Phase III study comparing GVHD prophylaxis with ATG-thymoglobulin to ATLG-grafalon in elderly patients with acute myeloid leukemia or myelodysplatic syndrome and receiving an allogeneic hematopoietic stem cell transplantation with a 10/10 HLA matched unrelated donor following a reduced intensity conditioning regimen by fludarabine-treosulfan

OPTISAGE

CLINICAL TRIAL ON MEDICINAL PRODUCT FOR HUMAN USE

Version N°2.0 dated 17/06/2024
Project Code: APHP230276 / EU CT number: 2023-504555-27-00

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Version no.2.0 dated: 17/06/2024

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

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CHANGE HISTORY

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1 SUMMARY

Full title	Phase III study comparing GVHD prophylaxis with ATG-thymoglobulin to ATLG-grafalon in elderly patients with acute myeloid leukemia or myelodysplatic syndrome and receiving an allogeneic hematopoietic stem cell transplantation with a 10/10 HLA matched unrelated donor following a reduced intensity conditioning regimen by fludarabine-treosulfan
Acronym/reference	OPTISAGE / APHP230276 / EU CT n°2023-504555-27-00
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Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative therapy in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Most of the patients requiring an allo-HSCT are above 50 years of age and are transplanted with a reduced intensity conditioning (RIC) regimen. The optimal RIC and GVHD prophylaxis regimen allowing a good control of the disease while preventing GVHD remains to be determined for elderly patients. A phase III trial comparing the conventional RIC fludarabine-busulfan 2 days to fludarabine-treosulfan demonstrated an advantage for the flu-treosulfan arm in terms of event free survival (EFS), that should therefore be considered as the new standard of RIC regimen for AML and MDS. GVHD prevention has a crucial role in post-transplant outcomes by potentially interfering with the graft-versus-leukemia (GVL) effect and immune reconstitution. Anti-thymocyte globulins (ATG) are recommended to reduce the risk of acute and chronic GVHD in transplants performed with matched unrelated donors. However, the optimal type of ATG between the 2 approved brands (ATG-thymoglobulin and ATLG-grafalon) displaying distinct characteristics and the optimal dose of ATG are still unknown. In a retrospective study of patients transplanted mainly with RIC with matched related and unrelated donors for haematological malignancies, we observed that ATLG was associated with a reduction of grade II-IV acute GVHD in comparison to ATG without increasing the incidence of relapse.

	In this phase III randomized study, we propose to compare GVHD prevention with ATG versus ATLG in AML and MDS patients above 50 years of age transplanted with a matched unrelated donor following a fludarabine-treosulfan RIC, with the hypothesis that ATLG would better control GVHD in this population of patients thus limiting the risk of morbidity and mortality of the procedure.
Main objective and primary endpoint	**Main objective:** to compare the incidence of grade II-IV acute GVHD at day 100 post-transplantation in MDS or AML patients transplanted with a 10/10 matched unrelated donor (MUD) following a reduced intensity conditioning with fludarabine-treosulfan between patients receiving a GVHD prophylaxis with ATG-thymoglobulin versus ATLG-grafalon. **Primary endpoint** Incidence of grade II-IV acute GVHD according to the MAGIC classification (Appendix 19.9 Section 1) at day 100 post-transplantation.
Secondary objectives and endpoints	**Secondary objectives**: 1. To evaluate the effect of the 2 GVHD prophylaxis on the engraftment and graft failure, 2. To evaluate the effect of the 2 GVHD prophylaxis on the incidence of grade I acute GVHD and of chronic GvHD, 3. To evaluate the effect of the 2 GVHD prophylaxis on incidence of infections 4. To evaluate the effect of the 2 GVHD prophylaxis on progression free survival 5. To evaluate the effect of the 2 GVHD prophylaxis on relapse incidence 6. To evaluate the effect of the 2 GVHD prophylaxis on non-relapse mortality 7. To evaluate the effect of the 2 GVHD prophylaxis on overall survival 8. To evaluate the effect of the 2 GVHD prophylaxis on GVHD and relapse free survival (GRFS) 9. To evaluate the effect of the 2 GVHD prophylaxis on health-related Quality of life (FACT BMT) 10. To evaluate the effect of the 2 GVHD prophylaxis on chimerism 11. To evaluate the effect of the 2 GVHD prophylaxis on immune reconstitution (T, B, NK, regulatory T cell levels in the peripheral blood) 12. To evaluate the effect of the 2 GVHD prophylaxis on days of hospitalisation during the first 12 months post-transplantation

	13. To evaluate the effect of the 2 GVHD prophylaxis on incidence and severity of VOD 14. To identify prognostic factors associated with the primary endpoint for each prophylaxis arm: search for treatment-by-covariate interactions on the primary endpoint 15. To evaluate the effect of the 2 GVHD prophylaxis on the incidence of late acute GvHD (after day 100), overlap syndromes and chronic GvHD. **Secondary endpoints:** 1. Hematopoietic recoveries: at least 7consecutive days with neutrophils > 0.5 G/L, with platelets > 20 G/L 2. Immune reconstitution by analyzing T, B, NK, regulatory T cell and gammaglobulin levels in the peripheral blood at M1, D+100, M6, M12 and M24 post-transplantation 3. Chimerism at M1, D+100, M6, M12 4. Grade I acute GVHD incidence (Appendix 19.9, section 1) and acute GvHD treatments: first line treatment, response to steroids, treatment courses for refractory acute GVHD 5. Chronic GvHD incidence (date and grading) at M12 and M24 (NIH classification [48], Appendix 19.9 section 4) 6. Relapse incidence at M12 and M24 (relapse will be defined by the reappearance of leukemic cells or MDS features after allo-HSCT in the bonne marrow (cytology +/- cytogenetic analysis from bone marrow aspiration) or extra-medullary sites (proven by a biopsy). 7. Progression free survival at M12 and M24 8. Severe infections (CTAE grade 3-4) at D+100 and M12 will be fully described 9. Incidences of CMV and EBV reactivations at D+100, M6 and M12 10. Non-relapse mortality at M6, M12 and M24 11. Overall survival at M12 and M24 12. GVHD and relapse free survival (GRFS) defined by being alive without disease relapse and without having developed acute grade III-IV or severe chronic GVHD 13. Health-related Quality of life, assessed by using the FACT-BMT-v4 questionnaire at inclusion and at D+100, M6, M12 post-transplantation

	14. Number of days of hospitalization for the transplant and after the hospitalization for transplantation related complications until M12 15. Incidence and severity of VOD at D+100 16. Lymphocyte counts on standard blood counts before conditioning (D-7) 17. Late acute GvHD, overlap syndromes and chronic GvHD from D+100 to D+120.
Design of the study	Phase III multicenter randomized, controlled open-label trial, comparing GVDH prophylaxis with ATG versus ATLG in patients with AML or MDS transplanted with a MUD following fludarabine-treosulfan RIC.
Category	Cat 3: Low intervention
Population of study participants	Patients above 50 years of age presenting AML or MDS with an indication for allogeneic stem cell transplantation
Inclusion criteria	1. Age ≥ 50 and ≤ 70 years 2. Patient between 50 and 55 years should be unfit for a myeloblative conditioning. 3. AML requiring allogeneic stem cell transplantation (intermediate or high-risk AML) in complete cytologic response (CR1 or above) **or** MDS requiring allogeneic stem cell transplantation (IPSS≥ 1.5 or IPSS-R > 4.5 or IPSS-R > 3-4.5 with risk features [rapide blast increase, life-threatening neutropenia (<0.3 G/L) or thrombopenia (<30G/L) or high transfusion needs (>2/month for 6 months)] 4. Without an HLA matched related donor 5. Having an identified matched HLA 10/10 unrelated donor 6. With usual criteria for HSCT: a) ECOG performans status ≤ 2 b) No severe and uncontrolled infection c) Cardiac left ventricular ejection fraction ≥50% d) Lung DLCO > 40% e) Adequate organ function: ASAT and ALAT ≤ 3N, total bilirubin ≤ 2N, creatinine clearance ≥ 50 mL/min (except if those abnormalities are linked to the hematological disease) 7. With health insurance coverage 8. Having signed a written informed consent 9. Contraception methods must be prescribed during all the duration of the research NB: The authorized contraceptive methods are:

	- *For women of childbearing age and in absence of permanent sterilization*: oral, intravaginal or transdermal combined hormonal contraception - oral, injectable or implantable progestogen-only hormonal contraception - intrauterine device (IUD) - intrauterine hormonal releasing system (IUS) - bilateral tubal occlusion - vasectomised partner - sexual abstinence (only if this the preferred and usual lifestyle of the participants) - *For man in absence of permanent sterilization*: sexual abstinence, condoms
Exclusion criteria	1. Carcinomas in the last 5 years (except basal cell carcinoma of the skin or “in situ” carcinoma of the cervix) 2. Uncontrolled infection 3. Seropositivity for HIV or HTLV-1 or active hepatitis B or C 4. Yellow fever vaccine and all others live virus vaccines within 2 months before transplantation 5. Heart failure according to NYHA (II or more) or Left ventricular ejection fraction < 50%. 6. Lung DLCO ≤ 40% 7. Preexisting acute hemorrhagic cystitis 8. Renal failure with creatinine clearance < 50ml / min 9. Pregnancy (β-HCG positive) or breast-feeding 10. Patients with any debilitating medical or psychiatric illness, which would preclude the realization of the SCT or the understanding of the protocol 11. Patient under state medical aid 12. Patient under legal protection (protection of the court, or in curatorship or guardianship). 13. For Grafalon: Any contraindication mentioned in the SmPC of GRAFALON 14. For Thymoglobulin: Hypersensitivity to rabbit proteins or to any of the excipients 15. Participation in other clinical trials on medicinal products for human use or being in the exclusion period at the end of a previous study 16. Any contraindication mentioned in the SmPC of all auxiliary medicinal products planned to be used in the trial: cyclosporine, mycophenolate mofetil, fludarabine, treosulfan
Investigational medicinal product(s)	*Phase III* • Grafalon: 10 mg/Kg/day IV for 3 consecutive days (day -3 to -1 before transplantation)

	• Thymoglobuline: 5 mg/Kg IV over 2 to 3 days before transplantation
Transplantation modalities	**1. Conditionning regimen**: All patients will receive the same conditioning regimen: - fludarabine 30 mg/m2/day IV for 5 days (day-6 to day-2) - treosulfan 10 g/m2/day IV for 3 days (day -4 to day -2) **2. Donor and Stem Cell source:** HLA 10/10 matched unrelated donor Only GCSF-mobilized peripheral blood stem cells will be accepted, CD34 target dose ≥4 × 10^6/kg of body weight **3. GVHD Prophylaxis:** Prophylaxis of GvHD will depend on the randomization arm: -ATLG-grafalon 10 mg/Kg/day IV for 3 consecutive days (day -3 to -1) (ATLG-grafalon) **OR** -ATG-thymoglobuline (ATG-Thymo): Two schedules of administration of anti-thymocyte globulin (ATG) are accepted: 2.5 mg/kg/day IV for 2 consecutive days (day-3 and -2). **OR** 0.5 mg/kg IV on day -4, followed by 2 mg/kg IV on day -3 and 2.5 mg/Kg on day -2. In addition, patients will receive cyclosporine (CsA) (3 mg/kg/day) and mycophenolate mofetil (MMF) (30 mg/kg/day) as follows: CsA from Day-1 to month 4 or 6 after a progressive withdrawal starting by 3 months post-SCT if no aGvHD and according to the practice of the center and MMF from Day + 1 to Day +45 in both arms
Interventions added for the study	– Randomisation (ratio 1:1) between ATG and ATLG for GVHD prophylaxis. – Health-related Quality (FACT-BMT v4) of life at D+100, M6, M12 – Biological studies and biocollection: o PK of ATLG from frozen plasma 5 ml (1 tube 5ml with EDTA) on days -3, -2, -1 and on D0, D14, D28, D60 and D+100 in accordance with the decree of February 17, 2021. o Biocollection of blood PBMCs, plasma and dry pellets 28 ml (4 tubes 7 ml with EDTA) at point: D-9 (base line), D+100, M6 and M12 (via cryostem) and at D14, D21 D28, M2 40 ml (5 tubes 8 ml with

	EDTA), in accordance with the decree of February 17, 2021.
Ancillary study	– Bio collection of PBMC, plasma and dry pellets from total blood cells will be performed on D-9 (base line), D14, 21, 28, 56, 100, M6 and M12 in 60 patients per arm for future biological studies that would be performed after finding complementary funding. The collections will be organized via Cryostem. In order to better understand the modulation of the immune response between the two ATG brands. – Plasma collection for ATG PK analysis in the ATLG arm (samples collected before and after each administration of ATLG on days-3 to -1 and at Day 0, 14, M1, M2 and D+100, frozen in each center). Data will be analyzed according to pre-conditioning lymphocyte counts and correlated to post-transplant outcomes (GVHD, relapse, NRM) to be able to determine of a formula to optimize ATLG dose to lymphocyte counts for future studies. This plasma collection will start including patients after finding complementary funding.
Expected benefits for the participants and for society	We expect to demonstrate a benefice in terms of reduction of acute GVHD in the ATLG arm and to improve the outcome of elderly AML and MDS patients
Number of participants included	324
Number of centres	26 in France
Duration of the study	Inclusion period: 36 months Participation period: 24 months Total duration: 60 months
Number of enrolments expected per site and per month	0.35 patients/month/centre
Statistical analysis	Our hypotheses are based on a reduction on the incidence on day 100 post-HSCT of grade II-IV acute GVHD from 40% (ATG arm) to 23% (ATLG arm), and assuming a 10% risk of randomised patients who would not reach transplant and an incidence of 5% for the competing risk (death without GvHD) in each arm. When accounting for competing risks, a two-sided logrank test with an overall sample size of 324 subjects (162 in the control group and 162 in the treatment group) achieves 91% power at a 0,05 significance level to detect a hazard ratio of 0,50 with a follow-up time of 100 days. In total, 162+162=324 patients will be included. No interim analysis is scheduled to be performed..
Funding sources	The study is funded by industrial support from NEOVII and MEDAC

Study will have a Data Safety Monitoring Board	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative therapy in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Most of the patients requiring an allo-HSCT are above 50 years of age and are transplanted with a reduced intensity conditioning (RIC) regimen. Older recipient age is also associated with an increased risk of graft-versus-host-disease (GVHD), a major complication of allo-HSCT, responsible for a high morbidity and a probability of mortality of about 20% in this population of patients. In addition, disease relapse after transplantation with RIC occurs in more than 30% of patients transplanted for AML or MDS Thus, the probability of event free survival (EFS), in patients transplanted for AML or MDS with a matched unrelated or related donor above 50 years of age is between 40 and 50% at 2 years and needs to be improved [1, 2].

The optimal conditioning and GVHD prophylaxis regimen allowing a good control of the disease while preventing GVHD remains to be determined for elderly patients. The most frequently RIC regimen used in France is fludarabine-busulfan 6.4 mg/kg (Flu-Bu2). A phase III trial comparing Flu-Bu2 to Fludarabine-Treosulfan reported an improved 2-year EFS with fludarabine-treosulfan, mainly because of a reduction of transplant related mortality [3]. Thus, fludarabine-treosulfan should be considered as the new standard of RIC regimen for AML and MDS.

The prevention of GVHD has a crucial role in post-transplant outcomes by potentially interfering with the graft-versus-leukemia (GVL) effect, immune reconstitution, and the risk of fatal infections. Anti-thymocyte globulins (ATG) are recommended to reduce the risk of acute and chronic GVHD in transplants performed with matched unrelated donors [4]. However, the optimal type of ATG between the 2 approved brands (ATG-thymoglobulin and ATLG-grafalon) displaying distinct characteristics and the optimal dose of ATG are still unknown after RIC regimen because of a potential induction of a higher relapse risk [4]. In a retrospective study of patients transplanted mainly with RIC with matched related and unrelated donors for haematological malignancies, we observed that ATLG was associated with a reduction of grade II-IV acute GVHD in comparison to ATG without increasing the incidence of relapse, leading to improved severe GVHD and relapse free survival (GRFS) in the ATLG group [5].

In this phase III randomized study, we propose to compare GVHD prevention with ATG versus ATLG in AML and MDS patients above 50 years of age transplanted with a matched unrelated donor following a fludarabine-treosulfan RIC, with the hypothesis that ATLG would better control GVHD in this population of patients thus limiting the risk of morbidity and mortality of the procedure.

2.2 Description of knowledge relating to the condition involved

Results of allo-HSCT for AML and MDS in elderly patients

Despite progress in chemotherapy, targeted therapy and immunotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the main curative procedure for acute myeloid leukemias of intermediate and high cytogenetic and molecular risks, as well as in higher risk MDS (IPSS score ≥2 or IPSS-R ≥3.5). Two donors versus no donor retrospective

studies performed in AML and MDS patients, respectively, showed an advantage of overall survival in patients having a donor and receiving allo-HSCT [2, 6]. The therapeutic advantage of allo-HSCT over chemotherapy is related to the graft-versus-leukemia (GVL) effect developed from the immunocompetent cells contained in or generating from the hematopoietic stem cell graft. AML and MDS in the elderly are characterized by higher cytogenetic and molecular risks and are more prone to chemo-refractoriness and relapse [7]. Allo-HSCT is therefore often the only curative option in most of those patients. However, despite its unique antitumoral activity, allo-HSCT is restricted to a limited number of patients mainly due to the toxicity of the procedure for patients above 50 years of age. While intensive myeloablative conditioning regimens might better control disease burden and reduce post-transplant relapse, such conditionings are highly toxic above 50 years [8]. Reduced intensity conditionings have therefore been developed to reduce the toxicity of the procedure.

The most common RIC used in France is the combination of fludarabine (150 mg/kg), 2 days of intravenous busulfan (6.4 mg/kg) and ATG (mainly thymoglobulin 5 mg/kg) with sibling donors or matched unrelated donors (MUD). Retrospective studies of AML transplanted in complete remission with this conditioning in France and Europe have reported 2-year non-relapse mortality of 13-20%, relapse incidence of 28-35%, leukemia free survival of 50-55% with an incidence of severe acute and chronic GVHD of 24-30% [9-11]. Similar results have been reported in transplanted MDS (3 year non relapse mortality of 19% relapse incidence of 43%, LFS of 44%) [12].

Although there is no randomized prospective studies, large retrospective studies from the EBMT or the CIBMTR comparing fludarabine-busulfan to fludarabine-melphalan or thiotepa-fludarabine-busulfan reduced intensity conditionings failed to demonstrate an advantage of the other conditioning regimens for AML patients with similar overall and leukemia free survivals despite potential reduction of relapse rates associated with higher non-relapse mortality after fludarabine-melphalan [13-15].

Incidence of acute GVHD is highly variable between studies and is dependent on the type of donor, recipient age, the intensity of the conditioning regimen, disease status at transplantation and the type of GVHD prophylaxis [16, 17]. In a retrospective studiy using the conventional RIC Flu-Bu2-ATG thymoglobulin RIC in AML patients above 50 years of age transplanted with a matched unrelated donor, the incidence of grade II-IV acute GVHD was between above 40% with 33% of grade III-IV [18].

There is therefore a crucial need to improve the results of allo-SCT for elderly AML and MDS patients by reducing the incidences of severe acute GVHD and of relapse while maintaining a low rate of non-relapse mortality.

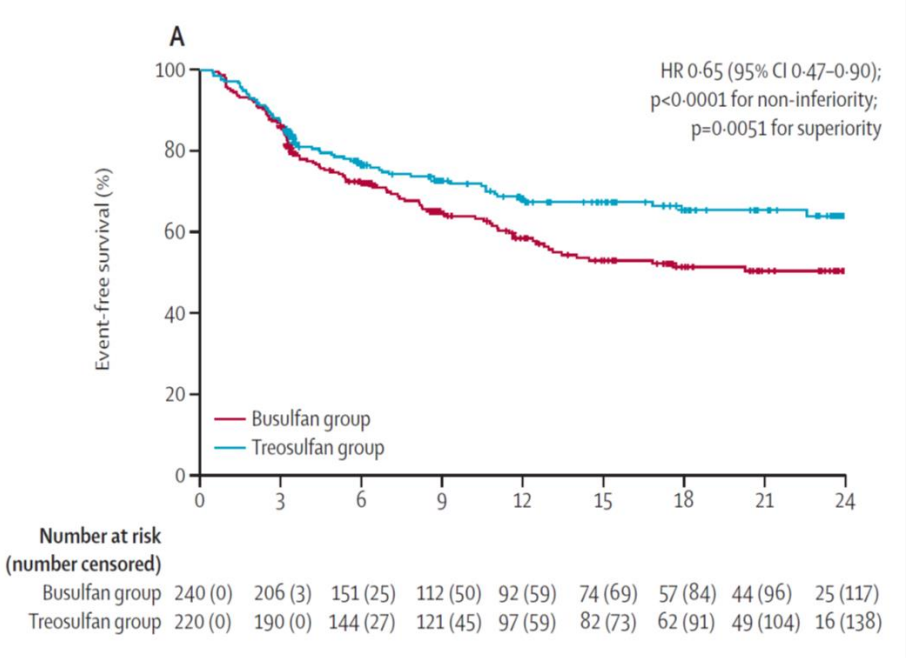
2.3 Summary of relevant pre-clinical experiments and clinical trials
Justification of the use of Fludarabine-treosulfan RIC conditioning

Treosulfan has been approved for conditioning of allo-HSCT. Retrospective studies suggest that treosulfan might have a lower toxicity profile compared to busulfan and a higher anti-leukemic effect [19, 20]. Patients receiving treosulfan developed less mucositis and GVHD as compared to those receiving myeloablative doses of busulfan without increase of relapse [20].

In both studies, relapse risk was reduced with treosulfan in comparison to busulfan-based reduced intensity conditioning (RIC) [19, 20].

A prospective phase III European multicentric randomized trial performed in patients with AML and MDS compared fludarabine-busulfan to fludarabine-treosulfan RIC, both arms received ATG or ATLG in case of matched unrelated donor [3]. The study primary endpoint was 2-year EFS with an hypothesis of non-inferiority and the possibility to demonstrate a superiority. The study enrolled 240 and 220 patients in the busulfan and treosulfan groups, respectively. Two-year event free survival was 64·0% (95% CI 56·0–70·9) in the treosulfan group and 50·4% (42·8–57·5) in the busulfan group (HR 0·65 [95% CI 0·47–0·90]; p<0.0001 for non-inferiority and p=0.0051 for superiority) [3].

Figure 1: Event-free survival (EFS) in the fludarabine-treosulfan versus fludarabine-busulfan RIC randomized study [3]



The advantage in EFS in the treosulfan group was particularly significant in patients transplanted with a matched unrelated donor (HR=0.61, 95% CI 0.42-0.9, p=0.012) and in patients older than 50 years (HR=0.65, 95% CI 0.47-0.91, p=0.013) [3].

Overall survival at 2 years was 71.3% and 56.4% in the treosulfan and busulfan groups, respectively (HR=0.61, 95% CI 0.42-0.88). The differences are explained by reduced 2-year toxicity related mortality in the treosulfan group (12.1% versus 28.2%, HR=0.54, 95% CI 0.32-0.91). Relapse incidence at 2 years was similar in both groups (23.3% versus 24.6%, HR=0.87, 95% CI 0.59-1.30) [3].

Thus, the results of this unique randomized trial on the type of reduced intensity conditioning suggest that fludarabine-treosulfan might now be considered as a new standard reduced intensity conditioning (RIC) for AML and MDS and is currently the referenced RIC in other European countries.

Impact of GVHD prophylaxis on post-transplant outcomes and justification of the choice of randomization of GVHD prophylaxis

Distinct GVHD prevention strategies have been progressively developed according to the type of stem cell source and the level of HLA compatibility between donor and recipient. In addition to standard post-transplantation immunosuppression with a calcineurin inhibitor and a cell-cycle inhibitor (methotrexate or mycophenolate mofetil), several prospective randomized studies have demonstrated the interest of adding anti-thymocyte globulin (ATG) to prevent acute and chronic GVHD without impairing the graft-versus leukemia (GVL) effect in the context of myeloablative conditioning regimens [21-24]. Reduction of severe chronic GVHD was also associated to an improvement of quality of life and of GRFS [4, 23, 25]. No randomized study has been performed with reduced intensity conditionings, but similar observations have been made from retrospective studies [10, 11].

Two brands of ATG have been approved for GVHD prophylaxis: ATG-thymoglobulin and ATLG-grafalon. They correspond to polyclonal IgG obtained from sera of rabbits immunized by either human thymocytes (ATG thymoglobulin) or human Jurkatt leukemic-T cell line (ATLG grafalon) [26]. They both deplete recipient T cells to avoid donor stem cell rejection and partially deplete potential alloreactive donor T cells contained in the hematopoietic stem cell graft. Because of their distinct origin, the 2 brands have distinct affinities to T and other immune cells in vitro [26, 27], which explains the differences of doses required to deplete T cells in vivo. Whether these distinct characteristics have an impact on their efficacy to deplete alloreactive T cells or other immune cells in vivo and prevent GVHD has never been explored in a prospective comparative study.

Furthermore, the dose of each ATG has an impact on transplant outcomes. Higher doses increase viral infections such as EBV and CMV reactivations and might also increase the risk of relapse, in particular with RIC [4]. Lower doses are associated with increased incidence of GVHD [28]. The recommended dose for ATG-Thymoglobulin is between 4.5 and 6 mg/kg in 2 or 3 days [10]. The optimal dose for ATLG-grafalon has not been determined yet but many groups have adopted the dose of 30 mg/kg for RIC and matched unrelated donors [29, 30].

Post-transplant cyclophosphamide (PT-Cy) represents another GVHD prophylaxis strategy in allo-HSCT. Administration of cyclophosphamide on days 3 and 4 after transplantation induces the depletion of early activated alloreactive donor T and preserves regulatory T cells [31]. Post-transplant cyclophosphamide was initially shown to efficiently prevent acute and chronic GVHD in haplo-identical stem cell transplantation [32, 33]. In matched related or unrelated donor transplants, PT-CY was superior to standard post-transplant GVHD prophylaxis without ATG in preventing acute and chronic GVHD (De Jong. ASH 2019). However, comparisons between PT-Cy and ATG showed comparable results in retrospective and prospective studies [34, 35].

In a retrospective study, including 64 patients having received ATLG to 50 patients receiving ATG for an allo-HSCT with matched related donors or MUD for distinct haematological malignancies and diverse conditioning regimen, we observed that the use of ATLG was associated with a reduction of the incidence of II-IV acute GVHD in both uni and multivariate analyses (cumulative incidence on day 100 of grade II-IV aGVHD: 49% with ATG vs 21.5%

with ATLG; HR (HR 0.36 [0.18–0.75], p=0.006) [5]. Biologically, in comparison to ATG, ATLG was associated with reduced IL-15 production during the first month post-HSCT that was compensated by higher production of IL-21; reduced proportions of TsCM CD8 T cells during the first 2 months after transplantation and significant reduction of the expression of PD1 on T CD4 and T CD8 memory cells suggesting reduced activation of T cells (manuscript under preparation). Thus, ATLG and ATG might have distinct effects on the regulation of allorective T cells leading to distinct regulation of the GVH/GVL effects after transplantation.

In this study, we propose to randomize for the first time the 2 brands of ATG in association with the fludarabine-treosulfan RIC in patients above 50 years of age and transplanted for AML or MDS.

Impact of GVHD prophylaxis on immune reconstitution and role of PK of ATG and lymphocyte counts

GVHD prophylaxis by ATG has an impact of post-transplant immune reconstitution, mainly by delaying naïve CD4 and CD8 T cell reconstitution [26, 36-38]. Delayed immune reconstitution in associated to increased risk of infections and relapse [39, 40]. Recent studies have shown that the clearance and pharmacokinetic of ATG thymoglobulin has an impact on immune reconstitution after allo-HSCT [41]. Remaining active ATG in the peripheral blood is measurable by flow cytometry. A slow clearance of active ATG is associated with slower immune reconstitution and increased risk of infections and/or relapse, while a fast clearance is associated with higher risk of GVHD and increased non-relapse mortality [41]. Clearance of ATG is related to the dose and type of ATG brand [42]. Furthermore, PK of ATG is influenced by lymphocyte counts before administration of ATG. At constant dose of ATG, patients with high lymphocyte counts will have a faster clearance of active ATG, while those with low lymphocyte counts will have a slower clearance. Thus, dose adaptation of ATG might be adapted to lymphocyte counts rather than to patient body weight [41, 43]. However, calculation of the optimal dose of ATG according to lymphocyte counts requires to perform an exploration of the correlations between lymphocyte counts before conditioning and PK of ATG for each conditioning regimen since the conditioning by itself has an impact on lymphocyte counts [41, 44].

We propose to explore in an ancillary study lymphocyte counts and PK of ATLG to determine a dose calculation formula adapted for the fludarabine-treosulfan RIC that could be further applied in future studies.

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

This study will be proposed to elderly patients aged above 50 years and having an indication of allogeneic stem cell transplantation for AML or MDS [45, 46]:

-intermediate and high-risk AML according to 2022 ELN AML classification (Appendix 19.9 section 2)

-high risk MDS patients as defined by
-IPSS ≥1,5 (Appendix 19.9 section 3a)
-or IPSS-R > 4.5 (Appendix 19.9 section 3b)

-or intermediate IPSS-R > 3-4.5 with poor-risk features: rapid blast increase [> 50% increase or reaching >15% BM blasts], life-threatening cytopenias [neutrophil counts < 0.3 G/L; platelet counts < 30 G/L), high transfusion intensity >2 units per months for 6 months

2.5 Identification and description of the investigational medication or medications

Considering the objective of the research, ATG and ATLG will be considered as investigational medicinal products (IMP). They are both products authorized for a long time and available under the names:

- Thymoglobuline®: anti-human thymocytes rabbit globulin, 25 mg/5 ml per vial.
- Grafalon®: anti-human lymphocytes rabbit globulin, 20 mg/ml, available as 40 mg or 100 mg vials.

Their marketing authorisations include either GVHD prevention following HSCT, or HSCT conditioning.

Others medicinal products, including fludarabine and treosulfan, will be considered as auxiliary medicinal products.

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

Grafalon: the SmPC will be followed.

Thymoglobuline: According to the SmPC, in case of prevention of GVHD, it is recommended to use 2.5mg/kg/day from day -4 to day -2 or -1 resulting in a cumulative dose of 7,5 to 10 mg/kg.
In this study, ATG-thymo will be used following two possible schedules of administration, depending on the investigator's usual practice, the cumulative dose being 5mg/kg for both schedule:

- either at 2,5 mg/kg/day from day -3 to day -2
- or at 0.5mg/kg at day -4, then 2mg/kg at day -3, then 2.5mg/kg at day -2.

As described in previous sections of this protocol, several studies have tried to identify the optimal dose of ATG-thymo with a reduced conditioning, by comparing doses ranging from 2.5 to 10 mg/kg (Crocchiolo, 2013)(Devillier, 2013)(Remberger, 2013)(Butera, 2021). They have showed that the dose of 2.5 mg/kg was inefficacious to reduce the risk of GVHD and that doses above 6 mg/kg were associated with a higher risk of flare and mortality due to infections. These results were confirmed by an American study showing that the probability of survival without flare and without severe GVHD was higher with a dose of 4.5 mg/kg than with 7.5 mg/kg in patients transplanted for an acute myeloid leukemia with an unmatched 10/10 HLA donor and attenuated conditioning (Bashir, 2012). Based on these studies, the recommended dose of ATG-thymo with a reduced or attenuated conditioning for HLA 10/10 donor is 4.5 to 6 mg/kg (Baron, 2017) and the dose used in France is 5 mg/kg.
The second scheme (increasing doses) has been proposed to reduce the intensity of the immune-allergic reaction responsible for fever, skin reaction and potentially blood pressure drop, a frequent side effect mainly observed during the first infusion of ATG (4). Both administration schedules have shown to prevent the occurrence of graft versus host disease (2, 3). In addition, it is known from pharmacokinetic studies that the clearance of ATG takes several weeks suggesting that the administration of a first 10% of the total dose will not dramatically change the pharmacokinetic of the drug elimination (5). The administration of the

5 mg/kg total dose ATG is frequently split in 3 days in many centers. We therefore would allow the possibility to use this second schedule in the study.

2.7 Summary of the known and foreseeable benefits and risks for the Clinical Trial participants

Benefits will be evaluated in terms of potential reduction of the incidence of grade II-IV acute GVHD which affects the quality of life of the patients, the risk of secondary infections and the risk of toxic mortality of SCT.

Risks related to ATLG-grafalon and ATG thymoglobulin include Infusion reactions, symptoms related to cytokine release, hypersensitivity reactions such as anaphylaxis and other allergic phenomena, increased susceptibility to infections and appearance of secondary malignancies (lymphoproliferative syndromes, lymphoma).

Risks of the study are also related to SCT itself, not to the randomization (ATG vs ATLG arm). Essentially a risk of non-engraftment due to the reduced intensity of conditioning and infectious complications due to immune deficiency. The post-transplant events will obviously be studied carefully: engraftment, GVHD, infectious complications, relapse and survival.

Risks of the study are also related to blood samples: mild bleeding, hematoma, mild pain.

3 OBJECTIVES

3.1 Primary objective

The main objective is to compare the incidence of grade II-IV acute GVHD at day 100 post-transplantation in MDS or AML patients transplanted with a 10/10 matched unrelated donor following a reduced intensity conditioning with fludarabine-treosulfan between patients receiving a GVHD prophylaxis with ATG-thymoglobulin versus ATLG-grafalon.

3.2 Secondary objectives

1. To evaluate the effect of the 2 GVHD prophylaxis on the engraftment and graft failure,
2. To evaluate the effect of the 2 GVHD prophylaxis on the incidence of grade I acute GVHD and of chronic GvHD,
3. To evaluate the effect of the 2 GVHD prophylaxis on incidence of infections
4. To evaluate the effect of the 2 GVHD prophylaxis on progression free survival
5. To evaluate the effect of the 2 GVHD prophylaxis on relapse incidence
6. To evaluate the effect of the 2 GVHD prophylaxis on non-relapse mortality
7. To evaluate the effect of the 2 GVHD prophylaxis on overall survival
8. To evaluate the effect of the 2 GVHD prophylaxis on GVHD and relapse free survival (GRFS)
9. To evaluate the effect of the 2 GVHD prophylaxis on health-related Quality of life (FACT BMT)
10. To evaluate the effect of the 2 GVHD prophylaxis on chimerism
11. To evaluate the effect of the 2 GVHD prophylaxis on immune reconstitution (T, B, NK, regulatory T cell levels in the peripheral blood)
12. To evaluate the effect of the 2 GVHD prophylaxis on days of hospitalization during the first 12 months post-transplantation
13. To evaluate the effect of the 2 GVHD prophylaxis on incidence and severity of VOD
14. To identify prognostic factors associated with the primary endpoint for each prophylaxis arm: search for treatment-by-covariate interactions on the primary endpoint
15. To evaluate the effect of the 2 GVHD prophylaxis on the incidence of late acute GvHD (after day 100), overlap syndromes and chronic GvHD

3.3 Objective of any potential ancillary study

The study will include:

- Plasma collection for ATG PK analysis in the ATLG arm (samples collected before and after each administration of ATLG on days-3 to -1 and at Day 0, 14, M1, M2 and D+100, frozen in each center). Data will be analyzed according to pre-conditioning lymphocyte counts and correlated to post-transplant outcomes (GVHD, relapse, NRM) to be able to determine of a formula to optimize ATLG dose to lymphocyte counts for future studies. This plasma collection will start including patients after finding complementary funding.

- Bio collection of PBMC, plasma and dry pellets from total blood cells will be performed on D-9 (base line), D14, 21, 28, 56, 100, M6 and M12 in 60 patients per arm for future biological studies that would be performed after finding complementary funding. The collections will be organized via Cryostem (https://www.cryostem.org/).

Biocollection will allow to perform comparative immunological studies between the two arms to explain the different effects of both ATG on the control of alloreactivity (immune reconstitution, cytokine levels, broad immune cell transcriptomic patterns, T cell repertoire …). Immune modulation by multiparameter flow cytometry analyses of T cell subtypes and activation/exhaustion phenotype, monocytes, dendritic cells, NK cells, T cell repertoire reconstitution and single cell transcriptomic analyses of different immune cell subtypes (monocytes, DCs, T, B and NK cells, regulatory T cells, iNKT, MDSCs) at early time points after allo-HSCT (D-9 (base line), D14, D21, D28, D56, D100) would be of interest to better understand the modulation of the immune response between the two ATG brands.

4 STUDY DESIGN

4.1 Study endpoints

4.1.1 Primary endpoint

Incidence of grade II-IV acute GVHD according to the MAGIC classification [47] (Appendix 19.9 section 1) at day 100 post-transplantation.

4.1.2 Secondary endpoints

1. Hematopoietic recoveries: at least 7 consecutive days with neutrophils > 0.5 G/L, with platelets > 20 G/L
2. Immune reconstitution by analyzing T, B, NK, regulatory T cell and gammaglobulin levels in the peripheral blood at M1, D+100, M6, M12 and M24 post-transplantation
3. Chimerism at M1, D+100, M6, M12
4. Grade I acute GVHD incidence (Appendix 19.9 section 1) and acute GvHD treatments: first line treatment, response to steroids, treatment courses for refractory acute GVHD
5. Chronic GvHD incidence (date and grading) at M12 and M24 (NIH classification [48], Appendix 19.9 section 4)
6. Relapse incidence at M12 and M24 (relapse will be defined by the reappearance of leukemic cells or MDS features after allo-HSCT in the bonne marrow (cytology +/- cytogenetic analysis from bone marrow aspiration) or extra-medullary sites (proven by a biopsy).
7. Progression free survival at M12 and M24
8. Severe infections (CTAE grade 3-4) at D+100 and M12 will be fully described
9. Incidences of CMV and EBV reactivations at D+100, M6 and M12
10. Non-relapse mortality at M6, M12 and M24
11. Overall survival at M12 and M24
12. GVHD and relapse free survival (GRFS) defined by being alive without disease relapse and without having developed acute grade III-IV or severe chronic GVHD
13. Health-related Quality of life, assessed by using the FACT-BMT-v4 questionnaire at inclusion and at D+100, M6, M12 post-transplantation
14. Number of days of hospitalization for the transplant and after the hospitalization for transplantation related complications until M12
15. Incidence and severity of VOD at D+100
16. Lymphocyte counts on standard blood counts before conditioning (D-7)
17. Late acute GvHD, overlap syndromes and chronic GvHD from D+100 to D+120.

4.2 Description of research methodology

4.2.1 Design of the study

Phase III multicenter, randomized, controlled, open-label trial, comparing with 2 parallel-groups in a homogeneous population of patients (AML or MDS, age 50-70, fludarabine-treosulfan conditioning): ATG-thymoglobulin versus ATLG-grafalon.

Participants distributed between groups at a ratio of 1:1 (1 ATG-thymoglobulin / 1 ATLG-grafalon)

4.2.2 Number of participating sites

This is a national multi-center study including 26 adults transplant centres of the SFGM-TC.

- Recruitment centres

Patients will be recruited in the hematology units and referred to the transplant team for the pre-transplant assessment.

4.2.3 Identification of participants

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

A randomisation arm (ATLG-Grafalon or ATG-Thymoglobulin) will also be assigned when the participant is randomized.

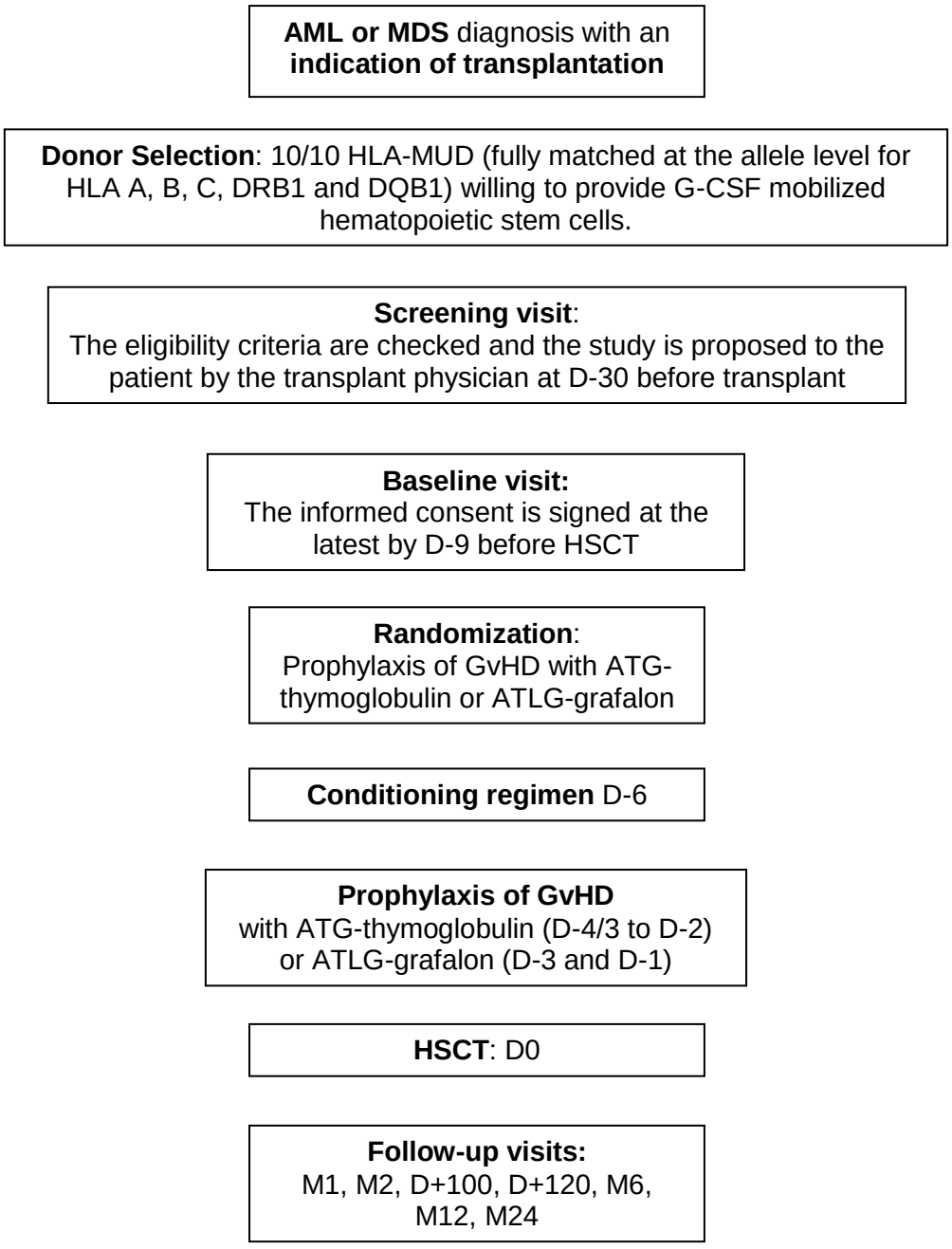
4.2.4 Randomisation

Randomisation will be centralised, computer-generated, by using permutation blocks of variable size. Patients will be randomised at a ratio of 1:1 in the 2 arms (1 ATG-thymoglobulin / 1 ATLG-grafalon).
Randomization will be stratified according to centre, disease (AML or MDS and age (<or ≥60 years), using eCRF-linked software for randomisation process.
Patients, after signing written informed consent, will be included by the investigators and randomised on eCRF CleanWebTM Telemedicine Technologies. The physician will receive a confirmation of the inclusion and the result of randomisation by email.

5 IMPLEMENTATION OF THE STUDY

The start of the clinical trial is the inclusion of the first patient.

5.1 Study Scheme



5.2 Screening visit

The screening visit will take place at about D-30 before transplantation. The investigator will check the eligibility criteria and will propose the study to the patient. Information about the protocol is delivered by the transplant physician in charge of the patient. Triplicated information and consent forms will be given to the patient by the investigator.

No additional test or specific examinations are performed for research. The patient assessment is performed in the usual care of allogeneic transplant.

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
The individual participating in the study	The transplant physician (investigator of research)	Screening visit D-30 before transplant;	At the latest by D-9 before HSCT (baseline visit (respecting the minimum reflection time of 24 hours)

5.3 Baseline visit and randomisation visit

At this visit, the inclusion and exclusion criteria are verified. The consent of the patient will be collected at the latest by D-9 before HSCT. A Patient Information Sheet and consent form are given to the patient by the investigator. The investigator will keep the original, a copy is given to the patient and a third copy is kept for the Sponsor.
Then, patients are randomized on eCRF CleanWeb for receiving prophylaxis of GvHD with ATG-thymoglobulin or ATLG-grafalon. Baseline visit also consists in physical examination, biological testing and imagery. This assessment is performed according to the practice of the investigator.

The patient assessment is performed in the usual care of allogeneic transplant.

- Physical examination
  - Reports of patient and disease history
  - ECOG performans status assessment
  - Sorror score of comorbidities
  - Complete physical examination with evaluation of tumor localization
  - Electrocardiogram
  - Echocardiogram with evaluation of left ventricular ejection
  - Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced vital capacity (FVC)
  - Liver ultrasound and doppler echography (baseline values)
- Disease assessment: Pre-transplant bone marrow aspiration and disease evaluation
- Biological tests
  - Complete Blood count
  - Prothrombin time (PT), Partial thromboplastin time (PTT)
  - ABO and Rh typing Blood cell
  - Chemistry panel (serum electrolytes with creatinine, calcium, glucose, uric acid, magnesium levels, ferritin, CRP)
  - Liver function tests (transaminases, alkaline phosphatase, gamma-GT and bilirubine)
  - Circulating protein electrophoresis
  - HLA compatibility check between recipient and donor
  - Chimerism markers' identification
  - Viral serologies: Serology for hepatitis B and C, Aspergillus antigen, EBV (IgG and M), CMV (IgG and M), HSV (IgG and M), HIV (2 Elisa tests), HTLV-1 and 2, toxoplasmosis (IgG and M), TPHA and VDRL
  - β-HCG for women of childbearing potential
- Imaging
  - Dental radiography
  - sinus, thorax and abdominal CT scan
- Health-related Quality of life: FACT-BMT-v4 questionnaire

5.4 Follow-up during hospitalization

Patients will be monitored daily during the hospitalization duration for possible complications related to the procedure or acute GVHD. The daily monitoring includes :

- Physical examination of the patient and safety assessment by collection of all adverse events/serious adverse events likely to occur as well as all actions taken because of these AEs. These AEs will be grading according to the CTC-AE v5.0scale (Annex 5).
- Complete Blood count, chemistry assessment with kidney and liver test will be performed
- Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 will be performed weekly (or according to clinical context)
- Grading of acute GVHD will be performed weekly during hospitalization and until D120

5.5 Follow-up visits (M1, M2, D+100, D+120, M6, M12, M24)

The minimum expected length of hospitalization is 21 days.

Patients will be assessed at M1, M2, D+100, M6, M12 and M24.

- Clinical examination, blood cell count, chemistry panel with creatinine and liver test will be performed at each visit (routine follow-up).
- Disease evaluation will be performed at D+100 and M12
- CD3/CD4/CD3/CD8/B lymphocytes/NK/ T reg cells, protein electrophoreris and ferritin levels at M1, D+100, M6, M12 and M24
- Chimerism evaluation at M1, M2, D+100, M6 and M12
- Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 and toxoplasmosis at M1, M2, D+100, M6, M12.
- Safety assessment by collection of all adverse events/serious adverse events at each visit.
- Health-related Quality (FACT-BMT v4) of life at D+100, M6, M12.
- Veino-occlusive disease (VOD) M1, M2 and D+100 date of diagnostic, grade, date of end and treatments.
- GVHD status
- Status of patient (alive/dead) and cause of death

Patient will be assessed at D+120:

- GVHD status

5.6 Early termination visit

Same assessments as the M24 visit.

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

The end of the research is defined as M24 of the last patient (last patient last visit).

Duration of enrolment period	36 months
The length of participation for participants, of which:	24 months (cf 5.5)
Maximum period between screening and enrolment	23 days

Duration of follow-up period for primary end point:	D+100
Duration of follow-up period for secondary end points:	24 months
Total study duration:	60 months

5.8 Table or diagram summarising the chronology of the study

	Screening visit	***Baseline visit***	*D-7*	*D-3*	*D-2*	*D-1*	*D0*	*D14*	*D21*	*M1 (+/- 3D)*	*M2 (+/- 3D)*	*D100 (+/- 10D)*	*D120 (+/- 6D)*	*M6 (+/- 6D)*	*M12 (+/- 6D)*	*M24 (+/- 6D)*
Information	X															
Informed consent signed		X														
Verification of inclusion and exclusion criteria	X	X														
Randomisation		X														
disease history		X														
(1) βHcG		X	X									X*	X*	X*	X*	X*
Clinical examination		X								X	X	X		X	X	X
(2) Imaging		X														
(3) Lung function test		X														
(4)Cardiac monitoring		X														
(5)Biological tests		X														
(6) Viral serologies		X														
blood cell count, chemistry panel with creatinine and liver test		X					X	X	X	X	X	X		X	X	X
Disease evaluation		X										X			X	
Blood Lymphocyte Counts			X									X			X	X
CD3/CD4/CD3/CD8/B lymphocytes/NK/ T reg cells, protein electrophoreris and ferritin levels										X	X	X		X	X	X
Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 ans toxoplasmosis										X	X	X		X	X	
Chimerism evaluation										X	X	X		X	X	
GvHD evaluation								X	X	X	X	X	X	X	X	X
Health-related Quality (FACT-BMT v4) of life		X										X		X	X	
Adverse events : serious adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
(7)Biocollection PK of ATLG: frozen plasma				X	X	X	X	X		X	X	X				
(8) Biocollection of blood PBMCs, plasma and RNA		X						X	X	X	X	X		X	X	

(1) βHcG : At Baseline, before start treatment D-7 (at hospital admission) and * If at any time during the participation period, a delay in menstrual period (over one month between menstruation) is observed

(2) Imaging: Liver ultrasound and doppler echography, Dental radiography, sinus, thorax and abdominal CT scan. For dental radiography : results obtained within 3 months before baseline can be used. For others : results must be obtained between screening and baseline.

(3) Lung function test: Pulmonary function tests including at least Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC), results obtained within 3 months before baseline can be used

(4) Cardiac monitoring: Electrocardiogram and echocardiogram with evaluation of left ventricular ejection and Evaluation of the cardiovascular risk factors (dyslipidemia, HBP, obesity, smoking), results obtained within 3 months before baseline can be used

(5) Biological tests: Complete Blood count, Prothrombin time (PT), Partial thromboplastin time (PTT), ABO and Rh typing Blood cell, Chemistry panel (serum electrolytes with creatinine, calcium, glucose, uric acid, magnesium levels, ferritin, CRP), Liver function tests (transaminases, alkaline phosphatase, gamma-GT and bilirubine), Circulating protein electrophoresis , HLA compatibility check between recipient and donor, Search of anti-HLA antibodies with LUMINEX technology (DSA), Chimerism markers' identification. Results must be obtained between screening and baseline.

(6) Viral serologies: Serology for hepatitis B and C, Aspergillus antigen, EBV (IgG and M), CMV (IgG and M), HSV (IgG and M), HIV (2 Elisa tests), HTLV-1 and 2, toxoplasmosis (IgG and M), TPHA and VDRL. Results must be obtained between screening and baseline.
(7) : *Biocollection PK of ATLG: frozen plasma. Plasma collection for ATG PK analysis in the ATLG arm (samples collected before and after each administration of ATLG on days-3 to -1 and at Day 0, D14, M1, M2 and D+100, frozen in each center). This plasma collection will start after finding complementary funding and will be performed in 60 patients ATLG arm.*
(8): biocollection will be performed in 60 patients per arm

5.9 Distinction between standard care and study

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

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with standard care**	**Interventions, procedures and treatments added for research purposes**
Treatments	Allogenic transplantation, conditioning regimen, GVHD prophylaxis as well as infection prophylaxis HSCT overall follow-up	Randomization (prophylaxis of GvHD: arm ATG-thymoglobulin or arm ATLG-grafalon)
Blood samples	At each visit β-HCG: baseline, D-7	β-HCG: D+100, D+120, M6, M12, M24 - Biocollection (120 patients: 60 patients in each arm) of blood PBMCs, plasma and dry pellets at D-9 (base line), D14, D21, D28, M2, D+100, M6 and M12 (via cryostem) - PK of ATLG (60 patients) from frozen plasma on days -3, -2, -1 and on D0, D14, D28, D60 and D100 (samples frozen in each center). This plasma collection will start after finding complementary funding.
Hospitalisations - Consultations	Patients will be monitored daily during the hospitalization duration; the minimum expected length of hospitalization is 21 days. Patients will be assessed (routine follow up) weekly after hospitalization **until D+100, D+120, M6, M12 and M24**	No
Questionnaire Quality of life		FACT-BMT-v4 questionnaire at baseline, D+100, M6 and M12

5.10 Biological samples collection

- Biocollection (120 patients: 60 patients in each arm) of blood PBMCs, plasma and dry pellets at D-9 (base line), D14, D21, D28, M2, D+100, M6 and organised through Cryostem (http://www.cryostem.org). Cryostem will manage the implementation of the biocollection.

- Plasma collection for ATG PK analysis in the ATLG arm (samples collected before and after each administration of ATLG on days-3 to -1 and at Day 0, 14, M1, M2 and D+100, frozen in each center). Data will be analyzed according to pre-conditioning lymphocyte counts and correlated to post-transplant outcomes (GVHD, relapse, NRM) to be able to determine of a formula to optimize ATLG dose to lymphocyte counts for future studies. This plasma collection will start after finding complementary funding.
At the end of the study, the samples will be kept until PK analyses and for further immune biological studies that would be performed after finding complementary funding.

Depending on the type of analysis, the analysis will be performed by:

- **IMoPA, CNRS UMR 7365**, Biopôle de l'Université de Lorraine, Nancy (France) under the responsibility of Pr Marie-Thérèse RUBIO
- **INSERM U976,** Human Immunology, Pathophysiology, Immunotherapy (HIPI), Institut de recherche Saint Louis, AP-HP hôpital Saint-Louis (France) under the responsability of Dr David MICHONNEAU

The analysis will be performed after finding additional funding.

At the end of the study, the samples may be used for further analysis not described in the initial protocol but which may be useful for investigation of the condition (LAM and MDS)/in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form.

If the samples are kept at the end of the study, the sample collection will be declared to the ministry of research

Type of sample	Quantity	Storage location (name and entity)	Supervisor of the sample collection (name and entity)	Purpose of the sample collection	Storage duration	End use/Future (destruction, etc.)
Blood	- 40 ml (5 tubes 8 ml with EDTA) at D14, D21, D28 and M2 - 28 ml (4 tubes 7 ml with EDTA) at D-9, M3, M6 and M12	During the study: CRB of each centre Once samples have been collected for every patient: Laboratory performing analysis	During the study: Director of CRB of each centre Once samples have been collected for every patient: Pr RUBIO or Dr MICHONNEAU depending on the analysis	PBMCs, plasma and dry pellets for immune biological studies	15 years	No destruction
Blood	- 5 ml (1 tube 5ml with EDTA)	During the study: CRB of each centre Once samples have been collected for every patient: Laboratory performing analysis	During the study: Director CRB of each centre Once samples have been collected for every patient Pr RUBIO or Dr MICHONNEAU depending on the analysis	PK analyses	15 years	Destruction after PK analyses

The biocollection will be performed in selected centres only.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

1. Age ≥ 50 and ≤ 70 years
2. Patient between 50 and 55 years should be unfit for a myeloblative conditioning
3. AML requiring allogeneic stem cell transplantation (intermediate or high-risk AML) in complete cytologic response (CR1 or above)
   or MDS requiring allogeneic stem cell transplantation (IPSS≥ 1.5 or IPSS-R > 4.5 or IPSS-R > 3-4.5 with risk features [rapid blast increase, life-threatening neutropenia (<0.3 G/L) or thrombopenia (<30G/L) or high transfusion needs (>2/month for 6 months)]
4. Without an HLA matched related donor
5. Having an identified matched HLA 10/10 unrelated donor
6. With usual criteria for HSCT:
   a) ECOG performans status ≤ 2
   b) No severe and uncontrolled infection
   c) Cardiac left ventricular ejection fraction ≥50%
   d) Lung DLCO > 40%
   e) Adequate organ function: ASAT and ALAT ≤ 3N, total bilirubin ≤ 2N, creatinine clearance ≥ 50 mL/min (except if those abnormalities are linked to the hematological disease)
7. With health insurance coverage
8. Having signed a written informed consent
9. Contraception methods must be prescribed during all the duration of the research

NB: The authorized contraceptive methods are:

For women of childbearing age and in absence of permanent sterilization:

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

For man in absence of permanent sterilization: sexual abstinence, condoms

6.2 Exclusion criteria

1. Carcinomas in the last 5 years (except basal cell carcinoma of the skin or “in situ” carcinoma of the cervix)
2. Uncontrolled infection
3. Seropositivity for HIV or HTLV-1 or active hepatitis B or C
4. Yellow fever vaccine and all others live virus vaccines within 2 months before transplantation
5. Heart failure according to NYHA (II or more) or Left ventricular ejection fraction < 50%.
6. Lung DLCO ≤ 40%
7. Preexisting acute hemorrhagic cystitis
8. Renal failure with creatinine clearance < 50ml / min
9. Pregnancy (β-HCG positive) or breast-feeding
10. Patients with any debilitating medical or psychiatric illness, which would preclude the realization of the SCT or the understanding of the protocol
11. Patient under state medical aid

12. Patient under legal protection (protection of the court, or in curatorship or guardianship).
13. For Grafalon: Any contraindication mentioned in the SmPC of GRAFALON
14. For Thymoglobulin: Hypersensitivity to rabbit proteins or to any of the excipients
15. Participation in other clinical trials on medicinal products for human use or being in the exclusion period at the end of a previous study.
16. Any contraindication mentioned in the SmPC of all auxiliary medicinal products planned to be used in the trial: cyclosporine, mycophenolate mofetil, fludarabine, treosulfan

6.3 Birth control and pregnancy

6.3.1 Pregnancy testing

Serum β-HCG levels are checked at baseline and at D-7 (at hospital admission) to confirm the absence of pregnancy.

If at any time during the participation period, a delay in menstrual period (over one month between menstruation) is observed, pregnancy testing should be done.

Of note, the study includes patients aged from 50 years and above.

6.3.2 Birth control methods

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

- For women of childbearing potential:

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

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

Highly effective birth control method accepted in this study are:

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

- For men, in absence of permanent sterilization:

The methods accepted in this study are listed below and must be used from baseline until the end of the participation period:

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

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

6.4 Donor Selection

10/10 HLA-MUD (fully matched at the allele level for HLA A, B, C, DRB1 and DQB1) willing to provide G-CSF mobilized hematopoietic stem cells.

6.5 Recruitment procedure

The protocol is carried out by the Société Francophone de Greffe de Moëlle et de Thérapie Cellulaire (SFGM-TC). The majority of the adult centers of SFGM-TC accepted to participate to this research (26 sites). The interest of the trial has been validated by the French scientific council of the SFGM-TC. In the last 3 years, SFGM-TC registry reported about 200 patients per year eligible for this trial, which illustrate the feasibility of the study. The patients will be recruited during a standard of care visit at the hospital. Each involved centre expects to enrol 2 to 12 patients/year (380 expected/324 required)

Justification of sufficient recruitment capacity for the number of participants that need to be included:

	Number of subjects
Total number of subjects to be included	324
Number of sites	26
Enrolment period (months)	36
Number of subjects/site	12,5
Number of subjects/site/month	0,35

6.6 Termination rules

6.6.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
    - Regarding Experimental Treatments (ATG and ATLG) all patients will receive a premedication based on paracetamol, corticoids and anti-histaminic.
      In case of occurrence of immunological reactions, including shock, Cytokine Release Syndrome, the treatment will be immediately stopped (according to SmPC); once patient conditions have improved, premedication will be administrated again and the treatment will be readministered, as scheduled.

- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

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

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant until the serious adverse event is resolved. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

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

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

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:
- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.6.3 Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.

In case of severe adverse events, the investigator must notify the sponsor and monitor the subject until the serious adverse event is resolved. If study procedure is stopped prematurely due to a serious adverse event, a serious adverse event report will be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor.

6.6.4 Full or partial discontinuation of the study

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

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

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

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

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

7 TRANSPLANT PROCEDURE

Elderly patients (Age ≥ 50 and ≤ 70 years) with AML or high risk MDS receiving an allogeneic hematopoietic stem cell transplantation with a 10/10 HLA matched unrelated donor.

7.1 Conditioning regimen

All patients will receive the same conditioning regimen:

- fludarabine 30 mg/m2/day IV for 5 days (day-6 to day-2)
- treosulfan 10 g/m2/day IV treosulfan for 3 days (day -4 to day -2)

7.2 Stem cell source

Only GCSF-mobilized peripheral blood stem cells will be accepted
CD34 target dose ≥4 × 10^6/kg of body weight

7.3 GVHD Prophylaxis

Prophylaxis of GvHD will depend on the randomization arm:

-ATLG-grafalon :10 mg/Kg/day IV for 3 consecutive days (day -3 to -1) (ATLG-grafalon)

OR

-ATG-thymoglobulin: Two schedules of administration of anti-thymocyte globulin (ATG) are accepted.
2.5 mg/kg/day IV for 2 consecutive days (day -3 and -2).

OR
0.5 mg/kg IV on day -4, then 2 mg/kg IV on day-3 and 2.5 mg/Kg IV on day -2.

The choice of schedule is left to the decision of the investigator based on current practice.

In addition, patients will receive cyclosporine (CsA) (3 mg/kg/day) and mycophenolate mofetil (MMF) (30 mg/kg/day) as follows: CsA from Day-1 to month 4 or 6 after a progressive withdrawal starting by 3 months post-SCT if no aGvHD and according to the practice of the center and MMF from Day + 1 to Day+45 in both arms

7.4 Infection Prophylaxis

Prophylactic and curative anti-infectious treatments (antibiotics, antivirals, antifungals) will be administered according to the ECIL recommendations *(link: www.kobe.fr/ecil workshops, recommendations).*

- Prevention of fungal infection by azols according to ECIL5, adapted to the SCT risk group *(https://www.ebmt.org/Contents/Resources/Library/ECIL/Pages/ECIL.aspx)*
- Prevention of HHSV and VZV reactivation: Zovirax 5 mg / kg X3/D IV then Valaciclovir: 500mg /D po
- Prevention of toxoplasmosis reactivations and pneumocystis: Bactrim 800mg X3/week or Atovaquone 750 mg x 2/day in case of cytopenias after engraftment
- Prevention of encapsulated bacteria: Oracilline 1 M x2 /D (starting after engraftment)

Monthly polyvalent immunoglobulins if hypogammaglobulinemia (<4 g/L)

7.5 Post-transplant monitoring

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

All adverse events (AEs) will be recorded. All AEs (except GvHD or Infection) shall be graded according to CTCAE Toxicity Grading Scale V5.0. (cf. Appendix 19.9 section 5) Fungal infections shall be graded according to GREFIG scale and, for GvHD according to MAGIC criteria (weekly during hospitalization and up to D120). (cf. Appendix 19.9 section 5)

8 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

All the treatments used for the procedure of transplant (conditioning regimen and prophylaxis GVHD) have a Marketing Authorisation in France and used in their indications. So, the drugs will not be provided by Sponsor.

8.1 Investigational medicinal products:

- Grafalon: 10 mg/Kg/day IV for 3 consecutive days (day -3 to -1) (ATLG-grafalon)
- Thymoglobulin: Two schedules of administration of anti-thymocyte globulin (ATG) are accepted:

2.5 mg/kg/day IV for 2 consecutive days (day -3 and -2).

OR

0.5 mg/kg IV on day -4, then 2 mg/kg IV on day-3 and then 2.5 mg/Kg IV on day -2.

The choice of schedule is left to the decision of the investigator based on current practice.

The hospital pharmacist (with respect to usual procedures) will use the commercial stock of the drugs.

8.1.1 Presentation:

Each box of ATG and ATLG from commercial stock of the pharmacies and used for the study will not be labelled for this study. According to article 67 of the European Regulation No. 536/2014, authorized experimental medicines can be labeled in accordance with Title V of Directive 2001/83/EC, which is the standard marketed presentation, except if the specific circumstances of a clinical trial require a modified label.
In this study, the products are used in accordance with their MA. Simply comparing two care strategies, there are no specific circumstances that would necessitate a modified label to ensure patient safety.

8.1.2 Dispensing:

Pharmacies will dispense ATG and ATLG for each patient on the basis of a standard prescription.

8.1.3 Traceability information

IMPs are prescribed as part of a clinical trial promoted by the *Assistance Publique - Hôpitaux de Paris (AP-HP),* a public health establishment, in hospital and within the framework of their usual practice and financing.

In this institutional context, and according to Article L1121-16-1 of the French Public Health Code, the cost of treatments is covered by public health insurance. Therefore, treatments are not provided by the sponsor but through the usual prescription process.

To ensure patient monitoring and safety, the *Département des Essais Cliniques de l'Agence Générale des Equipements et Produits de Santé* (DEC-AGEPS) will provide a tracking document to record each dispensation of treatment with its batch number, in order to ensure traceability and follow-up of treatments.

8.2 Description of Auxiliary medicinal product(s) (treatments required to conduct the study)

According to the Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014, an auxiliary medicinal product is a medicinal product used in the context of a clinical trial but not as investigational medicinal product.

The auxiliary medicinal products used in this research are:

- cyclosporine (CsA) (3 mg/kg/day) from Day-1 to month 4 or 6 after a progressive withdrawal starting by 3 months post-SCT if no GvHD and according to the practice of the center
- mycophenolate mofetil (MMF) (30 mg/kg/day) from Day + 1 to Day+45 in both arms
- fludarabine 30 mg/m2/day IV for 5 days (day-6 to day-2)
- treosulfan 10 g/m2/day IV for 3 days (day -4 to day -2)

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

The investigator should be verified that patients should not have a contraindication of treatments use in the study.

- Authorized treatments

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

- Treatments forbidden

Yellow fever vaccine and all others live virus vaccine are not authorized before to 2 years after HSCT.

- Treatments to take into consideration, not recommended in association with

For Fludarabine:
- Pentostatin
- Dipyridamole or another inhibitor of adenoside captation

For ATLG-Grafalon and ATG-thymoglobulin:
- Attenuated vaccine
- Tacrolimus

With the exception of the drugs listed above the other drugs in reference with their SPC and “associations to be considered” will be administered according to the usual practice of the centre and at the discretion of the investigator.

9 EFFICACY ASSESSMENT

9.1 Description of efficacy endpoint assessment parameters

9.1.1 Acute GvHD

Acute GvHD is defined according to MAGIC consortium [47]. Each organ is rated with the diagnosis in stage, which allows to define a grade(I-IV) according to the MAGIC classification (Appendix 19.9 section 1). Similarly, the clinician is asked to rate the maximum grade of acute GvHD over the study period and maximum grade date. Histological documentation will be required for GI GVHD.

9.1.2 Chronic GvHD

Chronic GvHD is defined according to the NIH classification published in 2005 [48]. The diagnosis of chronic GVHD is made if there is a distinctive sign (1 alone is sufficient) or evocative signs associated with a supplementary examination in favor (biopsy, for example). We then define:

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

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

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

The severity of chronic GvHD is defined by the number of affected organs (Appendix 19.9 section 4).

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

9.1.3 Progression-free survival

Progression-free survival (PFS) is defined as the time from HSCT until the firs occurrence of any of the following events: refractory disease, defined as absence of response after 2 courses of treatment induction, relapse (cytological), death from any cause.

9.1.4 Overall survival

Overall survival (OS) is defined as the time from HSCT until death from any cause.

9.1.5 Survival free of severe GVHD and relapse (GRFS)

GRFS correspond to progression free survival without acute grade III-IV GvHD or without severe chronic GvHD and is defined as the time from HSCTuntil the first occurrence of any one of the following events: relapse (cytological), grade III-IV acute GVHD, grade 3 NIH cGVHD or death from any cause.

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

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

10 SPECIFIC STUDY COMMITTEES

10.1 Scientific Steering Committee

A scientific steering committee provides overall supervision for the research. It will be composed of the coordinator investigator and co-coordinator investigator, the statistician, representatives of the sponsor and of the Unit for Clinical Research (Clinician, project coordinator, clinical research associate).
It will take decisions about continuation or termination of the trial or substantial amendments to the protocol and will propose procedures to be followed during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.

11 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

11.1 Recording and reporting adverse events

11.1.1 Definitions

According to Article 2 of the Regulation (EU) No 536/2014:

- **Adverse event**

Any untoward medical occurrence in a subject, to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. .

- **Serious adverse event**

Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

- **Unexpected serious adverse reaction**

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

According to Article 53 of the Regulation (EU) No 536/2014:

- **Unexpected event**

An unexpected event which affects the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

According to Article 54 of the Regulation (EU) No 536/2014:

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects. The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

According to the article R. 1211-31 of the French Public Health Code [Code de la Santé Publique], are defined:

- **Incident:** any accident or error originating from the procedures performed on the elements, products or derivatives mentioned in part I.1° of the article R1211-29, which causes or is likely to cause:
  a) An adverse effect in subjects mentioned in part I.3° of the article R. 1211-29;
  b) The loss of the element, product or derivative
  c) A quality or security defect of the element, product or derivative.

- **Serious incident:**
  a) Any adverse event which causes or is likely to cause:
  - A serious adverse effect or an unexpected adverse effect in persons mentioned in part I.3° of the article R.1211-29;

- Any important loss of the element, product or derivative which prevents the graft transplant from being performed or the product from being administered;
b) An abnormal increased rate of adverse events or unexpected adverse effects
c) Any donor or graft's information that has been accidentally found out after the graft collection which is likely to impact patients and recipients' health

- **Unexpected adverse effect:**
Any adverse effect (serious or not) for which the nature, severity or outcome is not expected according to criteria defined in article R. 1211-33, part 7° recognized by the Biomedicine Agency [Agence de Biomédecine] or with the health condition of the persons mentioned in article R. 1211-29, part 3°.

11.1.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

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

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal product(s)
The method used by the investigator is based on 2 causality terms (EVCTM method):

- Related
- Not related

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

The investigator notifies the sponsor without undue delay but not later than within 24 hours on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in article 41 of Regulation (EU) N°536/2014, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

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

Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, require the investigator to notify the sponsor without delay.

11.1.2.2 Specific features of the protocol

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

- Adverse events deemed "medically significant"

– Severe Infusion reactions (grade 3-4 CTCA-E Grading Scale v5.0) related to ATLG-grafalon and ATG-Thymoglobulin: symptomatic bronchospasm, with or without urticaria;

parenteral intervention indicated; allergy-related edema/angioedema; hypotension or life threatening reaction requiring IV intervention)
- Bacterial, fungal, viral and opportunist infectious complications of grade 4 (CTC-AE Grading Scale v5.0) meaning life threatening severe sepsis or septic choc occurring at any time after transplantation
- Bacterial, fungal, viral and opportunist infectious complications of grade 3 (CTC-AE Grading Scale v5.0) corresponding to any infection requiring IV intervention occurring after stem cell transplant engraftment with the exclusion of asymptomatic EBV reactivation requiring IV Rituximab administration.
- Secondary malignancies (EBV-induced lymphoproliferative syndromes, lymphoma)
- Non engraftment
- Veino-occlusive disease (moderate to severe)
- Severe Thrombotic Microangiopathy
- Bronchiolitis obliterans (all stage)
- Severe neurological disorders (coma, convulsion, encepthalitis occurring the first month post SCT)
- Cardiac toxicities (all stage) occurring in the first month post SCT
- Acute GVHD grade 3-4 and severe chronic GVHD
- Overdose report related to ATLG-grafalon and ATG-Thymoglobulin and leading to adverse reaction

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

- ***In utero* exposure**

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

- Exposure **while breastfeeding**

Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product *via* the breast milk of a mother being treated with an investigational medicinal product.
Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

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

These serious adverse events are only recorded in the case report forms. An eCRF extraction of these serious adverse events will be performed by the clinical trial unit for the preparation of the DSMB meeting. This extraction will be sent to the DRCI safety department at the following address: expertisecsi.drc@aphp.fr.

- *Normal and natural course of the condition*:
  - Planned hospitalisation for monitoring the condition under investigation [no deterioration in the participant's condition compared to baseline],

- Hospitalisation for routine treatment or for monitoring of the condition under investigation, not associated with a deterioration in the participant's condition,
- Emergency hospitalisation at inclusion or prolonged hospitalisation after inclusion to monitor the studied condition in the context of the study
- Worsening of the condition under investigation except those leading to death

- *Special circumstances*
  - Hospitalisation for a pre-existing illness or condition
  - Hospitalisation for a medical or surgical treatment scheduled prior to the study
  - Admission for social or administrative reasons

- *All the following events which are frequent after transplantation have <u>not</u> to be notified without delay to the sponsor and only recorded to e-CRF:*
  -
  - Infection of grade 3 (CTC-AE Grading Scale v5.0) occurring during the expected aplasia after conditioning (febrile aplasia)
  - Disturbance of biological values corresponding to an adverse event of grade ≤ 3 and no other clinical symptoms associated with this adverse event,
  - Grade I-II acute GvHD and mild or moderate chronic GVHD
  - EBV reactivation without post-transplant EBV-induced lymphoma requiring Rituximab IV administration

- *The following events not associated with a seriousness criterion which are frequent after transplantation have <u>not</u> to be recorded to eCRF:*
  - Digestive disorders with diarrhea, nausea, vomiting, abdominal pain, lack of appetite, modified taste
  - Inflammation on the mouth (mouth ulcers) or throat (like angina)
  - Rows, itching, burns
  - Asthenia or feeling dizzy or difficulty concentrating
  - Sleeping troubles
  - Bone, joint or muscle pain
  - Headache
  - Hair loss
  - Fever without clinical complications
  - Isolated bleeding without clinical complications

- *Serious Adverse events <u>exclusively</u> related to authorized auxiliary medicinal products (conditioning regimen) and related to treatments prescribed as part of the care provided during the study follow-up (concomitant treatment)*

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV).

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

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:
- from the date on which the subject begins GVHD prevention
- throughout the whole follow-up period required for the trial
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities

11.1.2.4 Procedures and deadlines for notifying the sponsor

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

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

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

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

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

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

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

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

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

11.1.2.5 Regulatory obligations of the health professionals (investigator, local biovigilance representative, manufacturer or head of the cell therapy unit or any unexpected adverse effect occurring to the donor)

Every serious incident must be reported without delay after knowing of its occurrence by any health professional. Health professionals may include the investigator and/or co-investigator. The severe adverse event declaration form must be completed in the research case report form.
For every serious incident, the health professionals must complete the Pharmacovigilance declaration form sends it to the Vigilance division of the DRCI (AP-HP) by e-mail (eig-vigilance.drc@aphp.fr) without delay after knowing of its occurrence. It is possible to send the SAE to the Safety department by fax on 01 44 84 17 99 only in case of unsuccessful attempt to send the SAE and to avoid duplicates.
Incidents which may be related to the graft transplant chain are not to be reported to the Biovigilance. These non-compliances and should be handled by the continuous quality management system of the institution (medical care facility, cell therapy unit).
However, only incidents which may be related to the final validated product whether it has been infused or about to be infused are to be reported without delay. Likewise, incidents related to unvalidated products potentially causing a loss of chance for the recipient (eg. product loss, low quality product which does not comply with specifications), a product shortage or a risk for the donor (eg. need for another donor's cell collection).
In general, it's not necessary to wait for all elements expected during the incident investigation to report to the sponsor. Additional information will be provided when available.
Whenever possible, the investigator will provide the sponsor with any documents that may be useful (hospitalization reports, batch release form, chimerism results, etc.).

Upon complementary information request by the sponsor, the local biovigilance representative or any backup health professional proceeds with appropriate investigations and informs the sponsor about the investigation's results.

11.1.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

11.1.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product and any other treatments,
  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product(s): refer to the SmPC must have been obtained from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php) enclosed in CTIS platform.

❖ For serious adverse events that may be related to the auxiliary medicinal product(s):

- refer to the SmPC that must have been obtained from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php) enclosed in CTIS platform.

❖ The serious adverse events potentially related to the interventions, procedures or examinations specific to the study are:
- Adverse events related to blood samples: mild bleeding, hematoma, mild pain.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs) via Eudravigilance, within the regulatory time frame, to the competent authority:
- in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;
- in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;
- in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening
- in the uncompleted case of fatal or life-threatening suspected unexpected serious adverse reactions, all additional information to complete this case have to be reported as soon as possible and in any event not later than eight days after the initial report
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 15 days starting from when the sponsor had this information.

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

11.1.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

The sponsor will report in CTIS platform and to ANSM without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

11.1.3.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,

- summary tables of all the serious adverse events that have occurred since the start of the study.

The sponsor produces one annual safety report (Development Safety Update Report - DSUR) for one clinical trial.

The report must be submitted in CTIS no later than 60 days after the anniversary of the date on which the competent authority authorised the trial.

11.1.4 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) may be established by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of such a committee to the Competent Authority and to the Ethics Committee).

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the Ethics Committee).
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB members are:
Pr Baron (Liège, Belgique), Pr André Tichelli (Bâle, Suisse), Pr Jakob Passweg (Bâle,Suisse)
The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

12 DATA MANAGEMENT

12.1 Identification of data recorded directly in the CRFs which will be considered as source data

Source data recorded directly in the CRFs as disease history, clinical examination, viral serologies, biological tests results, will be taken from medical file including original biological examination results, summary from imaging examinations, etc.

12.2 Right to access data and source documents

12.2.1 Data access

In accordance with GCPs and appendix 1 of the European Regulation N°536-2014:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the Sponsor declares that investigators and participating institution will ensure the persons in charge of monitoring, quality control and auditing or inspecting the clinical trial have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force

12.2.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. Source documents include: medical file, original biological examinations, imaging examinations…). These documents will be kept

in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

12.2.3 Data confidentiality

The persons responsible for the quality control of clinical studies will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy.
During and after the clinical trial, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

12.3 Data processing and storage of research documents and data

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

The management and processing of the data will be done by the Service de Biostatistique et Information Médicale (sBIM), hôpital saint Louis, Paris (Pr. Sylvie Chevret).
Data will be entered electronically via a web browser.

12.3.2 Data entry

Non-identifying data will be entered electronically via a web browser.

12.4 Data ownership

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

13 STATISTICAL ASPECTS

13.1 Description of statistical methods to be used including the timetable for the planned interim analyses

As a general strategy, continuous measures will be summarized using median and interquartile range (IQR). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints.

Disposition of the Study Subjects: The disposition of subjects will be described with summaries by treatment group of the number of subjects enrolled, the number of subjects treated, and the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation).

Demographic and Baseline Characteristics: Demographic and baseline characteristics will be summarized by treatment group and overall..

Primary endpoint:
Incidence of grade II-IV acute GVHD according to the MAGIC classification (Appendix 19.9 section 1) at day 100 post-transplantation.

