.06	Int		Int		
Low-risk MDS intermediate cytogenetics	Early†	516	1.09	Int		Int		
HL PR		225	1.09	Int		Int		
Low-risk MDS intermediate cytogenetics	Advanced†	235	1.18	Int		Int		
Indolent NHL	Advanced†	128	1.21	Int		Int		
CLL	Advanced	265	1.22	Int		Int		
High-risk MDS intermediate cytogenetics	Early	364	1.24	Int		Int		
Aggressive NHL PR		205	1.26	Int		Int		
T-cell NHL	Advanced†	93	1.41	High	20	High	33	31-35
AML favorable cytogenetics	Advanced†	34	1.42	Int		High		
HL	Advanced†	85	1.48	High		High		
High-risk MDS intermediate cytogenetics	Advanced†	179	1.56	Int		High		
High-risk MDS adverse cytogenetics	Early	80	1.58	High		High		
ALL CR2		407	1.58	Int		High		
AML adverse cytogenetics CR		175	1.59	High		High		
Mantle cell lymphoma	Advanced†	46	1.59	High		High		
High-risk MDS adverse cytogenetics	Advanced†	30	1.59	Very high		High		
BL‡ CR		23	1.65	NA		High		
Multiple myeloma	Advanced†	150	1.65	High		High		
ALL CR3		61	1.70	Int		High		
Low-risk MDS adverse cytogenetics	Advanced†	32	1.86	Very high		High		
AML intermediate cytogenetics	Advanced	1227	1.89	High		High		
CML blast phase		52	2.02	Int	4	Very high	23	20-27
ALL	Advanced†	235	2.23	High		Very high		
Aggressive NHL	Advanced†	154	2.54	High		Very high		
AML adverse cytogenetics	Advanced †	76	2.83	Very high		Very high		
BL‡ PR	Advanced †	12	5.21	NA		Very high		

Int, intermediate.
*Hazard ratio for mortality compared with AML intermediate cytogenetics in CR1.
†Advanced stage refers to induction failure or active relapse, including stable or progressive disease for NHL, HL, and CLL.
‡Those categories were not included in the original DRI.

APPENDIX 7 : SORROR SCORE (FROM SORROR AND AL, BLOOD 2005).

COMORBIDITE		SCORE	
Arythmie	Fibrillation auriculaire ou flutter ; Maladie rythmique auriculaire; arythmie ventriculaire	1	
Atteinte Cardiaque	Coronaropathie*, Infarctus du myocarde, Insuffisance cardiaque congestive, FES ≤ 50%	1	
Diabète	Nécessitant un traitement médicamenteux (insuline ou hypoglycémiants oraux) mais pas une simple diète	1	
Maladie inflammatoire du tube digestif	Maladie de Crohn ou RCH	1	
Atteinte cérébro-vasculaire	Accident ischémique transitoire ou accident vasculo-cérébral	1	
Désordre psychiatrique	Nécessitant une prise en charge ou un traitement spécialisé	1	
Atteinte hépatique légère	Hépatite chronique, bilirubine ≤ 1.5 x la normale ; ASAT ou ALAT ≤ 2.5 x la normale	1	
Obésité	Index de Masse Corporelle > 35 kg/m²	1	
Infection	Infection nécessitant la continuation d'un traitement antimicrobien après jour 0	1	
Atteinte rhumatologique	LED, polyarthrite rhumatoïde, polymyosite, connectivite, fibromyalgie	2	
Ulcère peptique	Nécessitant un traitement	2	
Atteinte Pulmonaire modérée	DLCO ou VEMS > 65% et < 80% ou dyspnée lors d'une activité modérée	2	
Atteinte Rénale modérée ou sévère	Créatinine > 180 µmol/L (2 mg/dl)	2	
ATCD de Tumeur solide	Traitée à n'importe quel moment dans l'histoire du patient (sauf cancer cutané non mélanome)	3	
Valvulopathie cardiaque	Sauf prolapsus de la valve mitrale	3	
Atteinte pulmonaire sévère	DLCO ou VEMS ≤ 65% ou dyspnée au repos ou nécessitant une oxygénothérapie	3	
Atteinte Hépatique modérée ou sévère	Modérée ou sévère : cirrhose ; fibrose ; bilirubine > 1.5 x la normale ; ASAT ou ALAT > 2.5 x la normale	3	
		Total	

APPENDIX 8 : ELN 2022 CLASSIFICATION (FROM DOHNER ET AL, BLOOD 2022)

Table 6. 2022 European LeukemiaNet (ELN) risk classification by genetics at initial diagnosis[a]

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[b,c] • Mutated *NPM1*[b,d] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*[e]
Intermediate	• Mutated *NPM1*[b,d] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype,[h] monosomal karyotype[i] • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*[j] • Mutated *TP53*[k]

APPENDIX 9 : SUMMARY OF PRODUCT CHARACTERISTICS FOR CLOFARABINE

http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0390498.htm

APPENDIX 10 : SUMMARY OF PRODUCT CHARACTERISTICS FOR FLUDARABINE

http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0232698.htm

ANNEXE 11 : COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE), VERSION 5.0, PUBLISHED ON NOVEMBER 27, 2017

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf