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Randomized prospective Phase III clinical trial comparing HLA 10/10 matched unrelated donor and haploidentical allogeneic hematopoietic stem cell transplantation after myeloablative conditioning regimen
« MAC-HAPLO-MUD »

INTERVENTIONAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version N°1.0 of /mm/yyyy
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Sous l'égide de la société francophone Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)

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PROTOCOL SIGNATURE PAGE

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

Coordinating Investigator:
Pr **Régis Peffault de Latour** Date: ……/……/……..
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The study was approved by the Ethic committee (CPP) of ……. on …… and authorised by the ANSM on ……...

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1- SUMMARY

Full title	Randomized prospective Phase III clinical trial comparing HLA 10/10 matched unrelated donor and haploidentical allogeneic hematopoietic stem cell transplantation after myeloablative conditioning regimen
Abbreviated title	**MAC-HAPLO-MUD**
Coordinating Investigator	Pr Régis Peffault de Latour
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	An unrelated adult donor who is HLA-matched to the recipient at the allele-level (at HLA-A, -B, -C, -DQB1 and -DRB1) is considered the best choice in the absence of an HLA-matched sibling for patients needing hematopoietic stem cell transplantation (SCT). However, using matched unrelated donors (MUD) is limited by (1) a prolonged time to identify and schedule donation for some MUD allowing some patients to relapse before transplantation can be performed, and (2) limited availability of fully HLA-MUD for the non-Caucasian population. Alternative donors (single HLA mismatched unrelated donor, unrelated umbilical cord blood and grafts from haploidentical related donors) are still associated with higher non-relapse mortality and delayed immune reconstitution. A more recent strategy for haploidentical (haplo) related donor SCT (haplo-SCT) have improved dramatically outcomes using T-cell replete grafts with administration of post-transplantation cyclophosphamide (PTCy, which targets alloreactive T cells generated early after an HLA-mismatched transplant, sparing regulatory T cells and leaving unaffected the non-dividing hematopoietic stem cells) and standard post-transplant immune suppression with a calcineurin inhibitor (CNI) and mycophenolate mofetil. From retrospective studies, haplo-SCT with PTCy are associated with similar overall and progression-free survivals as with MUD stem cell transplantation (MUD-SCT), but with lower rates of toxicity and graft versus

	host disease (GvHD), and thus potentially better results than MUD-SCT after reduced intensity conditioning regimen. A phase III randomized trial is currently addressing this question in France for elderly patients using a reduced intensity conditioning regimen (HaploMUDelederly-01 /PHRC-K 14-045 / PI: D Blaise Institut Paoli Calmettes). A randomized prospective Phase III clinical trial comparing HLA 10/10 MUD and haplo-SCT after myeloablative conditioning regimen is urgently needed to answer to this question.
Main objective and primary endpoint	M**ain objective:** to improve the 1-year progression free survival, without acute grade II-IV GvHD and without moderate or severe chronic GvHD, using of the haplo donor compared with 10/10-HLA MUD after myeloablative SCT. **Primary endpoint:** a 1-year progression free survival without Grade II-IV acute GvHD and without moderate or severe chronic GvHD of 65% after haplo SCT versus 50% after 10/10-HLA MUD.
Secondary objectives and endpoints	**Secondary objectives:** 1) to compare the two arms in terms of clinical and biological outcomes: • Kinetic of haematopoietic reconstitution and Graft failure, GvHD, progression free survival, relapse, non relapse mortality, overall survival, • Interval between inclusion and transplant • Rehospitalizations • Treatment related morbidity • Quality of life • Chimerism • Immune reconstitution 2) to search for prognostic factors of the main outcome globally and in each arm 3) to search for treatment-by-covariate interactions on the main outcome **Secondary endpoints:** • Interval between inclusion and transplant • Absolue numbers of neutrophils and platelets at M1, M2, M3, M6 and M12. • Chimerism at M1, M3, M6, M12, M24 • Acute GvHD incidence and grading • Chronic GvHD incidence and grading • Relapse incidence • Progression free survival • Severe infections (CTC-AE grade 3-4) • Incidence of veino-occlusive disease • Incidence of cardiac toxicities • Non-relapse mortality • Overall survival • Quality of life questionnaire (EBMT)

	• Number of new days of hospitalization after the hospitalization for transplantation • Immune reconstitution at M1, M3, M6, M12, M24 (T lymphocytes, CD4, CD8, B, NK lymphocytes and gammaglobulines)
Design of the trial	Randomized prospective Phase III clinical trial comparing HLA 10/10 matched unrelated donor and haploidentical allogeneic hematopoietic stem cell transplantation after myeloablative conditioning regimen
Population of trial subjects	Patients 15 year of age or older with high risk hematological malignancies and with an indication of allogeneic hematopoietic stem cell transplantation
Inclusion criteria	**- Patients :** - Aged 15 to 55 years old - With AML/ALL/SMD/SMP requiring allogeneic stem cell transplantation - At least in partial response of their malignant disease - Without HLA matched related donor - With a strong probability to have both a related haplo - donor and a HLA-10/10 matched donor available (the patient needs to have at least 5 MUD identified outside - the book "BMDW (Bone Marrow Donors Worldwide)" or using the easy match software, to be included). - With usual criteria for HSCT: ▪ ECOG ≤ 2 ▪ No severe and uncontrolled infection ▪ Cardiac function compatible with high dose of cyclophosphamide ▪ Adequate organ function: ASAT and ALAT ≤ 2.5N, total bilirubin ≤ 2N, creatinine < 150 µmol/L (except if those abnormalities are linked to the hematological disease) - With health insurance coverage - Understand informed consent or optimal treatment and follow-up - Prescription of two effective contraception methods must be prescribed during all the duration of the study - Having signed a written informed consent (2 parents for patients aged less than 18)
Exclusion criteria	**- Patients :** - With cancer in the last 2 years (except basal cell carcinoma of the skin or "in situ" carcinoma of the cervix) - With uncontrolled infection - With seropositivity for HIV or HTLV-1 or active hepatitis B or C - Yellow fever vaccine - Heart failure according to NYHA (II or more) - Bile duct obstruction - Preexisting acute hemorrhagic cystitis - Renal failure with creatinine clearance <30ml / min

	- With pregnancy (β-HCG positive) or breast-feeding - With any debilitating medical or psychiatric illness which preclude the realization of the SCT or the understanding of the protocol - Under protection by law (tutorship or curatorship) - Unwilling or unable to comply with the protocol
Experimental group	Haplo donor myeloablative SCT with use of Cyclophosphamide, 50 mg/Kg/day, by intravenous route, at D+3 and D+4 after stem cell transplantation
Control group	HLA-MUD 10/10 myeloablative SCT
Treatment (transplant modalities)	1/ **Conditioning regimen** : For patients with myeloid malignancies a) for haploidentical SCT -Thiotepa (5mg/kg/day: day -7 and -6) -Fludarabine (40mg/m2/day: day-5 to-2) - IV Busulfan (3,2mg/kg/day : day-5, to-3) b) for HLA-matched unrelated donor SCT -Fludarabine (30mg/m2/day: day-6 to-2) -IV Busulfan (3,2mg/kg/day, D-6, to-3) For patients with ALL. -Fludarabine 30 mg/m2/day on days -7 to -5 and TBI 200 cGy twice daily on days -4 to -2 (total dose 1200 cGy) 2/ **Stem cell source** : -Bone marrow for haploidentical SCT -Peripheral blood stem cell (PBSC) for HLA-matched unrelated transplantation 3/ **GVHD Prophylaxis :** For haploidentical SCT : • cyclophosphamide 50 mg/Kg/day at D+3 and D+4 • ciclosporine and mycophenolate (MMF) from D+5 For HLA-matched unrelated donor SCT : • anti-thymocyte globuline (Thymogobuline) 5 mg/Kg total dose (2.5mg/Kg at day -3 and -2) • Cyclosporine at Day -1 and MMF at Day +1 In the absence of GvHD, MMF will be stopped at D+35 in both arms
Interventions added for the trial	Randomization of the donor between haplo and 10/10 MUD. Blood sample for biobanking (M1)
Risks added by the trial	Risks are related to the SCT itself, not to the randomization (haplo or MUD arm). There is no risk difference between both arms.
Scope of the trial	Our goal is to show a superiority of haplo-SCT (primary endpoint) but even if similar results between both arms are obtained, this study might revolutionize the strategy of SCT since haplo donors will be used in priority compared with MUD (quick procedure, cheaper, and available for

	almost all patients).
Number of subjects included	344
Number of sites	36 centres
Duration of the trial	Inclusion period: 36 months Participation period : 24 months Total duration: 60 months
Number of enrolments expected per site and per month	0.4 patient/month/centre
Statistical analysis	**Justification of sample size** We hypothesize the 1-year progression free survival without Grade II-IV acute GvHD and without moderate or severe chronic GvHD will be of 65% after haplo SCT versus 50% after 10/10-HLA MUD. 172 patients in both arms (n=344 overall) are required to demonstrate such a difference, based on a two-sided logrank test, α = 0.05 and power = 0.80 (HR= 0.62), with a required total number of events of 146. The Bayesian interim analysis will not inflate α. **Interim analysis at mid-inclusion** This will be based on the Bayesian computation of stopping rules based on the modeling of the log Hazard ratio (HR) of the main endpoint (Spiegelhalter 1994). Non informative prior of the logHR will be considered. **Terminal analysis** after the observation of the required number of events
Sources of funding for the trial	*Industrial and patients associations funding*
Trial will have a Data Monitoring Committee	*Yes*

2- SCIENTIFIC JUSTIFICATION FOR THE TRIAL

2.1 Hypothesis for the study

An unrelated adult donor who is HLA-matched to the recipient at the allele-level (at HLA-A, -B, -C, -DQB1 and -DRB1) is considered the best choice in the absence of an HLA-matched sibling for patients needing hematopoietic stem cell transplantation (SCT). However, using matched unrelated donors (MUD) is limited by (1) a prolonged time to identify and schedule donation for some MUD allowing some patients to relapse before transplantation can be performed, and (2) limited availability of fully HLA-MUD for the non-Caucasian population. Alternative donors are used for transplantation in patients without a fully-MUD including single HLA mismatched unrelated donor, unrelated umbilical cord blood and grafts from haploidentical related donors but are associated with higher non-relapse mortality and delayed immune reconstitution.
A more recent strategy for haploidentical (haplo) related donor SCT (haplo-SCT) have improved dramatically outcomes using T-cell replete grafts with administration of post-transplantation cyclophosphamide (PTCy, which targets alloreactive T cells generated early after an HLA-mismatched transplant, sparing regulatory T cells and leaving unaffected the non-dividing hematopoietic stem cells) and standard post-transplant immune suppression with a calcineurin inhibitor (CNI) and mycophenolate mofetil. From retrospective studies, haplo-SCT with PTCy are associated with similar overall and progression-free survivals as with MUD stem cell transplantation (MUD-SCT), but with lower rates of toxicity and graft versus host disease (GvHD), and thus potentially better results than MUD-SCT after reduced intensity conditioning regimen. Haplo-SCT with PTCy is thus highly discussed nowadays motivating prospective trials to confirm the benefit of this procedure (ref 1 et ref 2). A phase III randomized trial is currently addressing this question in France for elderly patients (HaploMUDelederly-01 /PHRC-K 14-045 / PI: D Blaise Institut, Paoli Calmettes, NCT 02623309).
Few retrospective non-controlled registry studies recently suggest that outcomes after haplo-SCT using PTCy approach might also be superior in terms of GVHD free survival to that after MUD-SCT in the setting of a myeloablative conditioning regimen in adults with high risk hematological malignancies. A randomized prospective Phase III clinical trial comparing HLA 10/10 MUD and haplo-SCT after myeloablative conditioning regimen is thus urgently needed to answer to this question.

2.2 Existing knowledge relating to the condition under investigation

Stem cell transplantation as a curative treatment for hematological malignancies
Despite progress in chemotherapy, targeted therapy and immunotherapy, allogeneic hematopoietic stem cell transplantation (SCT) is a recognized curative procedure for hematological malignancies. It is now well known that this is related to the graft-versus-tumor (GVT) effect developed from the immunocompetent cells contained in or generating from the donor graft. Despite this unique antitumoral activity, SCT has been restricted to a limited number of patients mainly due to two major limitations: the toxicity of the conditioning regimen and the absence of a donor for every single patient. The first concern was solved by the introduction of reduced intensity conditioning (RIC) regimen (3, 4) which allow the use of SCT for older patient who can now benefit from GVT without an excess rate of toxicity. Regarding transplantation in patients without a fully-MUD, alternative donors have been used including single HLA mismatched unrelated donor, unrelated umbilical cord blood and grafts from haploidentical related donors but until recently with higher non-relapse mortality and delayed immune reconstitution.

Haplo-SCT using T-replete graft after reduced intensity conditioning regimen associated with adequate immunosuppression
By the past, several strategies of T-cell depletion of haploidentical graft associated with highly myeloablative conditioning have been introduced in the 90's: although this conducted usually to

engraftment and limited occurrence of severe GVHD, enthusiasm has been tempered by the complexity of the procedures, the high rates of severe infectious complications and of relapse (5 ; 6).
Recently, several groups successfully explored new platforms using T-replete graft associated with adequate immunosuppression. In this development, RIC have been regularly used as conditioning regimen. Basically, two strategies of immunosuppression have been promoted:
1) Teams from Seoul and Beijing used high dose antithymocyte globulins (ATG) followed by post graft immunosuppression.
" Beijing (7):
• Conditioning: CYTARABIN (4 g/m2 x2)+BU (12mg/kg x 3)+ CYCLOPHOPHAMIDE (1.8 g/m2 x2)+CCNU (250 mg/ m2 x1)
• ATG: 2.5 mg/kg x 4
• Graft: primed BM and PBSC
• Post graft Immunosuppression: CSA + MTX + MMF
" Seoul (8):
• Conditioning: BU (3.2mg/kg x 2)+ Fludarabine ((30 mg/m2 x 6)
• ATG: 3 mg/kg x 4
• Graft: PBSC
• Post graft Immunosuppression: CSA + MTX
" Both approaches, mainly performed in young patients (median age: 25 and 40 in Beijing and Seoul respectively) achieved good results with 100% engraftment, low rate of severe GVHD and a 18% 1-year non relapse mortality.

2) The Baltimore group developed another approach using haploidentical related donors, RIC, T-replete bone marrow and post-transplant high dose cyclophosphamide (pT-HDCy) in patients with advanced hematological malignancies (9). High dose, post-transplantation Cy administered early at a fixed time point after bone marrow infusion, has shown to eradicate alloreactive donor and host T-cells, activated by respective antigens, thereby reducing the incidence of GVHD reaction (10). It has been shown that post-transplantation Cy does not affect engraftment due to the enzymatic resistance to this agent of hematopoietic stem cells (11) Two studies including more than 118 patients showed the feasibility of this approach with an engraftment rate over 90%, an incidence of acute grade> II GVHD about 35%, with less than <10% grade III-IV, a low incidence of chronic extensive GVHD (<5%) and a 1-year NRM < 15%. The relapse incidence was> 45%, probably explained by a majority of patients with advanced disease at transplant (12). The Baltimore group has updated its results in 2011: among 210 patients (including 66 NHL, 43 AML, 30 Hodgkin disease transplanted with this protocol, the graft failure was of 13% (7% after exclusion of patients in relapse), the median time for neutrophil count recovery (500 / mm3) was 15 days, the incidence of grade II-IV GVHD was 27%, with only 5% of acute grade III-IV GVHD, the incidence of chronic GVHD was 13%. The relapse rate was 55%, and the NRM was 18% at 3 years. Deaths were related to relapse in 79 patients, infections in 15, pulmonary complications in 7, GVHD in 5. At 3 years, the OS was of 41% and EFS of 32%. Three-year OS in patients with ALL was 50%, for ALL, versus 45% in MDS and myeloproliferative disorders 35% in AML, 62% in Hodgkin's disease, 41% in non- Hodgkin lymphoma (NHL), and 22% in chronic lymphocytic leukemia (13,14). Several other groups have also reported their experience in haplo-identical transplant with PT-Cy, using varied conditioning regimen (15,16).
Because of those promising results, a phase III randomized trial is currently addressing this question in France for elderly patients (HaploMUDelederly-01 /PHRC-K 14-045 / PI: D Blaise Institut Paoli Calmettes).

2.3 SUMMARY OF RELEVANT PRE-CLINICAL AND CLINICAL TRIALS

Justification for the use of a myeloablative conditioning regimen in Haplo-SCT using T-replete graft after myeloablative conditioning regimen using pT-HDCy
In HLA-matched related or unrelated allogeneic SCT for acute leukemia, several studies have already reported a dose dependent effect of the intensity of the conditioning regimen on disease control (17, 18) Very recently, a phase III randomized trial comparing MAC with RIC in patients with

acute myeloid leukemia or myelodysplastic syndromes confirmed again this statement. Patients aged 18 to 65 years were randomly assigned to receive MAC (n = 135) or RIC (n = 137) followed by HCT from HLA-matched related or unrelated donors. Accrual ceased at 272 patients because of high relapse incidence with RIC versus MAC (48.3%; 95% CI, 39.6% to 56.4% and 13.5%; 95% CI, 8.3% to 19.8%, respectively; P < .001). At 18 months, OS for patients in the RIC arm was 67.7% (95% CI, 59.1% to 74.9%) versus 77.5% (95% CI, 69.4% to 83.7%) for those in the MAC arm (difference, 9.8%; 95% CI, -0.8% to 20.3%; P = .07). TRM with RIC was 4.4% (95% CI, 1.8% to 8.9%) versus 15.8% (95% CI, 10.2% to 22.5%) with MAC (P = .002). RFS with RIC was 47.3% (95% CI, 38.7% to 55.4%) versus 67.8% (95% CI, 59.1% to 75%) with MAC (P < .01). In conclusion OS was higher with MAC, but this was not statistically significant. However, RIC resulted in lower TRM but higher relapse rates compared with MAC, with a statistically significant advantage in RFS with MAC. These data support the use of MAC as the standard of care for fit patients with acute myeloid leukemia or myelodysplastic syndromes (19). In this context, the reduced risk of relapse after MAC is counterbalanced by higher NRM leading to similar overall survival in MAC and RIC [(20, 21)], which justify to use MAC regimen in younger patients, in whom TRM is lower. Moreover, in T-replete haplo-SCT, low risks of acute and chronic GVHD, resulting in <20 % NRM at 1 to 5 years after RIC and MAC, have been reported [22, 23). Relapse incidence, however, varies from 35 to 60 % at 1-year posttransplant and is still the major detrimental event after T-replete haplo-SCT performed with RIC and PT-Cy (22, 23, 24, 25). Although these differences could be related to disease risk at transplant (26, 27, 28), these observations raise the question of the role of the conditioning regimen intensity on disease control and transplant outcomes after T-replete haplo-SCT, which need to be address in a prospective randomized trial, the reference treatment being 10/10 MUD SCT.

Justification for the use of thiotepa-based myeloablative conditioning regimen in patients with myeloid hematological malignancies in Haplo-SCT using T-replete graft and pT-HDCy

The Genoa group conducted by Bacigalupo has developed a haploidentical transplant approach with a myeloablative but reduced intensity toxicity regimen (TBF associating: Thiotepa 10 mg / kg, Busilvex 9.6 mg / kg, fludarabine 150 mg / m2), followed by an unmanipulated bone marrow and a GVHD prevention based on PT-Cy (50 mg/ kg/d at D3 and D5), cyclosporin from D0 and MMF from D1. G-CSF was administered from D5. In a series of 55 patients with hematological malignancies, including 27 advanced stage diseases, acute and chronic GVHD rates were 12 and 10%, respectively. The 1-y NRM was of 18%, the 1-y DFS was of 68 % when transplants were performed in CR1, and of 37% when transplant was performed in progressive disease (29, 30).

The MD Anderson group has developed a conditioning regimen with Thiotepa 10 mg/kg, Fludarabine 160 mg/ m2, Melphalan 140 mg/m2, unmanipulated bone marrow, PT-Cy, tacrolimus and MMF. The study included 32 patients, whose 60% were not in remission at transplant. The 1-y NRM was 16%, the incidence of grade II-IV acute GVHD 27%, of chronic GVHD 8%; finally, OS was 66% and DFS 45% (31).

Justification for the use of Fludarabine Busulfan-based myeloablative conditioning regimen in patients with myeloid hematological malignancies in MUD-SCT

In younger patients (ie, aged 18–40 years) the combination of a myeloablative dose of intravenous busulfan with cyclophosphamide is a standard preparative regimen, which compares favourably with the combination of cyclophosphamide and ablative doses (usually 12 Gy) of total body irradiation in patients with myeloid malignancies (32, 33). However, myeloablative regimens are associated with substantial treatment-related toxicity in patients older than 40 years. Non-relapse mortality in older patients was the major driver for the development of reduced intensity conditioning (RIC) regimens, which aimed to minimize regimen-related toxicity while securing engraftment and providing a platform for the graft-versus-leukaemia effect. (3, 4). Rapidly, after initial enthusiasm, it was reported that RIC regimens were associated with a significantly increased risk of relapse (34). Overall, the benefit of reduced non-relapse mortality that RIC regimens provide is counterbalanced by an increased risk of relapse (35). Conditioning regimens need to be developed that will retain the antileukaemic activity of myeloablative conditioning, while reducing the transplant-related toxicity to the level of reduced RIC regimens: these programs are tentatively referred to as reduced toxicity

regimens (36). One such regimen is based on the combination of a myeloablative dose of intravenous busulfan (12·8 mg/kg or equivalent) with fludarabine (160 mg/m2 or similar), which has been reported to be effective for patients with acute myeloid leukaemia in retrospective studies (37, 38, 39). Two randomized trials investigating these conditioning regimens in younger patients have been reported. In the first (40), which was done in a patient population that included patients with acute myeloid leukaemia, acute lymphoblastic leukaemia, and other haematological malignancies, the busulfan plus fludarabine regimen did not prove to be a suitable replacement for busulfan plus cyclophosphamide because a higher incidence of relapse was noted in the busulfan plus fludarabine regimen compared with the busulfan plus cyclophosphamide regimen. Conversely, in another trial in young patients with acute myeloid leukaemia, the busulfan plus fludarabine regimen was reported to be associated with less toxicity than the busulfan plus cyclophosphamide regimen, but had similar antileukaemic activity (41). More recently, a randomised trial compared the standard myeloablative busulfan plus cyclophosphamide regimen with the reduced toxicity busulfan plus fludarabine regimen for older patients (40–65 years) with acute myeloid leukemia undergoing allogeneic SCT (Lancet). In this trial,252 patients received either busulfan plus cyclophosphamide (n=125) or busulfan plus fludarabine (n=127). 1-year non-relapse mortality was 17·2% (95% CI 11.6–25.4) in the busulfan plus cyclophosphamide group and 7.9% (4.3–14·3) in the busulfan plus fludarabine group (Gray's test p=0·026). Cumulative incidence of relapse was similar between the 2 arms. Overall, the 2 latest prospective studies comparing busulfan plus cyclophosphamide or busulfan plus fludarabine was in favor of the use of the latter association which is associated with lower transplant-related mortality than busulfan plus cyclophosphamide, but retains potent antileukaemic activity. Accordingly, this regimen is to date the standard of care in such patients.

Justification for the use of a 12 gray Total Body Irradiation-based regimen in patients with lymphoid hematological malignancies (for haplo and MUD SCT)

AlloHCT is used as part of consolidation treatment of adults with acute lymphoblastic leukemia with intention to reduce the risk of relapse. Although comparison of TBI with myeloblative chemotherapy in a setting of ALL has never been a subject of a prospective trial, some retrospective analyses confirmed the advantage of TBI (42, 43, 44). A very recent retrospective study on more than 4,500 patients on behalf of the acute leukemia working party of the European society for blood and marrow transplantation confirmed this finding (45). Among procedure-related factors, the use of TBI-based conditioning was the strongest predictor of relapse and was associated with an over 50% reduction of the risk of this event. New, irradiation free regimens based on the use of thiotepa are under development; however, their utility requires further evaluation (46).

Haplo-SCT has also been developed using 12 Gy TBI. In a series of 30 patients (Atlanta group) transplanted with PBSC after a MAC associating 12 GY TBI + fludarabine, the aGVHD grade II to IV and III and IV was seen in 43% and 23%, respectively. The cumulative incidence of chronic GVHD was 56% (severe in 10%). After a median follow-up of 24 months, the estimated 2-year overall survival, disease-free survival, non relapse mortality, and relapse rate were 78%, 73%, 3%, and 24%, respectively. Two-year DFS and relapse rate in patients with low/intermediate risk disease was 100% and 0%, respectively, compared with 39% and 53% for patients with high/very high risk disease (47, 48)

Overall, the standard of care for patients with acute lymphoblastic leukemia using standard regimen should include 12 Gy TBI . We thus decided to use a unique conditioning regimen for both arms associating fludarabine and TBI in MAC-HAPLO-MUD.

Justification for the choice of the stem cell source after haplo or 10/10 MUD transplantation

Regarding haplo-SCT, very few studies have been published after myeloablative conditioning regimen. The mostly used source of stem cell was bone marrow to avoid higher incidence of GVHD induced by the use of PBSC. According to Raiola et al, the cumulative incidence of acute GvHD grade II-III is 12% with no grade IV, while chronic GVHD was 26% using marrow as source of stem cells after a myeloablative conditioning regimen (49). Using Peripheral blood, Solomon et al reported a cumulative incidence of acute GvHD grade II-IV of 40% including 10% of grade III-IV of while chronic GVHD was 35% (50). The primary endpoint of MAC-HAPLO-MUD study has been defined according to the use of marrow as source of stem cells regarding haplo-SCT because of the

larger number of studies using this source of stem cells in this context and lower rates of acute and chronic GvHD.
Regarding MUD transplantationa phase 3, multicenter, randomized trial of transplantation of peripheral-blood stem cells (PBSC) versus bone marrow (BM) from unrelated donors to compare 2-year survival probabilities with the use of an intention-to-treat analysis was published in 2012 (51). Between March 2004 and September 2009, 551 patients were enrolled at 48 centers. The overall survival rate at 2 years in the PBSC group was 51% (95% confidence interval [CI], 45 to 57), as compared with 46% (95% CI, 40 to 52) in the BM group (P = 0.29), with an absolute difference of 5 percentage points (95% CI, −3 to 14). The overall incidence of graft failure in the PBSC group was 3% (95% CI, 1 to 5), versus 9% (95% CI, 6 to 13) in the BM group (P = 0.002). The incidence of chronic GVHD at 2 years in the PBSC group was 53% (95% CI, 45 to 61), as compared with 41% (95% CI, 34 to 48) in the BM group (P = 0.01). In conclusion, no significant survival differences between PBSC and BM transplantation from unrelated donors was identified. Exploratory analyses of secondary end points indicated that PBSC may reduce the risk of graft failure, whereas BM may reduce the risk of chronic GVHD. PBSC will be used with anti-thymocyte globuline to reduce the risk of chronic GvHD (see below).

Justification for the GvHD prophylaxis
Regarding haplo-SCT, PT-Cy based GVHD prophylaxis has been evaluated by several groups in T repleted haplo-identical MAC or RIC transplant. PT-Cy allows an effective prevention of GVHD, especially cGVHD with an incidence of extensive cGVHD less than 15% in most studies (see also section 2.2).
Concerning MUD transplantation, the association of cyclosporine and methotrexate is the historical reference treatment as described by the Seattle group more than 30 years ago (52). However, patients are exposed to a higher rate of acute grade II-IV GvHD using this prophylaxis and PBSC as source of stem cells (see section 3.3, justification of the source of stem cells) which justify to add anti-thymocyte globuline (ATG) in this situation. Retrospective studies (53) as well as prospective randomized trials clearly showed that adding ATG in this situation reduce both risk of severe acute as well as chronic GvHD without exposing the patient to a higher risk of relapse (ref 47-48 BIG). Previous studies performed in patients given grafts after myeloablative conditioning showed that low or moderate doses of ATG (<6 mg/Kg for thymoglobuline) did not significantly increase the relapse risk but decrease the risk for chronic GvHD (54, 55, 56). This is the reason GvHD prophylaxis in patients who will received a MUD transplantation will associate CSA and MTX but also thymoglobuline 5mg/Kg total dose.

2.4 Description of the population of trial subjects and justification for the choice of subjects

1) **Hematologic malignancies**: the publication available so far concern only patients with malignant hematological disorders where the intensity of the conditioning regimen might play a role in lower the incidence of relapse. It would thus be non reasonable to include in this trial patients with aplastic anemia where the conditioning regimen does not need to be myeloablative or patients with hemoglobinopathy (sickle cell disease or thalassemia) since publications in such patients are limited using our approach to allow randomization. In addition, the use of MAC is not recommended for highly pretreated lymphomas having an indication for alloHSCT because of a high risk of NRM.

2) **Disease risk and age**:
   Because of various risk in our population of malignant disorders, we decided to use the disease risk index (low/intermediate versus high) using e CRF-linked software for randomization process (57). We will then be able to include the same number of patients in each arm according to their risk at time of HSCT.
   It is widely accepted that patients between 15 years and 18 years of age are receiving the same treatment than older patients. This is why we are assisting since almost 10 years to the development of adult and young adolescent unit (AYA) dedicated to patients aged between 15 and 25 years of age. After discussion with our pediatric colleagues through the

pediatric scientific council of the SFGM-TC, we thus decided to include patients aged less than 18 but 15 years of age or more in the MAC-HAPLO-MUD study.

2.5 Name and description of the investigational medicinal product(s)

In this study, we use Cyclophosphamide, 50 mg/Kg/day, by intravenous route, at D+3 and D+4 after haploidentical SCT.

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

As developed before (section 2.2 “Haplo-SCT using T-replete graft after reduced intensity conditioning regimen associated with adequate immunosuppression” part 2), the Baltimore group developed the pT-HDCy using haploidentical related donors with intra-venous injection at day +3 and day +4, using T-replete bone marrow in patients with advanced hematological malignancies (9). High dose, post-transplantation Cy administered early at a fixed time point after bone marrow infusion, has shown to eradicate alloreactive donor and host T-cells, activated by respective antigens, thereby reducing the incidence of GVHD reaction (10). This approach has been used by many French centres using RIC protocols. The SFGM-TC did a report on more than 500 haploidentical related donors HSCT with pT-HDCy mostly done at day+3 and day+4 with an acceptable and expected toxicity profile (the report is accessible on demand). For all those reasons, we decided to used pT-HDCy at day +3 and day +4 intravenously.

2.7 Summary of the known and foreseeable benefits and risks for the study participants

Benefits will be evaluated in terms of efficacy: progression free survival at 1 year, without acute grade II-IV GvHD and without moderate or severe chronic GvHD.
Risks are related to SCT itself, not to the randomization (haplo or MUD arm). Essentially a risk of not 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, GvH, infectious complications, relapse and survival.
PT-HDCy will also be strictly followed in MAC-HAPLO-MUD due to the known cardiac toxicity of cyclophosphamide and hemorrhagic cystits related to its use in this situation.

3- OBJECTIVES

3.1 Main objective

The main objective is to assess the benefit in terms of the 1-year progression free survival without acute grade II-IV GvHD and without moderate and severe chronic GvHD, of the haplo donor myeloablative transplantation compared to 10/10-HLA MUD

3.2 SECONDARY OBJECTIVES

- Compare the two arms in terms of clinical and biological outcomes:
  - Kinetic of haematopoietic reconstitution and graft failure, GvHD, progression free survival, relapse, non relapse mortality, overall survival,
  - Interval between inclusion and transplant
  - Rehospitalizations
  - Treatment related morbidity
  - Quality of life
  - Chimerism
  - Immune reconstitution
- Search for prognostic factors of the main outcome in each arm

- Search for treatment-by-covariate interactions on the main outcome

4- DESCRIPTION OF THE TRIAL

4.1 Concise description of the primary and secondary endpoints

4.1.1 Primary endpoint

One year progression free survival, without acute grade II-IV GvHD and without moderate and severe chronic GvHD.

- For myeloid malignancies, the relapse will be defined by the reappearance of leukemic cells after SCT.
- For ALL, the relapse will be defined by :
- -the reappearance of leukemic cells after SCT.

-and/or an increase of at least 50 % of the smallest measure of any lymphnode considered abnormal at patients in partial response and non-responder in pre-transplant

- the appearance of any new lesion to compared with the pre-transplantation evaluation .

4.1.2 Secondary endpoints

- Interval between inclusion and transplant
- Absolue numbers of neutrophils and platelets at M1, M2, M3, M6 and M12.
- Chimerism at M1, M3, M6, M12, M24
- Acute GvHD incidence and grading
- Chronic GvHD incidence and grading
- Relapse incidence
- Progression free survival
- Severe infections (CTAE grade 3-4)
- Incidence of veino-occlusive disease
- Incidence of cardiac toxicities
- Non-relapse mortality
- Overall survival
- Quality of life questionnaire (EBMT) at inclusion, M3, M12, M24
- Number of new days of hospitalization after the hospitalization for transplantation

- Immune reconstitution at M1, M3, M6, M12, M24 (T lymphocytes, CD4, CD8, B, NK lymphocytes and gammaglobulines)

4.2 Research methodology

4.2.1 Design of the trial

Phase III multicenter, randomized clinical trial, open, with two parallel arms based on two types of transplantation: Haplo donor myeloablative transplantation (experimental group) or HLA-MUD myeloablative transplantation. 172 patients will be included in each group, ie 344 patients in the whole study.

4.2.2 Number of participating sites

This is a national multi-center study including most adult and paediatric transplant centres of the SFGM-TC (36 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 the subjects

The subjects participating in this study will be identified as follows:
Site number (3 digits) - Sequential selection 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 trial.

A randomization arm (HLA-MUD or HAPLO donor) will also be assigned when the participant is randomized.

4.2.4 Randomization

Randomization will be centralized, performed using permutation blocks, the size of which will not be communicated to the physicians in charge of the patients, and stratified according to the type of disease (myeloid versus lymphoid) and the disease risk index (low/intermediate versus high) using eCRF-linked software for randomization process.
Patients, after signing written informed consent, will be included by the investigators and randomized on eCRF CleanWebTM Telemedicine Technologies. The physician will receive a confirmation of the inclusion and the result of randomization by email.

5- PROCEDURE FOR THE TRIAL

5.1 Screening visit and informed consent

The screening visit takes place between D-60 and D-30 before transplant. The investigator checks the eligibility criteria and proposes the study to the patient. Information about the protocol is delivered by the transplant physician in charge of the patient

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

	Who informs the individual and collects their consent	**When is the individual informed**	**When is the individual's consent collected**
Patient or 2 parents for patients aged less than 18 years	The transplant physician (investigator of research)	Screening visit	After a sufficient time to think after the inclusion visit and before randomization

5.2 Baseline visit

At this visit, the consent of the patient will be collect at the latest by D-15 of transplantation. A Patient Information Sheet and consent form are given to the patient by the investigator; the original is conserved by the investigator and the third copy for the sponsor.
Then, patients are randomized for receiving transplant from HLA-MUD or HAPLO-donor.

- <u>Physical examination</u>

- Reports of patient and disease history
- ECOG assessment
- Sorror score of comorbidities
- Complete physical examination with evaluation of tumor localization
-Electrocardiogram

- Echocardiogram with evaluation of left ventricular ejection
- Evaluation of the cardiovascular risk factors (dyslipidemia, HBP, obesity, smoking).
- 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)

- Biological test

- 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
- Pregnancy test (for women of childbearing age)
- HLA compatibility check between recipient and donor
- Search of anti-HLA antibodies with LUMINEX technology (DSA)
- Chimerism markers' identification

- Dental radiography
- Infectious assessment

- Urine culture
- 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
-sinus and thorax CT scan

- Tumor assessment: Pre-transplant disease evaluation

This assessment is performed according to the practice of the investigator.

- Quality of life

5.3 Follow-up visits (Weekly before M1, M1, M2, M3, M6, M12, M24)

Patients will be assessed on a weekly basis the first month (S1, S2, S3, S4), then at M2, M3, 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 M3 and M12
CD3/CD4/ CD3/ CD8 / B lymphocytes and NK cells protide electrophoreris and ferritin levels at M1, , M3, M6, M12
chimerism evaluation at M1, M2, M3, M6, M12, M24,
Aspergillus antigen, toxoplasmosis according to risk of infection, PCR for CMV, EBV, adenovirus, HHV-6 at M1, M2, M3.M6, M12
Cardiologic monitoring : Evaluation by echography and electrocardiogram will be performed systematically before HSCT (base line). Before and after infusion of cyclophosphamide and during the days following the administration of cyclophosphamide, a dosage of troponine and proBNP will be done on a daily basis. Weight measure will be done twice a day to identify quickly cardiac problems. A new echocardiography will be immediately done if necessary. The patient will also be monitored continually during the perfusion of cyclophosphamide. For all patients, a systematic screening (physical cardiac exam, electrocardiogram and cardiac echography) will be done at month 3.
Quality of life at M3, M12, M24

5.4 EXPECTED LENGTH OF PARTICIPATION, CHRONOLOGY AND DURATION OF THE STUDY.

Maximum period between screening and enrolment	2 months
Inclusion period	36 months
Duration of participation for each subject, of which: • Treatment period:	

• Follow-up period:	24 months
Total study duration:	60 months

5.5 Table or diagram summarising the chronology of the study

	Screening	*Inclusion*	*D0*	*J7*	*J14*	*J21*	*M1*	*M2*	*M3*	*M6*	*M12*	*M24*
Information: (between D-60 and D-30)	x											
Signature of the consent form (before D-15 of transplant)		x										
Randomization		x										
Inclusion exclusion criteria check	x	X										
Sorror comorbidities score		X										
Physical examination		X	x	x	x	x	X	X	X	x	X	x
Disease evaluation		x							x		X	
Pre-transplant evaluation		X					X	X	X			
Lung function test		x										
Echocardiogram		x										
Blood cell count		x	x	x	x	x	x	x	x	x	X	x
Chemistry panel with creatinine, liver test		x	x	x	x	x	x	x	x	X	X	x
Aspergillus antigen, PCR for CMV, EBV, adenovirus, HHV-6			X				x	x	x	x	x	
Chimerism		X					x		x	x	X	x
CD3/CD4/ CD8/ / B lymphocytes (CD19) and NK cells(CD56), and protide electropheris ferritin level		X					x		x	x	X	x
Quality of life questionnaire (EBMT)		x							x		x	x
Adverse events/serious adverse event *All toxicity not attributed to GvHD or infection will be classified according to CTC-AE toxicity* *Infections will be defined according to EBMT criteria (cordonnier, www.ebmt.org) and severity according GREFIG score*			X	x	x	x	X	X	X	x	X	x

5.6 Distinction between standard care and research

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

Procedures and treatments to be provided during the study	**Procedures and treatments associated with <u>standard of care</u>**	**Procedures and treatments added for the <u>study</u>**
Treatments	Allogenic transplantation, conditioning regimen, GVHD prophylaxis for HLA-MUD as well as infection prophylaxis HSCT overall follow-up	Randomization (haplo or MUD arm) Cyclophosphamide 50mg/kg/day for GVHD prophylaxis(haploidentical)
Hospitalizations-Consultations		no
Blood samples	At each visit	3 x 5 ml at M1

Imaging, etc.	Dental radiography	No

5.7 Biological samples

The samples at M1that are taken during the trial will be stored in a biological sample bank. The other time points are scheduled by the crystem protocol.

The modalities are following the cryostem protocol (https://www.cryostem.org/cryostem).

5.8 Termination and exit rules

5.8.1 Criteria and procedures for prematurely terminating the study procedure

- Temporary suspension of study procedure: the investigator must document the reason for suspending and resuming the treatment in the subject's source file and the case report form (CRF)
- Premature termination of study procedure, but the subject remains enrolled in the study until the end of the subject's participation: the investigator must document the reason
-

The investigator must:

- Document the reason(s)
- Schedule further follow-up visits, especially in case of a serious adverse event.

5.8.2 Criteria and procedure for premature withdrawals and exits from the study

- Subjects may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests.

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

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

The case report form must list the various reasons why the subject exited or was withdrawn from the study:

5.8.3 Monitoring subjects after the premature termination of treatment

If a subject exits the trial this will in no way affect the standard care received for his/her condition.
In case of severe adverse events, the investigator must notify the sponsor and monitor the subject for one month) following the premature termination of study procedure .If study procedure is stopped prematurely due to a serious adverse event, a serious adverse event report will be sent by fax (01 44 84 17 99) to the sponsor. The serious adverse reaction will be monitored until it is resolved.

In all the case, the participating subjects will be follow-up according to the usual practice of each centre.

5.8.4 Full or partial cancellation of the study

AH-HP (the sponsor) or the Competent Authority (ANSM) may prematurely discontinue all or part of the trial, temporarily or permanently in the following situations:

- first, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the two treatment arms, requiring a reassessment of the benefit-risk ratio for the trial .
- if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy It will be based on the Bayesian computation of stopping rules based on the modeling of the log Hazard ratio (HR) of the main endpoint (Spiegelhalter 1994). Non informative prior of the logHR will be considered.
- similarly, AH-HP, as the sponsor, or the Competent Authority (ANSM) may prematurely cancel the trial due to the discovery of unexpected facts or new information about the product, in light of which the objectives of the study or clinical program are unlikely to be achieved**.**
- APHP, as the sponsor, reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

In all the case, the participating subjects will be followed-up according to the usual practice of each centre.

If the study is cancelled prematurely, APHP will inform the Competent Authority (ANSM) and the Institutional Review Board of its decision within 15 days, together with justification for the decision and any recommendations from the Data Monitoring Committee.

6- ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Aged 15 to 55 years old
- With AML/ALL/SMD/SMP requiring allogeneic stem cell transplantation
- At least in partial response of their malignant hemopathy
- Without HLA matched related donor
- With a strong probability to have both a related haplo donor and a HLA-10/10 matched donor available (the patient needs to have at least 5 MUD identified outside the book “BMDW (Bone Marrow Donors Worldwide)” or using the easy match software to be included).
- With usual criteria for HSCT:
  - -ECOG ≤ 2
  - -No severe and uncontrolled infection
  - -Cardiac function compatible with high dose of cyclophosphamide
  - -Adequate organ function: ASAT and ALAT ≤ 2.5N, total bilirubin ≤ 2N, creatinine < 150 µmol/L (except if those abnormalities are linked to the hematological disease)
- With health insurance coverage (bénéficiaire ou ayant droit)
- Understand informed consent or optimal treatment and follow-up
- Prescription of two effective contraception methods must be prescribed during all the duration of the study
- Having signed a written informed consent (2 parents for patients aged less than 18)

6.2 Exclusion criteria

- Cancer in the last 2 years (except basal cell carcinoma of the skin or “in situ” carcinoma of the cervix)
- Uncontrolled infection
- Seropositivity for HIV or HTLV-1 or active hepatitis B or C

-- Yellow fever vaccine
- Heart failure according to NYHA (II or more)
- Bile duct obstruction
- Preexisting acute hemorrhagic cystitis
- Renal failure with creatinine clearance <30ml / min
- Pregnancy (β-HCG positive) or breast-feeding.
- Patients with any debilitating medical or psychiatric illness, which would preclude the realization of the SCT or the understanding of the protocol
- Tutorship or curatorship
- Unwilling or unable to comply with the protocol

6.3 Recruitment methods

The protocol is carried out by the Société Francophone de Greffe de Moëlle et de Thérapie Cellulaire (SFGM-TC) (adult and pediatric centres), so most of the members of SFGM-TC will participate to this research. Patients with a strong probability to have both a 10/10 HLA-MUD (the patient needs to have at least 5 MUD identified outside the book or using the easy match software to be included) and a haplo donor will be included in the protocol.

	Number of subjects
Total number of subjects to be included	344
Number of sites	36
Enrolment period (months)	24
Number of subjects/site	9-10
Number of subjects/site/month	0.4

In the last 3 years, SFGM-TC registry reported > 500 patients eligible for this trial (myeloablative HSCT using MUD as donor source), which illustrates the feasibility of the study

7- 7 CONDUCT OF STUDY

7.1 Donor selection

- 10/10 HLA-Matched Unrelated Donor
- Haploidentical donor

7.2 Transplants modalities

7.2.1 Conditioning regimen

Two type of transplantation (haplo and 10/10 MUD) performed with the same myeloablative conditioning regimen. The conditioning regimen depends to the type of hematologic malignancy.

For patients with myeloid malignancies.

a) for <u>haploidentical SCT</u>
-Thiotepa (5mg/kg/day: day -7 and -6)
-Fludarabine (40mg/m2/day: day-5 to-2)

- IV Busulfan (3,2mg/kg/day : day-5, to-3)

b) for HLA-matched unrelated donor SCT
-Fludarabine (30mg/m2/day: day-6 to-2)
-IV Busulfan (3,2mg/kg/day, D-6, to-3)

For patients with ALL.
- Fludarabine 30 mg/m2/day on days -7 to -5
- TBI 200 cGy twice daily on days -4 to -2 (total dose 1200 cGy

7.2.2 Type of stem cell source

-Bone marrow for haploidentical SCT. The bone marrow collection is carried out according to the practice of each centre with a minimal target dose of 2x10e8 TNC/kg.
-Peripheral blood stem cell (PBSC) for HLA-matched unrelated SCT will be mobilized by G-CSF (Neupogen®) administered to the donor from Day-4 to Day-1) subcutaneously (10µg/kg/day) with the minimal target dose of 4.10e6 CD34+ cells/kg.

7.2.3 GVHD prophylaxis

Prophylaxis of GvHD is depend to the type of SCT.

For haploidenticalSCT :
-Cyclophosphamide 50 mg/Kg/day at D+3 and D+4 The injection of cyclophosphamide will be accompanied by systematic injection of Mesna (Uromitexan®, 50 mg / kg) for the prevention of urinary toxicity. The dose of Mesna is twice the one of cyclophosphamide divided in 4 injections per day of 30 minutes each. The first injection of Mesna is done at the time of cyclophosphamide injection and then 3 hours, 6 hours and 9 hours after it. Patients must not receive any immunosuppressive agents between the graft infusion and until day +5.
- Cyclosporine and mycophenolate (MMF) from D+5

a) Cyclosporine

- IV Cyclosporine : 3mg/Kg at D+5 (residual 200 à 300ng/l) to start 24 hours after the last dose of cyclophosphamide
- Cyclosporine will be injected intravenously over 24 hours or twice daily. When the oral route is possible, the treatment will be taken twice daily.

b) Mycophenolate acid (Cellcept) will be intravenously injected at the dose of 15mg/Kg x3/day or orally from J+5, to start 24h after the last dose of cyclophosphamide.

For HLA-matched unrelated donor SCT :
- anti-thymocyte globuline (Thymogobuline) 5 mg/Kg total dose (2.5mg/Kg at day -3 and -2.)
- Cyclosporine at Day -1 and MMF at Day +1

In absence of GvHD, MMF will be stopped at D35 in both arms
It is planned to stop the treatment with ciclosporine before J180 after a progressive decrease from 3 months post-SCT in both arms.

7.2.4 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 infections: by - 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 Wellvone 750 mg x 2/day in case of cytopenias after engraftment
- Prevention of encapsulated bacteria: Oracilline 1 M x2 /D

- Monthly polyvalent immunoglobulins if hypogammaglobulinemia (<4 g / l)

7.3 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.

7.3.1 Authorized treatments

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

7.3.2 Treatments forbidden

Yellow fever vaccine is contraindicated.

7.3.3 Treatments not recommended

- For cyclophosphamide :

- Attenuated vaccine
- Phenytoin

- For Fludarabine

- Pentostatine
- Dipyridamole or other inhibitor of adenoside captation

- For Thiotepa :

- Phenytoin , Fosphénytoïne
- For Busulfan:
- Phenytoin for prophylaxis

Patients receiving, Benzodiazepines, Carbamazepine, Corticosteroids, Chloral hydrate, Phenobarbital Rifampicin, should be closely monitored for signs of toxicity
With the exception of the drugs listed above, the other drugs will be administered according to the usual practice of the centre and at the discretion of the investigator

7.4 Traceability information for the medicinal product(s)

The products including cyclophosphamide will be taken from the pharmacy stock of each centre. The pharmacist in the care facility will be responsible for the storage, dispensing and management of the products use in the study. Medicinal products are dispensed by the pharmacy in a nominative way under the responsibility of the pharmacist. Traceability of all products used in clinical trials will be ensured throughout the study period.

More specifically, cyclophosphamide will be administered in a strictly hospital setting in the first few days following transplantation, while patients are closely monitored. Administrations will be carried out through allograft centres of the SFGM-TC network and will be drawn by the nursing staff within the patient's medical record. All these centers have a centralized cytostatic reconstitution unit within their pharmacy, which will be in charge of the preparation of cyclophosphamide. These units all have strict rules of traceability and quality insurance to ensure compliance with the prescribed dose and guarantee, via the labeling, a correct identification of the product and the patient for whom it is intended.
These rules are applied daily by these centers, which have considerable experience not only in the overall management of chemotherapy but also in the cyclophosphamide which they all commonly use under conditions, in particular dose conditions, analogous.

That it is not necessary to put in place complementary measures which would only be redundant with pre-existing procedures to secure the circuit of chemotherapy and in particular cyclophosphamide.

8- EFFICACY ASSESSMENT

8.1 Description of parameters for assessing efficacy endpoints

8.1.1 Progression-free survival

PFS is defined as the time from graft until the occurrence of following events : refractory disease, relapse (cytological). death from any cause

8.1.2 Acute GvHD

Acute GvHD is defined according to Gluckberg-Thomas criteria. Each organ is rated with the diagnosis in stage which allows to define a grade. Similarly, the clinician is asked to rate the maximum grade of acute GvHD over the period and maximum grade date

8.1.3 Chronic GvHD

Chronic GvHD is defined according to the NIH classification published in 2005 (ref 58)). The diagnosis of chronic GVHD is retained if there is a distinctive sign (1 alone is sufficient) or evocative signs associated with a supplementary examination in favor (biopsy, for example). We then define:

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

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

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

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

Affected organ	**Light**	**Moderate**	**Severe**
Number of organ affected	1-2	≥3	≥3
Score of the achievement of each organ	1 (except lung)	2 or lung 1	3 or lung ≥2

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

The parameters for assessing efficacy were collected according to the schedule in table paragraph 5.5

9- SPECIFIC COMMITTEES FOR THE TRIAL

9.1 Scientific steering Committee

- Members of the committee: Pr Régis Peffault de Latour, Pr Marie-Thèrése Rubio, Pr Sylvie Chevret, DRCD: Project manager and Clinical Research Assistant
- Missions:
  The scientific steering committee will define the general organization and the conduct of the research. He will determine the initial methodology and oversee the trial.
  He will propose procedures to be followed during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.