Primary analysis will test differences of incidence of grade II-IV acute GVHD will be tested using Gray test (Gray RJ (1988) A class of K-sample tests for comparing the cumulative incidence of a competing risk, Annals of Statistics, 16:1141-1154.). This test is a rank based test, extendingthe logrank test in presence of competing risks. Measure of treatment effect will be based on the subdistribution hazard ratio (SHR) from the Fine and Gray model.
Secondary analyses will used the cause-specific hazard ratio (cHR) estimated from the Cox model as the measure of treatment effect.

Secondary endpoints:
Differences of incidence of Hematopoietic recoveries will be tested using the Gray test.
Immune reconstitution by analysing T, B, NK, regulatory T cell and gammaglobulin levels in the peripheral blood at M1, D+100, M6, M12 and M24 post-transplantation
Levels of T, B, NK, regulatory T cell and gammaglobulin levels will be compared using linear model with patient random effect on intercept.
Proportion of chimerism at M1, D+100, M6, M12 will be compared using logistic model with patient random effect on intercept.
First line treatment, response to steroids, treatment courses for refractory acute GVHD will be fully described within each arm.
Differences of incidence of Chronic GvHD, of relapse, of the incidence of CMV and EBV reactivations, of non-relapse mortality (NRM) will be similarly tested using the Gray test. Estimations at M12 and M24 will be given with their 95% Confidence Intervals (95%CI) using the cumulative incidence function in the competing risks setting.
Differences of Progression free survival (PFS), of GVHD and relapse-free survival (GRFS) , and of overall survival (OS) will be tested using the logrank test. Estimations at M12 and M24 will be given with their 95% Confidence Intervals (95%CI) using Kaplan Meier estimator.
Distribution of late acute GvHD, overlap syndromes and chronic GvHD from D+100 to D+120, will be compared, handling those who developed acute GvHD earlier and those who died free of GvHD before D+100, using an exact Fisher test.

Severe infections (CTAE grade 3-4) at D+100 and M12 will be fully described within each arm.
Health-related Quality of life, assessed by using theFACT-BMT-v4 questionnaire at D+100, M6, M12 post-transplantation levels will be compared using linear model with patient random effect on intercept.
Number of days of hospitalization for the transplant and after the hospitalization for transplantation related complications until M12 will be fully described within each arm.
Lymphocyte counts on standard blood counts before conditioning (D-7) will be fully described within each arm.

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

Our hypotheses are based on a reduction on the incidence on day 120 post-HSCT of grade II-IV aGVHD from 40% (ATG arm) to 23% (ATLG arm), and assuming a 10% risk of randomised patients who would not reach transplant and an incidence of 5% for the competing risk (death without GvHD) in each arm.

When accounting for competing risks, a two-sided logrank test with an overall sample size of 324 subjects (162 in the control group and 162 in the treatment group) achieves 91% power at a 0.05 significance level to detect a hazard ratio of 0.51 with a follow-up time of 120 days.
In total, 162+162=324 patients will be included.
The sample size computation used the formula provided by the following statisticians, and implemented in the PASS software (PASS 2023 Power Analysis and Sample Size Software (2023). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.).

References

Machin, D., Campbell, M.J., Tan, S.B., Tan, S.H. 2009. Sample Size Tables for Clinical Studies, Third Edition. Wiley-Blackwell, Chichester, United Kingdom.
Pintilie, M., 2006. Competing Risks: A Practical Perspective. John Wiley & Sons, Chichester, United Kingdom.
Pintilie, M., 2002. 'Dealing with Competing Risks: Testing Covariates and Calculating Sample Size'. Statistics in Medicine, Volume 21, pages 3317-3324

No interim analysis is scheduled to be performed.

13.3 Anticipated level of statistical significance

All tests will be based on a two-sided type I error rate (alpha) of 0.05.
No control for multiplicity will be performed.

13.4 Method for taking into account missing, unused or invalid data

In regression analyses, missing data on covariates of interest will be attributed by multiple imputation using chained equations (Multiple Imputation by Chained Equation: MICE).

13.5 Management of modifications made to the analysis plan for the initial strategy.

All modifications of the initial plan will be submitted to the scientific committee, the investigator and the sponsor.
An amendment will be filed in case of modification of the initial statistical analysis plan (SAP) and submitted to regulatory bodies.

13.6 Choice of individuals to be included in the analyses

Primary analyses of the trial will be performed on modified intention to treat (ITT) population, defined as the subset of patients who actually underwent HSCT, but analysed in the group they were allocated by the randomisation, independently of the actually received treatment.
Sensitivity analyses will consider (1) all patients randomized patients, regardless of the received HSCT, with time-to-event endpoints computed from randomisation time, and (2) per-protocol (PP) population, excluding those main deviations from the protocol.

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14 QUALITY CONTROL AND ASSURANCE

Every clinical trial sponsored by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored clinical trial.

14.1 General organisation

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

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

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

14.1.1 Strategy for centre opening

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

14.1.2 Scope of centre monitoring

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

14.2 Quality control

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

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

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

14.3 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and

relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
The investigator must archive a copy of the authenticated document that was issued to the sponsor.

14.4 Management of non-compliances

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

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

The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

14.5 Audits/inspections

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

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

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

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

14.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals, for France). The CV must include any previous involvement in clinical research and related training.
Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki. Each investigator will give the sponsor's representative a GCP certificate dated fewer than three years ago.

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

14.7 Suitability of the facilities

Before starting the study, each clinical trial sites will give the sponsor's representative a duly justified written statement on the suitability adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise.

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Methods for informing research participants and obtaining their consent

According to article 29 of European regulation N°536/2014, No clinical trials on medicinal products for human use can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in article 29.2 of the European Regulation.

A reflection period of **at least 24 hours** is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study. The consent of the patient will be collected at the latest by D-9 before HSCT.

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

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

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

15.2 Prohibition from participating in another clinical study or exclusion period set after the study

The participants are not allowed to enrol in another clinical trials on medicinal products for human use, except those evaluating treatments of post-transplant graft versus host disease (GVHD) for the duration of his or her participation.

The participants can however participate in other studies.

15.3 Compensation for participants

There will be no compensation for the participants.

15.4 Authorisation for the research location

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

15.5 Legal obligations

15.5.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and all national Laws. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

15.5.2 Request for authorisation

Prior to starting the study, AP-HP, as sponsor, must obtain authorisation from the Competent Authority and the Research Committee for this clinical trial on medicinal product for human use within the scope of its authority and in accordance with in force legislation and regulatory requirements.

15.5.3 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Commitment to comply with “Reference Methodology” MR-001

This research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this “Reference Methodology”

15.5.4 Start of the Clinical Trial

The sponsor shall notify each Member State concerned of the start of a clinical trial and the start of the recruitment through the EU portal. That notification shall be made within 15 days from the start of the clinical trial.

15.5.5 Amendments to the Clinical Trial

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

15.5.6 End of the Clinical Trial

The end of the Clinical Trial corresponds to the end of the participation of the last person who participate to the Clinical Investigation.
The end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified in CTIS. That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

15.5.7 Summary of the results of the clinical trial

According to article 37.4 of the European regulation n°536/2014, irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the CTIS a summary of the results of the clinical trial. This summary shall be accompanied by a summary written in a manner that is understandable to laypersons.

15.5.8 Archiving

Specific documents for a clinical trial on medicinal product for human use will be archived by the investigator and the sponsor for 25 years after the end of the research.

This indexed archiving includes, in particular:

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

16 FUNDING AND INSURANCE

16.1 Funding sources

This study will be supported by two pharmaceutical companies: MEDAC SAS and NEOVII Pharmaceuticals AG.

16.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm

is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article 76(1) of regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

17 PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must name the sponsor AP-HP (DRCI) and the source of funding, (see below for rules governing affiliation, and naming of the sponsor and funders).

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

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

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

- "The sponsor was Assistance Publique – Hôpitaux de Paris (Direction de la Recherche Clinique et de l'Innovation)"

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

The study was funded by MEDAC SAS and NEOVII Pharmaceuticals AG.

This study has been registered on the website http://clinicaltrials.gov/ under number *(add the registration number when the study is registered)*.

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19 ADDENDA

Each addendum and the log of addenda versions are attached, independently of the protocol. Each addendum can be modified (change of addendum version) without modifying the protocol version.

19.1 List of addenda

- List of investigators
- Serious adverse events notification form
- Pregnancy notification form
- Secondary cancer notification form
- SMPC

- Description of the Clinical Trial in the AP-HP Trials Register
- Questionnaire
- Scale (sections 1 to 5)

19.2 List of investigators

Version 1.0 of 03/07/2023

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19.3 Serious Adverse Events notification form

V1.0 of 10/07/2023

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Direction de la Recherche Clinique et de l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **Version 9 – 23/06/2022** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (4 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre les formulaires de notification d'EIG au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons.

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : **OPTISAGE**

Code de la Recherche : APHP 230276

Date de notification : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Titre complet de la Recherche :
Phase III study comparing GVHD prophylaxis with ATG-thymoglobulin to ATLG-grafalon in elderly patients with acute myeloid leukemia or myelodysplatic syndrome and receiving an allogeneic hematopoietic stem cell transplantation with a 10/10 HLA matched unrelated donor following a reduced intensity conditioning regimen by fludarabine-treosulfan

Risque : ☐ A ☐ B ☐ C ☒ D

Plan expérimental : ☒☐ Essai non comparatif
x Essai comparatif ☐ Double aveugle ☐ Simple aveugle ☒ Ouvert

☒ Randomisé ☐ Non randomisé

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....

Tél : ..... Fax : .....

Mail : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg

Taille : |__|__|__| cm

Date de naissance :
|__|__| |__|__|__|__|
mm aaaa

Age : |__|__|__|ans

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....
.....
.....
.....
.....
.....
.....

Date de signature du consentement : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ Groupe (GRAFALON)) ☐ Groupe (Tymoglobuline)

4. Médicament(s) <u>expérimental(aux)</u> (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*
Grafalon	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Thymoglobuline	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

5. Médicament(s) <u>auxiliaire(s) nécessaire(s) à la réalisation de la recherche : si applicable</u> [préciser le(s)quel(s)] avant la survenue de l'EIG ***(barrer l'encadré si traitement non débuté)***

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*
Ciclosporine	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Mycophénolate mofétil	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Fludarabine	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Tréosulfan	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

6. Préparation de thérapie cellulaire - administré avant la survenue de l'évènement ***(barrer l'encadré si traitement non débuté)***

Nom de la préparation de thérapie cellulaire	Voie[1]	Nombre de cellules administrées / Dose	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*
Greffe de CSH	.....	.....x 10^6/kg	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

PARTIE RESERVEE AU PROMOTEUR
Version 9
REFERENCE VIGILANCE :
Référence GED : REC-DTYP-0192

Acronyme : OPTISAGE
Référence de la personne se prêtant à la recherche : \|_\|_\|_\| - \|_\|_\|_\|_\|_\| - \|_\|_\| - \|_\|
n°centre **n° ordre de sélection** **initiale nom** **initiale prénom**

7. Procédures et actes ajoutés par la recherche ***(ex. : biopsies, IRM …)*** ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Prélèvements sanguins	|__|__| |__|__| |2|0|__|__|	☐	☐

8. Médicament(s) <u>concomitant(s)</u> au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable ***(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)***

➪ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours [2]	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

9. Evènement indésirable grave [EIG]

<u>Diagnostic</u> : ☐ Définitif ☐ Provisoire	**<u>Organe(s) concerné(s)</u> :**
.....	.....

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|
Préciser lesquels :
.....

.....
.....
.....
.....

Date d'apparition de l'EIG :
|__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
Heure de survenue : |__||__| hh |__||__| min
☐ *donnée manquante*

Délai entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :
|__||__| / |__||__| |__||__|
jj hh min

Critères de gravité :

☐ Nécessite ou prolonge l'hospitalisation :
du |__|__| |__|__| |_2_|_0_|__|__|
au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

☐ Décès
☐ Mise en jeu du pronostic vital
☐ Incapacité ou handicap important ou durable
☐ Anomalie ou malformation congénitale
☐ Autre(s) critère(s) médicalement significatif(s), préciser :
.....
.....

L'évènement a-t-il conduit à :
☐ aucune mesure prise concernant le ME
☐ diminution de la posologie du ME, préciser la nouvelle posologie : .....
date de début de la nouvelle posologie : |__|__| |__|__| |_2_|_0_|__|__|
☐ augmentation de la posologie du ME, préciser la nouvelle posologie : .....
date de début de la nouvelle posologie : |__|__| |__|__| |_2_|_0_|__|__|
☐ arrêt définitif du ME, préciser la date : |__|__| |__|__| |_2_|_0_|__|__|
☐ arrêt transitoire du ME, préciser la date : |__|__| |__|__| |_2_|_0_|__|__|
date de reprise : |__|__| |__|__| |_2_|_0_|__|__|
☐ ne sais pas

Récidive de l'EIG après ré-administration : ○ Non ○ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
○ Non applicable

Des mesures symptomatiques ont-elles été prises ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|Préciser : .....

.....

Une levée d'insu a-t-elle été nécessaire après la survenue de l'évènement ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| ☐ Non applicable

Degré de sévérité EN cas de GvH aigue : se référer à la classification MAGIC consortium 2016
☐ 1 ☐ 2 ☐ 3 ☐ 4

En cas de GvH chronique :
☐ léger ☐ modéré ☐ sévère

Pour les EIG : classification CTCAE v5.0 *:*
☐ Grade 1 ☐ Grade 2 ☐ Grade 3
☐ Grade 4 ☐ Grade 5

L'évènement fait-il suite à :

- une erreur médicamenteuse ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- un surdosage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- un mésusage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- autre (préciser) :	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|

PARTIE RESERVEE AU PROMOTEUR
Version 9
REFERENCE VIGILANCE :
Référence GED : REC-DTYP-0192

Acronyme : OPTISAGE
Référence de la personne se prêtant à la recherche : |__|__|__|-|__|__|__|__|-|__|-|__|
n°centre **n° ordre de sélection** **initiale nom** **initiale prénom**

Evolution de l'événement

☐ **Décès**
○ sans relation avec l'EIG
○ en relation avec l'EIG
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ **Sujet non encore rétabli**, préciser :
○ Etat stable ○ Amélioration ○ Aggravation

☐ **Résolu :**
○ sans séquelles
○ avec séquelles, préciser lesquelles :
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
|__|__| |__|__|
hh min

☐ **Evolution inconnue**

10. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : ……
……
……

11. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés]……
……
……

12. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié:

☐ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**

Lequel :GRAFALON ☐ **Lié** ☐ **Non lié**
Lequel :THYMOGLOBULINE ☐ **Lié** ☐ **Non lié**

☐ **au(x) médicament(s) auxiliaire(s) nécessaire(s) à la réalisation de la recherche : le(s)quel(s) ?**

Lequel : ciclosporine …… ☐ **Lié** ☐ **Non lié**
Lequel : mycophénolate mofétil…… ☐ **Lié** ☐ **Non lié**
Lequel : fludarabine…… ☐ **Lié** ☐ **Non lié**
Lequel : tréosulfan…… ☐ **Lié** ☐ **Non lié**

☐ **à la (aux) procédure(s)/acte(s) de la recherche : la/le(s)quel(les) ?**

Lequel : prélèvements sanguins…… ☐ **Lié** ☐ **Non lié**

☐ **à la progression de la maladie faisant l'objet de la recherche : (leucémie aigue myéloide ou syndrome myélodysplasique)**
☐ **à la greffe de CSH / complications de la greffe de CSH**
☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : ……**
☐ **à une maladie intercurrente, laquelle : ……**
☐ **autre, préciser : ……**

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

19.4 Pregnancy notification form

V1.0 of 10/07/2023

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Direction de la Recherche Clinique et de l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Formulaire de notification et suivi d'une grossesse apparue au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **Version 7 – 23/06/2022** **REFERENCE INTERNE :** Référence GED : REC-DTYP-0185

Ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre les formulaires de notification de grossesse au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons.

1. Identification de la recherche

Acronyme : **OPTISAGE**
Code de la recherche : **APHP 230276**
Risque : **D**

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Titre complet de la Recherche :
Phase III study comparing GVHD prophylaxis with ATG-thymoglobulin to ATLG-grafalon in elderly patients with acute myeloid leukemia or myelodysplatic syndrome and receiving an allogeneic hematopoietic stem cell transplantation with a 10/10 HLA matched unrelated donor following a reduced intensity conditioning regimen by fludarabine-treosulfan

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :
E-mail :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Date de naissance : |__|__| |___|___|__|__| (mm-yyyy)
Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|
Poids : |__|__|__| kg
Taille : |__|__|__| cm
Groupe de randomisation : ☐ (GRAFALON) ☐ (Thymoglobuline)
Date des dernières règles : |__|__| |__|__| |_2_|_0_|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |_2_|_0_|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Date de naissance : |__|__| |___|___|__|__| (mm-yyyy)
Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|
Groupe de randomisation :
☐ (GRAFALON) ☐ (Thymoglobuline)

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :

Chirurgicaux :

Obstétricaux : |__|__| geste |__|__| pare
Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle				
Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
Grafalon	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
Thymoglobuline	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)				

Acronyme : OPTISAGE

PARTIE RESERVEE AU PROMOTEUR
Version 7
RÉFÉRENCE INTERNE :
REC-DTYP-0192

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

6 . Médicament(s) auxiliaire(s) nécessaire(s) à la réalisation de la recherche administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle : si applicable				
Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
Ciclosporine	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
Mycophénolate mofétil	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
Fludarabine	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
Tréosulfan	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

7. Préparation de thérapie cellulaire - administré avant la survenue de l'évènement *(barrer l'encadré si traitement non débuté)*				
Nom de la préparation de thérapie cellulaire	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Nombre de cellules administrées / Dose
Greffe de CSH	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		……x 10^6/kg

8. Procédures et actes ajoutés par la recherche *(Barrez l'encadré si procédures et actes non réalisés)*	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
Prélèvements sanguins	|__|__| |__|__| |_2_|_0_|__|__|		

9. Médicament(s) concomitants administré(s) dans le cadre du soin
(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ Oui ☐ Non applicable)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)				

10. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

11. Grossesse en cours ☐ (envoyer par e-mail un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale) **ou issue de la grossesse** ☐ (compléter ci-dessous)
Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J
☐ Fausse couche → Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :
☐ Grossesse extra-utérine → Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :
☐ Interruption de grossesse → Raison : → Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :
☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne
Naissance multiple : ☐ Non ☐ Oui, précisez le nombre : Souffrance fœtale : ☐ Non ☐ Oui, précisez : Mort-né : ☐ Non ☐ Oui, précisez : Placenta normal : ☐ Oui ☐ Non, précisez : Liquide amniotique : ☐ Clair ☐ Autre, précisez : Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

Acronyme : OPTISAGE

PARTIE RESERVEE AU PROMOTEUR
Version 7
RÉFÉRENCE INTERNE :
REC-DTYP-0192

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

12. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et l'envoyer par e-mail)		
Sexe : ☐ Masculin ☐ Féminin Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____		
Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :		
Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :		
Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable		
Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

19.5 Secondary cancer notification form

V1.0 of 10/07/2023

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) *Direction de la Recherche Clinique et de l'Innovation (DRCI)*	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Formulaire de notification des cancers secondaires/myélodysplasies survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** ***Version 5 – 23/06/2022*** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0191

Ce formulaire doit être dûment complété (5 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre les formulaires de notification de cancers secondaires/myélodysplasies au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons.

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : **OPTISAGE**

Code de la Recherche : APHP 230276

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance du des cancer secondaire/myélodysplasie par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la Recherche :
Phase III study comparing GVHD prophylaxis with ATG-thymoglobulin to ATLG-grafalon in elderly patients with acute myeloid leukemia or myelodysplatic syndrome and receiving an allogeneic hematopoietic stem cell transplantation with a 10/10 HLA matched unrelated donor following a reduced intensity conditioning regimen by fludarabine-treosulfan

Risque : ☐ A ☐ B ☐ C ☒ D

Plan expérimental : ☐ Essai non comparatif ☒ Essai comparatif ☐ Double aveugle ☐ Simple aveugle ☒ Ouvert

☒ Randomisé ☐ Non randomisé

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....

Tél : ..... Fax : .....
Mail : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__| - |__| - |__|
(n°centre - n° ordre de sélection - initiale nom - initiale prénom)

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance : |__|__| |__|__|__|__| (m m a a a a)

Age : |__|__|__| ans

Date de signature du consentement : |__|__| |__|__| |2|0|__|__| (j j m m a a a a)

Date d'inclusion : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....

Date de randomisation : |__|__| |__|__| |2|0|__|__| (j j m m a a a a)

☐ Groupe (GRAFALON) ☐ Groupe (Tymoglobuline)

4. Diagnostic du cancer secondaire/de la myélodysplasie

4.1 Diagnostic clinique :	
Date du diagnostic : |__|__| |__|__| |_2_|_0_|__|__| j j m m a a a a	Diagnostic final retenu : ……
Confirmation histologique : ☐ **Non** ☐ **Oui**	
Confirmation cytologique : ☐ **Non** ☐ **Oui**	
4.2 Grade : (précisez l'échelle de classification ex : TNM)	☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV ……
4.3 Grade histologique	☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV
4.4 Si autre classification, précisez :	
4.5 Antécédents médicaux pertinents : ☐ Non ☐ Oui, précisez :	

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n°centre - n° ordre de sélection - initiale - initiale

5. Médicaments/procédures de la recherche

5.1 Médicament(s) <u>expérimental(aux)</u> (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Grafalon ……	……	……	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Thymoglobuline ……	……	……	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

5.2 Médicament(s) <u>auxiliaire(s) nécessaire(s) à la réalisation de la recherche : si applicable</u> [préciser le(s)quel(s)] avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Ciclosporine……	……	……	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Mycophénolate mofétil……	……	……	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Fludarabine ……	……	……	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Tréosulfan……	……	……	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

6. Préparation de thérapie cellulaire - administré avant la survenue de l'évènement ***(barrer l'encadré si traitement non débuté)***

Nom de la préparation de thérapie cellulaire	Voie(1)	Nombre de cellules administrées / Dose	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
Greffe de CSH……	……	……x 10^6/kg	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

7. Procédures et actes ajoutés par la recherche ***(ex. : biopsies, IRM …)*** ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Prélèvements sanguins……	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

8. Précision de l'imputabilité de l'investigateur

8.1 Selon l'investigateur, l'événement indésirable grave (cancer secondaire/myélodysplasie) est (plusieurs cases possibles)

Lié à la recherche :

☐ **Oui** : ○ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : Le(s)quel(s) ?**

Lequel : GRAFALON ..... ☐ Lié ☐ Non lié

Lequel : THYMOGLOBULINE ..... ☐ Lié ☐ Non lié

○ **au(x) médicament(s) auxiliaire(s) nécessaire(s) à la réalisation de la recherche : Le(s)quel(s) ?**

Lequel : ciclosporine ..... ☐ Lié ☐ Non lié

Lequel : mycophénolate mofétil ..... ☐ Lié ☐ Non lié

Lequel : Fludarabine ..... ☐ Lié ☐ Non lié

Lequel : tréosulfan..... ☐ Lié ☐ Non lié

○ **à la (aux) procédure(s)/acte(s) de la recherche : La/le(s)quel(les) ?**

La/lequel(le) : prélèvements sanguins ..... ☐ Lié ☐ Non lié

☐ **Non** : ○ **à la progression de la maladie faisant l'objet de la recherche :** (**leucémie aigue myéloide ou syndrome myélodysplasique**)

○ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) :** .....

○ **à une maladie intercurrente, laquelle :** .....

○ **autre, préciser :** .....

8.2 La survenue de cet EIG est-elle susceptible d'être liée à un manque d'efficacité du ME ?	☐ **Non** ☐ **Oui**

9. Détails de la chimiothérapie administrée pour traiter la pathologie initiale (phase)	
☐ Induction |__|__| |__|__| |_2_|_0_|__|__| j j m m a a a a	☐ Consolidation |__|__| |__|__| |_2_|_0_|__|__| j j m m a a a a
☐ Post greffe : renseignez la partie 6	☐ Maintenance |__|__| |__|__| |_2_|_0_|__|__| j j m m a a a a
☐ Autre :	☐ Interphase

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9.1 Médicament(s) ou produit(s) assimilé(s) de chimiothérapie anticancéreuse ou de thérapie ciblée avant la survenue du cancer secondaire/de la myélodysplasie *(barrez l'encadré si aucun traitement débuté) :*

Nom commercial ou Dénomination Commune International	Date de première administration Ou non administré	Date de dernière administration Ou en cours (2)	Voie d'adminis-tration(1)	Posologie / 24h	Lien de causalité avec l'EIG *(Relation selon méthode OMS)*
Pentostatin	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
Dipyridamole	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable

ATG-thymoglobulin	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
Cyclosporine	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
Tacrolimus	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
MMF	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ Non administré	|__|__| |__|__||_2_|_0_|__|__| j j m m a a a a ☐ En cours			☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
Vaccin atténué : ☐ Non ☐ Oui Si oui , précisez ci-dessous : …… Date : |__|__| |__|__||_2_|_0_|__|__| j j m m a a a a					☐ non lié ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)
(2) En cours au moment de la survenue de l'EIG

9.2 Greffe de cellules souches hématopoïétiques (CSH) pour le traitement de la pathologie initiale :

☐ Non ☐ Oui, précisez ci-dessous :

Date de la greffe : le |__|__| |__|__| |_2_|_0_|__|__| j j m m a a a a ☐ allogreffe	Si allogreffe : Donneur : ☐ Donneur non apparenté HLA 10/10

Origine CSH : ☐ CSP

Nombre de cellules administrées / Dose :……x 10^6/kg

Date de sortie d'aplasie : \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|
j j m m a a a a

9.3 Traitements de conditionnement de la greffe (immunosuppresseurs, irradiation corporelle, etc.) :

☐ Non applicable ☐ Applicable, précisez ci-dessous le schéma thérapeutique :

Nom commercial ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration	Voie d'administration(1)	Posologie / 24h
Fludarabine	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|		
Tréosulfan	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|		

10. Statut de la pathologie initiale à la date de survenue du cancer secondaire/de la myélodysplasie

(Joindre si possible les résultats du dernier myélogramme le cas échéant) **:**

☐ Rémission complète le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|
☐ Rémission avec séquelles le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|, précisez les séquelles :
☐ Rémission partielle le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|, précisez :
☐ Stable depuis le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|
☐ Maladie en progression
☐ Rechute depuis le\|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

11. Traitement du cancer secondaire/de la myélodysplasie

11.1 Hospitalisation(s) :

Hospitalisation (1) du |__|__| |__|__| |_2_|_0_|__|__| au |__|__| |__|__| |_2_|_0_|__|__|
Hospitalisation (2) du |__|__| |__|__| |_2_|_0_|__|__| au |__|__| |__|__| |_2_|_0_|__|__|
Hospitalisation (3) du |__|__| |__|__| |_2_|_0_|__|__| au |__|__| |__|__| |_2_|_0_|__|__|

11.2 Intervention chirurgicale : ☐ Non ☐ Oui, précisez ci-dessous :

Type d'intervention chirurgicale :	Date de l'intervention chirurgicale : |__|__| |__|__| |_2_|_0_|__|__|

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n°centre - n° ordre de sélection - initiale - initiale

11.3 Chimiothérapie : ☐ Non ☐ Oui, précisez ci-dessous :

Précisez le schéma thérapeutique, date(s) de début, les posologies et dates de fin si applicable :

11.4 Radiothérapie : ☐ Non ☐ Oui, précisez ci-dessous :

Précisez le schéma thérapeutique et les doses :	Date de début : |__|__| |__|__| |_2_|_0_|__|__|	Date de fin : |__|__| |__|__| |_2_|_0_|__|__|

11.5 Traitement(s) adjuvant(s) : ☐ Non ☐ Oui, précisez ci-dessous :

11.6 Une greffe de CSH a été réalisée pour le traitement du cancer secondaire/de la myélodysplasie : ☐ Non ☐ Oui, précisez ci-dessous :……

Date de la greffe : le |__|__| |__|__| |_2_|_0_|__|__| ☐ autogreffe ☐ allogreffe	Si allogreffe : Donneur : ☐apparenté ☐ fichier volontaires / banque

Origine CSH : ☐ CSP ☐ Moelle osseuse ☐ Sang de cordon

Date de sortie d'aplasie : \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

12. Evolution du cancer secondaire/de la myélodysplasie

12.1 Etat actuel (hors décès)

☐ Rémission complète le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|
☐ Rémission avec séquelles le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|, précisez les séquelles :
☐ Rémission partielle le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|, précisez :
☐ Stable depuis le \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|
☐ Maladie en progression
☐ Rechute depuis le\|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

12.2 Evolution fatale

Date du décès : \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\|

Autopsie effectuée : ☐ Non ☐ Oui (joindre le compte-rendu)

Veuillez spécifier la « cause du décès » rapportée dans le certificat de décès / le rapport d'autopsie :

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction :	Nom :	

19.6 SmPC

The SmPC must have been obtained from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php) and if absent from the ANSM website, use the SmPC from the Vidal compendium.

Grafalon:
agenceprd.ansm.sante.fr/php/ecodex/frames.php?specid=64898643&typedoc=R&ref=R0387691.htm

Thymoglobuline:
agenceprd.ansm.sante.fr/php/ecodex/frames.php?specid=62850870&typedoc=R&ref=R0363095.htm

19.7 Description of the Clinical Trial in the AP-HP Trials Register

Vous souffrez d'une leucémie aiguë myéloïde ou de syndrome myélodysplasique. Votre médecin vous a proposé une greffe de cellules souches hématopoïétiques à partir d'un donneur allogénique « ALLOGREFFE » comme traitement de votre hémopathie maligne après présentation de votre dossier à la Réunion de Concertation Pluridisciplinaire de votre établissement. La greffe de cellules souches hématopoïétiques est un traitement standard dans différents types de maladies hématologiques qui consiste à remplacer votre moelle osseuse malade par des cellules d'une moelle osseuse saine.

L'allogreffe « classique » est réalisée à partir d'un frère ou d'une soeur identique au niveau des antigènes HLA (qui sont les antigènes que l'on analyse pour déterminer la compatibilité entre deux personnes). En l'absence de donneur familial, une recherche de donneur compatible dans les fichiers de donneurs volontaires peut permettre de réaliser une allogreffe. Les résultats attendus, lorsqu'il existe une identité sur tous les antigènes HLA étudiés (compatibilité 10/10) sont globalement comparables à ceux des greffes faites à partir d'un donneur familial.

Les cellules du donneur non apparenté HLA compatible 10/10 seront issues des cellules souches périphériques pour la greffe.

Un problème fréquent qui peut survenir après la greffe de cellules souches allogéniques (à partir d'un donneur) est une maladie dénommée maladie du greffon contre l'hôte ou Graft-Versus-Host disease (GVH). Le mot greffon se réfère aux cellules du donneur que vous recevrez lors de votre transplantation. Le mot hôte se réfère à la personne (dans ce cas, vous) recevant les cellules. La GVH est une complication où les cellules du donneur peuvent entraîner des atteintes au niveau de vos tissus. Lorsqu'elle survient dans les 3 premiers mois après la greffe, on parle de GVH aigue. La GVH aigue peut causer une éruption cutanée et des problèmes intestinaux, tels que la diarrhée ou des vomissements. Elle peut aussi entraîner des problèmes hépatiques tels qu'une hépatite ou une jaunisse. Lorsqu'elle survient après 3 mois, on parle de GVH chronique et elle peut toucher plusieurs organes. La GVH peut également augmenter les risques d'infections.

Des médicaments dits immunosuppresseurs sont administrés systématiquement pour prévenir les réactions de GVH.