9.2 Data Safety Monitoring Board (DSMB)

See paragraph 10.2.4

10- SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

10.1 Description of parameters for assessing safety, anticipated methods and timetable for measuring, collecting and analysing the parameters for assessing safety

The safety assessment shall be done by collecting all adverse events that occur during the research. All adverse event (except GvHD or Infection) shall be graded according to CTC-AE Toxicity Grading Scale. Fungal infections shall be graded according to GREFIG scale and for GvHD according to Glücksberg-Thomas classification**.**

Adverse events shall be collected according to the schedule in table of paragraph 5.5 of the protocol.

10.2 Recording and reporting adverse events

10.2.1 Definitions

According to Article R1123-46 of the French Public Health Code:

- **Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product.

- **Adverse reaction to an investigational medicinal product**

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalization or prolongs hospitalization, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for clinical trial sponsors (ANSM):

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials..
For the clinical trials involving the first administration or use of an investigational medicinal product in healthy volunteers, any serious adverse reaction.
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction

b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.
Examples:

- a serious adverse event likely to be related to the interventions and the trial's diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk on the trial subjects such as ineffectiveness of the investigational medicinal product in treating a life-threatening illness under investigation,
- significant safety results from a recently completed non-clinical study (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted on the same investigational medicinal product in another country, for safety reasons,
- an unexpected serious adverse reaction associated with a non-experimental medication required for the conduct of the clinical trial, (e.g. challenge agents, rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, that may affect the safety of the trial subjects
e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

10.2.2 The role of the investigator

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

The investigator must **assess the severity** of the adverse events by using
CTA-AE Toxicity Grading Scale
GREFIG scale for Fungal infection
Glücksberg-Thomas classification for GvHD

The investigator must assess the **causal relationship** between the serious adverse events and the medicinal product(s) or the study procedure(s) e method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

Table : WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · that makes a relationship improbable (but not impossible)

Causality term	Assessment criteria*
	· Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
** Or study procedures

10.2.2.1 Serious adverse events that require a notification without delay by the investigator to the sponsor

As per article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP, except those which are listed in the protocol (see section xxx) and, if applicable, in the investigator's brochure as not requiring a notification without delay .

A serious adverse event is any untoward medical occurrence that:

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

10.2.2.2 Specific features of the protocol

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

- Adverse events judged as being "medically significant"
  -Non engraftment
  -Bacterial, fungal viral and opportunist infectious complications (grade 3-4)
  -Veino-occlusive disease
  -Severe Thrombotic microangiopathy
  -Idiopathic pneumoniae
  -Bronchiolitis obliterans
  - - Severe neurological disorders
  -

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see above).

- **In utero** exposure

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

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

These serious adverse events are simply recorded in the case report form.

- *Normal and natural course of the condition*:
  - Scheduled inpatient hospitalization for monitoring the condition under investigation [with no deterioration in the subject's medical condition compared to baseline]
  - Inpatient hospitalization for routine treatment or monitoring the condition under investigation, not associated with a deterioration in the subject's medical condition
  - Emergency inpatient hospitalization upon enrollment or prolongation of hospitalization upon enrollment for monitoring the condition under investigation

- Worsening of the condition under investigation
- In case of disturbance of biological values corresponding to an adverse event of grade ≤ 3 and no other symptoms (fever, etc.) associated with this adverse event, this event will not be declared to the promoter as a serious adverse event but only in the case report form.
- Deaths due to disease progression will not be reported as serious adverse events.

- *Special circumstances*

- Hospitalization for a pre-existing illness or condition
- Transfer to the emergency ward (< 12 hours)

- *Adverse events during the trial possibly related with the treatments prescribed as part of the patient's standard care*

The investigator must report these events to his *Centre Régional de Pharmacovigilance* (CRPV).

10.2.2.3 Period during which the investigator must send notification of SAEs to the sponsor without delay

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:
- starting from the date on which the subject signs the consent form
- up to 6 months after SCT
- indefinitely, if the SAE is likely to be due to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities)

10.2.2.4 Procedures and deadlines for notifying the sponsor

The investigator should initially complete a SAE reporting form (Appendix 2) (contained in the case report form). This report must be signed by the investigator.

The investigator must complete every section of the SAE form so that the sponsor can carry out the appropriate assessment.

The initial report sent to the sponsor must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized. In addition, the investigator must state the study acronym and the number and initials of the study participant on each paper.

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 subject has terminated his participation in the trial.

The initial report, the SAE follow-up reports and all other documents must be sent to the sponsor's safety Department by fax **only**, fax no. **+33 (0)1 44 84 17 99**.

For trials which use e-CRF :
- The investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by fax;
- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

The investigator must comply with all requests for additional information from the sponsor.
For all questions relating to an adverse event report, the safety Department can be contacted via email at vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the initial notification and follow-up report forms for pregnancy exposure during trial participation".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy ends, 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, termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy report form, the SAE follow-up forms and any other documents will be sent to the sponsor using the same modalities as described above.
If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

10.2.3 Role of the sponsor

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

10.2.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and medicinal product *or study procedures* and any other treatments,
  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expectedness assessment** 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, acting through its safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the medicinal product(s):
- refer to the SmPC for Cyclophosphamide, Fludarabin, Busulfan, MMF, thymoglobulin and ciclosporin enclosed in appendix 3 (reference http://base-données-publique.medicaments.gouv.fr).
- refer to the Investigator's Brochure .

The serious adverse events associated with the study procedures are :
-Non engraftment
-Acute and chronic GvHD
-Bacterial, fungal viral and opportunist infectious complications
-Veino-occlusive disease
-Thrombotic microangiopathy
-Idiopathic pneumoniae
-Bronchiolitis obliterans
-Hospitalization and re-hospitalization

Death due to disease progression or related to transplantation

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency) and to the relevant Ethics committee (CPP).

- The sponsor must send the initial report without delay upon receipt of the unexpected serious adverse reaction if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;
- The sponsor must provide all relevant additional information by sending follow-up reports, within 8 calendar days following receipt.

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

The sponsor must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

10.2.3.2 Analysis and declaration of other safety data

This relates to any new safety data that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

The sponsor will inform the competent authority and the Ethics committee without delay after becoming aware of the emerging safety issue and, if applicable, describe which measures have been taken.

Following the initial declaration of emerging safety issue, the sponsor will declare to ANSM any additional relevant information about the new safety issues in the form of a follow-up report, which must be sent no later than 8 days after becoming aware of the information.

10.2.3.3 Annual safety report

The sponsor must prepare once yearly throughout the trial duration an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of safety data concerning trial subjects
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial,

The report must be transmitted to ANSM no later than 60 days after the anniversary date corresponding to the date of authorization of the clinical trial by ANSM.

10.2.4 Data Safety Monitoring Board (DSMB)

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

A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first subject is enrolled. The DSMB's preliminary meeting should take place before the protocol submission to competent health authority (ANSM) and Ethics committee.

The members of the DSMB are:
Pr Yves Béguin (Liège, Belgique), Yves Chalandon (Genève, Suisse) et Jakob Passweg (Bâle,Suisse) *and Fabrice Carrat (APHP, Saint Antoine hospital, Paris)* The DSMB's principle missions and their operating procedures are described in the DSMB chart of the clinical trial.
The DSMB has a consultative role. The decision concerning the conduct of the clinical trial relies on the sponsor.

11- DATA MANAGEMENT

Data collection

~~data~~ 11.1 Identification of data recorded directly in the CRFs which will be considered as source data

11.2 Right to access source data and documents

11.2.1. Access to data

In accordance with GCP:
- 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.
- the investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.2..2 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period.

11.2..3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).
During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.
Under no circumstances will the names and addresses of the subjects be shown.
Only the subject's initials will be recorded, along with an identification code specific to the study indicating the order of enrolment.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.3 Data processing and storage of documents and data

Identification of the data processing manager and the location(s)The management and processing of the data will be done by the Centre de traitement de données INCA de l'APHP, Service de Diostatistique et Information Médicale (sDBIM), hôpital saint Louis, Paris (Pr. Sylvie Chevret). Data entry
Data will be entered electronically via a web browser.

11.3.1 Data processing in France

This trial is governed by the CNIL "Reference Method for processing personal data for clinical studies" (MR-001, amended). APHP, the study sponsor, has signed a declaration of compliance with this "Reference Method"

11.3.2 Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the trial.

This indexed archiving includes, in particular:

- A sealed envelope containing the originals of all information sheets and consent forms signed by all individuals at the site who participated in the study for the investigator;
- One copy of all the information sheets and signed consent forms signed for all individuals at the site who participated in the study for the sponsor;
- "Study" binders for the Investigator and the sponsor, containing:
  - all successive versions of the protocol (identified by version no. and date), and its appendices
  - the ANSM authorizations and CPP decisions
  - correspondence
  - the enrolment list or register
  - the appendices specific to the study
  - the final study report
- The data collection documents

11.4 Ownership of the data

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

12- STATISTICAL ASPECTS

12.1 Planned statistical methods, including the timetable for any planned interim analyses

The analysis will be based on the intent-to-treat basis, that is, including all randomized patients whatever they were administered the treatment under study or not. Only patient consent withdrawls with positive report of not using their data, if any, will be excluded.
One interim analysis will be performed at mid-inclusion, while the terminal analysis will be done once the required number of events (n=146) will be observed.

Baseline summary statistics, namely percentages or median [interquartile range, IQR], will be computed in each randomized arm, without any statistical test of comparison.

The right censored endpoint will be estimated using nonparametric methods. Kaplan Meier curves and cumulative incidence curves will be considered in case of non informative or informative censoring with comparison across randomized arms based on the log-rank test or the Gray test, respectively. Adjustment on potential confounders will used Cox proportional hazards models.

Statistical analyses will be performed on SAS (SAS Inc, Cary, NC) and R (https://www.R-project.org/) software packages.

12.2 Hypotheses for calculating the required number of subjects, and the result

We hypothesize the 1-year progression free survival without Grade II-IV acute GvHD and without moderate and severe chronic GvHD will be of 65% after haplo SCT versus 50% after 10/10-HLA MUD.
172 patients in both arms (n=344 overall) are required to demonstrate such a difference, based on a two-sided logrank test, α = 0.05 and power = 0.80(HR= 0.62), with a required total number of events of 146.

12.3 Anticipated level of statistical significance

The type I error is fixed at α=0.05.

12.4 Statistical criteria for termination of the study

An interim analysis will be performed at mid-inclusion.
It will be based on the Bayesian computation of stopping rules based on the modeling of the log Hazard ratio (HR), denoted θ , of the main endpoint (Spiegelhalter 1994).
It will be based on the posterior probability of ¯ , conditional on the data accumulated at the time of interim analysis. We will evaluate the two following criteria:
γ_0=P(θ<logHR_0 | data)>0.95
γ_1=P(θ>logHR_1 | data)>0.95
where HR_0 =1 and HR_1=0.62 denote the value of the hazard ratio postulated in the null and alternate hypotheses, respectively.
The posterior densities of the logHR, θ will be computed using MCMC methods.
Non informative prior of the logHR, θ will be considered.

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

12.6 Management of modifications made to the analysis plan for the initial strategy

All the analyses will be described in a statistical analysis plan (SAP) that will be written and signed before freezing of the data base.
All modifications to the original protocol will be described in the SAP.

12.7 Selection of populations

13- QUALITY CONTROL AND ASSURANCE

Every clinical study managed by APHP is ranked according to the projected risk incurred by the study participants using a classification system specific to APHP-sponsored clinical trials.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must have a quality assurance system for monitoring the implementation of the study at the research centres.

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

- the research subjects are safe, protected and their rights are being met
- the data being recorded is accurate, complete and consistent with the source documents

• the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

13.1.1 Strategy for site opening

The strategy for opening the sites is determined using the tailored 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.

13.1.2 Scope of site monitoring

For this study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore the sponsor, in agreement with the coordinating investigator, has agreed on a logistical score and impact and the corresponding study monitoring level of D level.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with Good Clinical Practice as well as with 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 by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: 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

13.3 Case Report Form

All information required by the protocol must be entered in the case report forms. The data must be collected as and when it is 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 instructions for using this tool.
Using on-line case report forms means 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, there are consistency checks to ensure the data are verified immediately upon being entered. The investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.4 Management of non-compliances

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

The sponsor has its own procedures for managing these non-compliances.

13.5 Audits/inspections

The investigators agree to accept 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 basis of medical secrecy.

An audit can be carried out at any time by independent individuals appointed by the sponsor. 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 trial 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 and the storage of the data used or produced as part of the study.

13.6 Principal Investigator's declaration of responsibility

Before starting the trial, each investigator will give the sponsor’s representative a signed and dated copy of his/her curriculum vitæ and RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

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

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCD document) which will be sent to the sponsor's representative.
The investigators and their co-workers will sign a delegation form specifying each person's role.

14- ETHICAL AND LEGAL CONSIDERATIONS

Methods for informing and obtaining consent from the research participants

In accordance with Article L.1122-1-1 of the French Public Health Code, no research can be carried out on a person without his/her free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The person’s free and informed written consent will be obtained by the investigator, or by a doctor representing the investigator after a sufficient time to think during inclusion visit and before randomization.

The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the doctor representing the investigator, will be sent to the individual prior to being enrolled on the trial.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

Information and consent of parents or legal guardians in the case of a trial involving a minor
In accordance with Article L.1122-2 of the French Public Health Code, when a trial involves a non-emancipated minor, consent must be given by the legal guardians.
The free and informed written consent of the legal guardians is obtained by the investigator, or by a doctor representing the investigator, before the minor is enrolled on the trial

Information for minors participating in the study

Minors will be given the information specified in Article L. 1122-1 of the French Public Health Code, adapted to suit their level of understanding, by both the investigator and their legal guardians.
Minors will be asked to agree to take part in the human research trial. In all cases, the investigator must accept a minor's refusal to participate or a withdrawal of their agreement.

A copy of the signed and dated consent form is given to the parents or legal guardians as well as to the investigator or the doctor representing the investigator. The investigator will retain the original.
At the end of the study, a copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

Information recorded in the minor's medical file
The investigator will record the minor's participation in the clinical study in the minor's medical file, along with the procedure for informing and obtaining consent from the legal guardians and for informing the minor and a record of the minor's agreement to take part.

Special rule: minors who reach the age of majority whilst still participating in the trial

Minors who reach the age of majority during their participation in the trial will be given the relevant information at that time. After they have been given this information, they will be asked to confirm their consent.

Legal obligations

The sponsor's role

Assistance Publique Hôpitaux de Paris (APHP) is the sponsor of this study and has delegated powers to its Clinical Research and Development Department (DRCD) in order to conduct the study in accordance with Article L.1121-1 of the French Public Health Code. APHP reserves the right to terminate the study at any time for medical or administrative reasons. In this case, the investigator will be informed accordingly.

Request for approval from the Institutional Review Board

APHP, as sponsor, obtains prior approval from the Institutional s Review Board for its clinical trials of medicinal products for human use, within the scope of the Board's authority and in accordance with statutory and regulatory requirements.

Request for approval from the ANSM

APHP, as sponsor, obtains prior authorisation from the ANSM for its clinical trials of medicinal products for human use, within the scope of the ANSM's authority and in accordance with statutory and regulatory requirements.

Declaration of compliance with the MR 001 "Reference Method"

APHP, the study sponsor, has signed a declaration of compliance with this "Reference Method".

Modifications to the trial

Any substantial amendment made to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to implementing the amendment, approval from the Institutional Review Board and authorisation from the ANSM, within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

Final study report

The final study report referred to in CSP Article R.1123-67 is written and signed by the sponsor and the investigator. A report summary, meeting the competent authority's guidelines, has to be sent to the competent authority and Institutional Review Board within one year of the end of the trial i.e. the end of the participation of the last study participant..

15- FUNDING AND INSURANCE

Sources of funding for the trial

The sources of the funding for the trial are Industrial and patients associations

Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own third party liability as well as the third party liability of all the doctors involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participant 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 (APHP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any collaborator (doctor or research staff), in accordance with Article L.1121-10 of CSP.

16-. PUBLICATION

The author(s) of any publication relating to this study must include the APHP among their affiliations and name the sponsor AH-HP (DRCD) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor

Mention of APHP affiliation for projects sponsored or managed by APHP

- If an author has several affiliations, the order in which the institutions are mentioned (APHP, University, INSERM, etc.) is not important
- However, if the trial is funded by an internal call for tenders at the APHP, the first affiliation must be "APHP"
- Each of these affiliations must be identified by an address and separated by a semicolon
- The APHP institution must feature under the acronym "APHP" first in the address, specifically followed by: APHP, hospital, department, city, postcode, France

Mention of the APHP manager (DRCD) in the acknowledgements of the text

- "The sponsor was *Assistance Publique – Hôpitaux de Paris* (Clinical Research and Development Department)"

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

17- BIBLIOGRAPHY

1- Related haploidentical donors are better choice than matched unrelated donors: point. Fuchs E. J., Blood advances, 2016; 1, (6): 397-400
2- Related haploidentical donors are better choice than matched unrelated donors: counterpoint. Shaw B. E., Blood advances, 2016; 1: (6): 401-406
3- Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Giralt S., Blood 1997; 89: 4531–36.
4- Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Slavin S., Blood 1998; 91: 756–63.
5- Successful engrafment of T-cell depleted haploidentical "three loci"incompatible transplants in leukemia patients by addition of recombinant human granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells to bone marrow inoculum. Aversa F : Blood,. 1994;1994 (84): 3498-3955
6- Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Ruggeri L, : Science. 2002;295(5562):2097-2100.
7- Haploidentical hematopoietic stem cell transplantation without in vitro Tcell depletion for the treatment of hematological malignancies. Huang XJ., Bone Marrow Transplant. 2006;38(4):291-297.
8- Reduced-intensity conditioning therapy with busulfan, fludarabine, and antithymocyte globulin for HLA-haploidentical hematopoietic cell transplantation in acute leukemia and myelodysplastic syndrome. Lee KH., Blood. 2011;118(9):2609-2617
9- HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biology of blood and marrow transplantation : Luznik L,. Journal of the American Society for Blood and Marrow Transplantation. 2008;14(6):641-650.
10- Posttransplantation cyclophosphamide facilitates engraftment of major histocompatibility complex-identical allogeneic marrow in mice conditioned with low-dose total body irradiation. Biology of blood and marrow transplantation : Luznik L, Journal of the American Society for Blood and Marrow Transplantation. 2002;8(3):131-138
11- 4-Hydroperoxycyclophosphamide inhibits proliferation by human granulocyte-macrophage colony-forming cells (GM-CFC) but spares more primitive progenitor cells. Gordon MY. Leuk Res. 1985;9(8):1017-1021.
12- HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Luznik, L, . Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant. 14, 641–650 (2008)
13- Post-transplantation cyclophosphamide for tolerance induction in HLA-haploidentical bone marrow transplantation. Luznik, L., Semin. Oncol. 39, 683–693 (2012).
14- Haploidentical transplantation for hematologic malignancies: where do we stand? Fuchs, E. J., Hematol. Educ. Program Am. Soc. Hematol. Am.Soc. Hematol. Educ. Program 2012, 230–236 (2012).
15- T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. Bashey, A., Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 31, 1310–1316 (2013).
16- Peripheral blood hematopoietic stem cells for transplantation of hematological diseases from related, haploidentical donors after reduced intensity conditioning, Raj K., BBMT 2014, 20 (6): 890-89
17- Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. Shimoni A., Leukemia. 2006;20(2):322–8.
18 - Braun T, Reddy P, Parkin B, Pawarode A, Mineishi S, et al. Allogeneic transplantation with myeloablative FluBu4 conditioning improves survival compared to reduced intensity FluBu2 conditioning for acute myeloid leukemia in remission. Magenau J.M., Ann Hematol. 2015;94(6):1033–41.
19- Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes.Scott, B.L.,J Clin Oncol. 2017 Apr 10;35 (11):1154-1161.
20- Reduced- intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Mohty M., Blood. 2010;116 (22):4439–43.
21- Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. Bornhauser M., Lancet Oncol. 2012;13 (10):1035–44.