Aussi, vous recevrez avant la greffe, un conditionnement d'intensité réduite (chimiothérapie) qui est une phase de préparation de votre corps à recevoir la greffe afin de faciliter la prise de greffe et éviter le rejet.

C'est également pendant le conditionnement à la greffe qu'il est recommandé de recevoir des sérums anti-lymphocytaires ou anti-thymocytes humains (ATG) afin de réduire les risques de la GVH.

Il existe deux molécules autorisées (ATG-thymoglobuline et ATLG-grafalon) présentant des caractéristiques distinctes. Une étude rétrospective a permis d'observer qu'un conditionnement avec ATLG était associé à une réduction de la GVHD aiguë de grade > 2 par rapport à un conditionnement avec ATG sans augmenter le risque de rechute.

Cette étude a donc pour but d'évaluer l'efficacité de la prévention de la GVHD par ATLG comparé à l'ATG reçu pendant le conditionnement de la greffe.

Il est prévu d'inclure 317 patients présentant une leucémie aiguë myéloïde ou un syndrome myélodysplasique avec indication de greffe à partir d'un donneur non apparenté HLA compatible 10/10. Il s'agit d'une étude multicentrique c'est-à-dire que cette recherche sera mise en place dans les établissements de soins affiliés à la Société Française de Greffe de Moelle et de Thérapie Cellulaire situés en France.

19.8 Questionnaire

Appendix V1.0 of 03/07/2023

FACT-EBMT quality of life evaluation- French version
FACT-BMT (4ème Version)

Vous trouverez ci-dessous une liste de commentaires que d'autres patients, atteints de la même maladie, ont jugé importants. **Veuillez indiquer, en entourant un chiffre sur chaque ligne, dans quelle mesure chacune de ces propositions était vraie en ce qui vous concerne durant ces 7 derniers jours.**

	BIEN-ÊTRE PHYSIQUE	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
GP1	Je manque d'énergie	**0**	**1**	**2**	**3**	**4**
GP2	J'ai des nausées	**0**	**1**	**2**	**3**	**4**
GP3	À cause de mon état physique, j'ai du mal à répondre aux besoins de ma famille	**0**	**1**	**2**	**3**	**4**
GP4	J'ai des douleurs	**0**	**1**	**2**	**3**	**4**
GP5	Je suis dérangé(e) par les effets secondaires du traitement	**0**	**1**	**2**	**3**	**4**
GP6	Je me sens malade	**0**	**1**	**2**	**3**	**4**
GP7	Je suis obligé(e) de rester alité(e)	**0**	**1**	**2**	**3**	**4**

Veuillez indiquer, en entourant un chiffre sur chaque ligne, dans quelle mesure chacune de ces propositions était vraie en ce qui vous concerne durant ces 7 derniers jours.

	BIEN-ÊTRE FAMILIAL/SOCIAL	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
GS1	Je me sens proche de mes amis	**0**	**1**	**2**	**3**	**4**
GS2	Ma famille me soutient moralement	**0**	**1**	**2**	**3**	**4**
GS3	Mes amis me soutiennent	**0**	**1**	**2**	**3**	**4**
GS4	Ma famille a accepté ma maladie	**0**	**1**	**2**	**3**	**4**
GS5	Je suis satisfait(e) de la communication avec ma famille au sujet de ma maladie	**0**	**1**	**2**	**3**	**4**
GS6	Je me sens proche de mon (ma) partenaire (ou de la personne qui est mon principal soutien)	**0**	**1**	**2**	**3**	**4**
Q1	*Quel que soit votre niveau actuel d'activité sexuelle en ce moment, pouvez-vous répondre à la question suivante. Si vous préférez ne pas y répondre, cochez cette case et passez à la section suivante*					
GS7	Je suis satisfait(e) de ma vie sexuelle	**0**	**1**	**2**	**3**	**4**

	BIEN-ÊTRE ÉMOTIONNEL	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
GE1	Je me sens triste	**0**	**1**	**2**	**3**	**4**
GE2	Je suis satisfait(e) de la façon dont je fais face à ma maladie	**0**	**1**	**2**	**3**	**4**
GE3	Je perds l'espoir dans le combat contre ma maladie	**0**	**1**	**2**	**3**	**4**
GE4	Je me sens nerveux (nerveuse)	**0**	**1**	**2**	**3**	**4**
GE5	Je suis préoccupé(e) par l'idée de mourir	**0**	**1**	**2**	**3**	**4**
GE6	J'ai peur que mon état s'aggrave	**0**	**1**	**2**	**3**	**4**

	BIEN-ÊTRE FONCTIONNEL	Pas du tout	Un peu	Moyen-nement	Beau-coup	Énormé-ment
GS1	Je me sens capable de travailler (y compris le travail à la maison)	**0**	**1**	**2**	**3**	**4**
GS2	Mon travail (y compris le travail à la maison) me donne de la satisfaction	**0**	**1**	**2**	**3**	**4**
GS3	Je suis capable de profiter de la vie	**0**	**1**	**2**	**3**	**4**
GS4	J'ai accepté ma maladie	**0**	**1**	**2**	**3**	**4**
GS5	Je dors bien	**0**	**1**	**2**	**3**	**4**
GS6	J'apprécie mes loisirs habituels	**0**	**1**	**2**	**3**	**4**
GS7	Je suis satisfait(e) de ma qualité de vie actuelle	**0**	**1**	**2**	**3**	**4**

Veuillez indiquer, en entourant un chiffre sur chaque ligne, dans quelle mesure chacune de ces propositions était vraie en ce qui vous concerne durant ces 7 derniers jours.

	AUTRES SUJETS D'INQUIÉTUDE	**Pas du tout**	**Un peu**	**Moyen-nement**	**Beau-coup**	**Énormé-ment**
BMT1	Je m'inquiète de ne pas pouvoir continuer à travailler (y compris le travail à la maison)	**0**	**1**	**2**	**3**	**4**
BMT2	Je me sens distant(e) des autres	**0**	**1**	**2**	**3**	**4**
BMT3	J'ai peur que la greffe ne réussisse pas	**0**	**1**	**2**	**3**	**4**
BMT4	Les effets du traitement sont pires que ce que j'imaginais	**0**	**1**	**2**	**3**	**4**
C6	J'ai bon appétit	**0**	**1**	**2**	**3**	**4**
C7	Je suis satisfait(e) de mon apparence physique	**0**	**1**	**2**	**3**	**4**
BMT5	Je peux me débrouiller seul(e)	**0**	**1**	**2**	**3**	**4**
BMT6	Je me sens fatigué(e) facilement	**0**	**1**	**2**	**3**	**4**
BL4	Le sexe m'intéresse	**0**	**1**	**2**	**3**	**4**
BMT7	J'ai peur de ne plus pouvoir avoir d'enfants.	**0**	**1**	**2**	**3**	**4**
BMT8	J'ai confiance en mes infirmières(iers)	**0**	**1**	**2**	**3**	**4**
BMT9	Je regrette d'avoir eu une greffe de la moelle osseuse	**0**	**1**	**2**	**3**	**4**
BMT10	J'ai de la mémoire	**0**	**1**	**2**	**3**	**4**
Br1	Je suis capable de me concentrer	**0**	**1**	**2**	**3**	**4**
BMT 11	J'ai fréquemment des rhumes ou des infections	**0**	**1**	**2**	**3**	**4**
BMT 12	Je vois trouble	**0**	**1**	**2**	**3**	**4**
BMT 13	Je suis gêné(e) par un changement de goût des aliments.	**0**	**1**	**2**	**3**	**4**
BMT 14	J'ai des tremblements	**0**	**1**	**2**	**3**	**4**
B1	J'ai le souffle court.	**0**	**1**	**2**	**3**	**4**
BMT 15	Je suis gêné(e) par des problèmes de peau (éruptions démangeaisons)	**0**	**1**	**2**	**3**	**4**
BMT 16	J'ai du mal à aller à la selle	**0**	**1**	**2**	**3**	**4**
BMT 17	Ma maladie est une lourde épreuve pour ma famille proche.	**0**	**1**	**2**	**3**	**4**
BMT 18	Le coût du traitement est un fardeau pour moi et pour ma famille	**0**	**1**	**2**	**3**	**4**

19.9 Scale

Appendix 19.9 V1.0 of 03/07/2023

Appendix 19.9, Section 1

Acute GVHD MAGIC classification according to Harris et al. BBMT 2016 [47]

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper gastro-intestinal tractus (GI)	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	< 2 mg/dl	No or intermittent nausea, vomiting or anorexia	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2–3 mg/dl	Persistent nausea, vomiting or anorexia	Adult: 500–999 ml/day or 3–4 episodes/day Child: 10–19.9 ml/kg/day or 4–6 episodes/day
2	Maculopapular rash 25 – 50% BSA	3.1–6 mg/dl	-	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day
3	Maculopapular rash > 50% BSA	6.1–15 mg/dl	-	Adult: >1500 ml/day or >7 episodes/day Child: > 30 ml/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation > 5% BSA	>15 mg/dl	-	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based upon most severe target organ involvement):

- **Grade 0**: No stage 1–4 of any organ
- **Grade I**: Stage 1–2 skin without liver, upper GI or lower GI involvement
- **Grade II**: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI
- **Grade III:** Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI
- **Grade IV**: Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI

Appendix 19.9, Section 2:

2022 ELN risk classification by genetics at initial diagnosis of AML according to Dohner et al. Blood 2022 [50]

Risk category	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ *CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged # • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*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,** monosomal karyotype †† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2* ‡‡ • Mutated *TP53* [a]

‡ Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization.
§ AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.
‖ Only in-frame mutations affecting the basic leucine zipper (bZIP) region of *CEBPA*, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.
¶ The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
# Excluding *KMT2A* partial tandem duplication (PTD).
** Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.
†† Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).
‡‡ For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
a *TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

Appendix 19.9, section 3
MDS prognostic scores

Section 3a: MDS IPSS score according to Greenberg, Blood 1997 [51]

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Good	Normal, -Y, del(5q), del 20q
Intermediate	others
Poor	-7 or Complex: ≥3 abnormalities

Prognostic variable	0	0.5	1	1.5	2
BM Blast %	< 5	5-10	-	11-20	21-30
Cytogenetics	Good	Intermediate	Poor		Intermediate
Cytopenias	0-1	2-3			

Cytopénias: hemoglobin < 10 g/dL, platelets < 100 G/L, ANC < 1.8 G/L

RISK CATEGORY	RISK SCORE
Low	0
Intermediate-1	0.5 - 1
Intermediate-2	1.5 - 2
High	≥ 2.5

Section 3b: MDS R-IPSS scoring according to Greenberg et al. Blood 2012[52]
IPSS-R Cytogenetic risk groups

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

IPSS-R Prognostic Score Values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor

BM Blast %	<=2%		>2-<5%		5-10%	>10%	
Hemoglobin g/dL	> 10		8-10	< 8			
Platelets G/L	>100	50-100	< 50				
ANC G/L	> 0.8	< 0.8					

IPSS-R Prognostic Risk Categories/Scores

RISK CATEGORY	**RISK SCORE**
Very Low	<=1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

Appendix 19.9, Section 4
Diagnostic and Gradation of chronic GVHD

Chronic GvHD is defined according to the NIH classification published in 2005 [48]

The diagnosis of chronic GVHD is retained if there is a distinctive sign (1 alone is sufficient) or evocative signs associated with a supplementary examination in favor (biopsy, for example).

We then define:

A- Classical chronic GvHD in patients with only evidence of chronic GvHD
B- The overlap syndrome when a patient presents both signs of acute GvHD and chronic GvHD
C- Late acute GvHD which corresponds to exclusive signs of acute GvHD without signs of chronic GvHD occurring after J100.

Organs affected by chronic GVHD (French)

Peau	Erythème, sécheresse, prurit, changement de pigmentation (vitiligo, hyperpigmentation) plaques papulosquameuses, nodules, exfoliation, rash maculo-papulaire ou urticaire, sclérodermie, morphée (une ou plusieurs lésions lisses indurées et circonscrites)
Ongles	Onychodystrophie, onycholyse, striés, fendus.
Cheveux	Canitie prématurée (cuir chevelu, cils, sourcils), alopécie, amincissement du cuir chevelu, raréfaction de la pilosité corporelle.
Bouche	Sécheresse, brûlures, gingivite, mucite, atrophie gingivale, érythème, lichen, ulcères, atrophie labiale, changement de pigmentation, contracture de la bouche, caries dentaires.
Yeux	Sécheresse, brûlures, photophobie, douleur, larmoiement, sensation de grain de sable
Organes Génitaux	Sécheresse, sténose vaginale, dyspareunie, érythème vulvaire, atrophie génitale, lichen
Foie	Élévation du bilan hépatique sanguin sans autre cause connue. En l'absence d'une autre atteinte organique, une biopsie est nécessaire pour confirmer le diagnostic.
Poumons	Bronchiolite oblitérante, toux, sifflements, dyspnée d'effort, bronchites chroniques ou sinusites.
Tube digestif	Anorexie, nausées, vomissements, perte de poids, diarrhées, dysphagie, malabsorption.
Fasciite	Ankylose et réduction des mouvements, avec occasionnellement gonflement, douleurs, crampes, érythème et induration, atteignant le plus fréquemment les avant- bras les poignets et les mains, les chevilles, les jambes et les pieds, incapacité d'étendre les poignets sans fléchir les doigts ou les coudes, contractures.
Muscles	Faiblesse proximale, crampes.

Squelette	Arthralgies proximales des articulations des os du bassin, et parfois d'articulation moins importantes
Séreuses	Douleurs pulmonaires ou cardiaques secondaires à une pleurésie ou une péricardite.

Cotation sévérité par organes:

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

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

The gradation of chronic GvHD is defined by the number and score of affected organ :

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

Appendix 19.9 section 5

Gradation of toxicities and infections severity

CTC-AE -Toxicity Grading scale for determining the severity of adverse event
CTCAE_v5.0_2017-11-27.xls (live.com)
Ou :
https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fevs.nci.nih.gov%2Fftp1%2FCTCAE%2FCTCAE_5.0%2FNCIt_CTCAE_5.0.xls&wdOrigin=BROWSELINK

SCORE GREFIG : SCORE DE SEVERITE DES INFECTIONS

EVENEMENTS	GRADE I	GRADE II	GRADE III
BACTERIEN	-Foyer bactérien traité en externe (à l´exception des broncho-pneumopathies)	-Bactériémie sans signe de gravité -Foyer ne mettant pas en jeu le pronostic vital et traité en hospitalisation	-Septicémie avec signes de gravité* -Foyer mettant en jeu le pronostic vital et traité en hospitalisation
FONGIQUES	-Candidose superficielle	-Foyer profond à Candida sans hémoculture -Hémocultures sans signe de gravité et sans foyer -Aspergillose sinusienne simple (sans atteinte osseuse) et isolée (pas d'autres localisations)	-Septicémie à Candida (≥ 1 hémoculture) avec signes de gravité* et/ou foyers profonds -Toutes autres situations (aspergillose pulmonaire prouvée ou probable, aspergillose disséminée)
VIRAL **CMV** **VZV**	 -Virémie ou antigénémie ou 2 PCR sans symptômes ni fièvre -Zona ou varicelle non compliqués, traités en externe	 -Idem + fièvre isolée ou syndrome mononucléosique -Zona ou varicelle non compliqués traités à l´hôpital	 -Maladie à CMV -Infection à VZV avec CIVD et/ou atteinte viscérale
Toute autre infection documentée (autres virus, Pneumocystis, Toxoplasma…) **ou** **Episode probablement infectieux non documenté**	-Infection ne justifiant pas d´hospitalisation (à l´exclusion des pneumopathies) -Fièvre non documentée en aplasie	-Infections bronchiques et/ou pulmonaires sans hypoxémie **ou** -Infection justifiant une hospitalisation sans nécessité de soins intensifs	-Infection avec pneumopathie hypoxémiante (PaO2≤65mmHg) **ou** -Infection nécessitant des soins intensifs **ou** -Toutes infections mettant en jeu le pronostic vital