22- HLA- haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Luznik L ., Biol Blood Marrow Transplant. 2008;14(6):641–50.
23- Nonmyeloablative conditioning, unmanipulated haploidentical SCT and post-infusion CY for advanced lymphomas. Castagna L., Bone Marrow Transplant. 2014; 49(12):1475–80
24 -Treatment of hematological malignancies with nonmyeloablative, HLA-haploidentical bone marrow transplantation and high dose, post-transplantation cyclophosphamide. Munchel AT., Best Pract Res Clin Haematol. 2011;24(3):359–68.
25- Unmanipulated haploidentical BMT following non-myeloablative conditioning and post-transplantation CY for advanced Hodgkin's lymphoma. Raiola A., Bone Marrow Transplant. 2014;49(2):190–4.
26- Unmanipulated haploidentical bone marrow transplantation and post-transplant cyclophosphamide for hematologic malignanices following a myeloablative conditioning: an update. Acigalupo A., Bone Marrow Transplant. 2015;50 Suppl 2:S37–9.
27- Virus infection in HLA-haploidentical hematopoietic stem cell transplantation: incidence in the context of immune recovery in two different transplantation settings. Ischer J, Ann Hematol. 2015;94(10):1677–88.
28 - Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high- dose posttransplantation cyclophosphamide. McCurdy S.R., Blood. 2015;125(19):3024–31.
29 - Unmanipulated haploidentical BMT following non-myeloablative conditioning and post-transplantation CY for advanced Hodgkin's lymphoma. Raiola, A.M., Bone Marrow Transplant. 49, 190–194 (2014).
30- Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. Raiola, A. M. , Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant. 19, 117–122 (2013)
31- Improved early outcomes using a T cell replete graft compared with T cell depleted haploidentical hematopoietic stem cell transplantation. Ciurea, S. O. , Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant. 18, 1835–1844 (2012).
32- Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning regimen—a report from the acute leukemia working party of the European group for blood and marrow transplantation. Nagler A., J Clin Oncol 2013; 31: 3549–56.
33- Better leukemia-free and overall survival in AML in first remission following cyclophosphamide in combination with busulfan compared with TBI. Copelan E.A., Blood 2013; 122: 3863–70.
34- Allogeneic hematopoietic stem-cell transplantation in patients with acute myeloid leukemia in first complete remission: new answers for an old question. Shimoni A., Leukemia 2005; 19: 891–93.
35- Current status of reduced intensity conditioning allogeneic stem cell transplantation for acute myeloid leukemia. Blaise D., Haematologica 2007; 92: 533–41.
36- Once-dailyintravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS. DeLimaM,. Blood 2004; 104: 857–64.
37- Once daily i.v. busulfan and fludarabine (i.v. Bu-Flu) compares favorably with i.v. busulfan and cyclophosphamide (i.v. BuCy2) as pretransplant conditioning therapy in AML/MDS. Andersson BS., Biol Blood Marrow Transplant 2008; 14: 672–84. .
38- New myeloablative conditioning regimen with fludarabine and busulfan for allogeneic stem cell transplantation: comparison with BuCy2. Chae YS., Bone Marrow Transplant 2007; 40: 541–47.
39- Outcomes following HSCT using fludarabine, busulfan, and thymoglobulin: a matched comparison to allogeneic transplants conditioned with busulfan and cyclophosphamide. Bredeson CN., Biol Blood Marrow Transplant 2008; 14: 993–1003.
40- Randomized trial of myeloablative conditioning regimens: busulfan plus cyclophosphamide versus busulfan plus fludarabine. Lee JH., J Clin Oncol 2012; 31: 701–09.
41- Busulfan plus fludarabine as a myeloablative conditioning regimen compared with busulfan plus cyclophosphamide for acute myeloid leukemia in first complete remission undergoing allogeneic hematopoietic stem cell transplantation: a prospective and multicenter study. Liu H., J Hematol Oncol 2013; 6: 15.
42- Comparison of preparative regimens in transplants for children with acute lym- phoblastic leukemia. Davies SM, J Clin Oncol. 2000; 18(2):340-347.
43- Comparison of total body irradiation plus cyclophosphamide with busulfan plus cyclophosphamide as conditioning regi- mens in patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplant. Eroglu C., Leuk Lymphoma. 2013;54(11):2474-2479.
44- Allogeneic marrow transplantation using T cell depletion for patients with juvenile chronic myelogenous leukemia without HLA-identical siblings. Bunin NJ., Bone Marrow Transplant. 1992 Feb;9(2):119-22
45- Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Giebel S., Haematologica 2017 Volume 102(1):139-149

46- Radiation-free allogeneic conditioning with fludarabine, carmustine, and thiotepa for acute lymphoblastic leukemia and other hematologic malignancies necessitating enhanced central nervous system activity. Christopoulos P., Biol Blood Marrow Transplant. 2012; 18(9):1430-1437.
47- Total Body Irradiation-Based Myeloablative Haploidentical Stem Cell Transplantation Is a Safe and Effective Alternative to Unrelated Donor Transplantation in Patients Without Matched Sibling Donors. Solomon S.R., Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant. 2015;21(7):1299–1307.
48- Comparison of Outcomes of Hematopoietic Cell Transplants from T-Replete Haploidentical Donors Using Post-Transplantation Cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 Allele-Matched Unrelated Donors and HLA-Identical Sibling Donors: A Multivariable Analysis Including Disease Risk Index. Bashey A. Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant. 2016;22(1):125–133.
49- Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. Raiola AM., Biol Blood Marrow Transplant. 2013 Jan;19(1):117-22.
50- Corticosteroid-Free Primary Treatment of Chronic Extensive Graft-versus-Host Disease Incorporating Rituximab. Solomon S.R, Biol Blood Marrow Transplant. 2015 Sep;21(9):1576-82
51- Peripheral-blood stem cells versus bone marrow from unrelated donors. Anasetti C., N Engl J Med. 2012 Oct 18;367(16):1487-96.
5**2-** Graft-versus-host disease. Ferrara J.L., Lancet. 2009;373(9674):1550-1561.
53- Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: a prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy. Yakoub-Agha .I., J Clin Oncol. 2006;24(36):5695-5702
54- Reduced incidence of acute and chronic graft-versus-host disease with the addition of thymoglobulin to a targeted busulfan/cyclophosphamide regimen. Deeg H.J., Biol Blood Marrow Transplant. 2006, May;12(5):573-84
55- Long-term outcome of unrelated donor transplantation for AML using myeloablative conditioning incorporating pretransplant Alemtuzumab. Das-Gupta E. P.,Biol Blood Marrow Transplant.2007, Jun;13(6):724-33.
56- Chronic graft-versus-host disease: long-term results from a randomized trial on graft-versus-host disease prophylaxis with or without anti-T-cell globulin ATG-Fresenius.Socié.G, Blood 2011, Jun 9;117(23):6375-82. doi: 10.1182
57- A disease risk index for patients undergoing allogeneic stem cell transplantation. Armand P, Blood. 2012;120(4):905-13. Epub 2012/06/20
58- National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report, Jagasia MH, Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1. doi: 10.1016

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Appendix 2 : Serious Adverse Events report form

Appendix 3 : Include the SPC

ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php); otherwise, use the SPC from Vidal.

Appendix 4 : Questionnaires or scales

CTC-AE -Toxicity Grading scale for determining the severity of adverse event

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

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

Cotation de la GVH aiguë :

Stades cliniques définis dans la classification de Glücksberg-Thomas

Stade	Peau	Foie	Tube Digestif * (TD)
1 (+)	Éruption maculopapuleuse touchant moins de 25 % de la surface corporelle	Bilirubine 2-3 mg/dl (34-50 µ m/l)	Diarrhée > 500 ml/jour ou nausée, anorexie ou vomissements avec confirmation d'une GVH dans le tractus gastro-intestinal haut par biopsie
2 (+ +)	Éruption maculopapuleuse touchant 25 à 50 % de la surface corporelle	Bilirubine 3,1-6mg/dl	Diarrhée > 1000 ml/jour

		(51-102 µ m/l)	
3 (+ + +)	Éruption maculopapuleuse touchant plus de 50 % de la surface corporelle	Bilirubine 6,1-15 mg/dl (103-255 µ m/l)	Diarrhée > 1500 ml/jour
4 (+ + + +)	Érythrodermie généralisée avec formation de bulles et desquamation	Bilirubine > 15 mg/dl (> 255 µ m/l)	Diarrhée > 1500 ml/jour + douleurs abdominales +/- iléus

Confirmation histologique nécessaire pour documenter la GVH

Correspondance entre grades de l'IBMTR et grades de Glucksberg,

Grade IBMTR	Grade Glucksberg	Stade Peau	Stade Intestin	Stade Foie
A	I	1	0	0
B	I	2	0	0
B	I I	0 – 2	1	0 – 1
B	I I	0 – 2	0 – 1	1
C	I I	3	1	0 – 1
C	I I	3	0 – 1	1
C	I I	3	0	0
B	I I I	0 – 2	2	0 – 2
B	I I I	0 – 2	0 – 2	2
C	I I I	3	0 – 3	2 – 3
C	I I I	3	2 – 3	0 – 3
D	I I I	0 – 3	0 – 3	4
D	I V	0 – 3	4	0 – 4
D	I V	4	0 - 4	0 - 4

Une GVH cotées de II à IV selon Glücksberg-Thomas et ne touchant qu'un seul organe doit être confirmée histologiquement (biopsie).

1. Cotation de la GVH chronique :

Manifestation de GVHD chronique

Dans le cas de manifestations cliniques parallèles comme un épisode infectieux ou une réaction médicamenteuse, cette évaluation ne sera pas prise en compte.

Un Karnofsky < 60% avec une perte de poids > 15% et des infections récurrentes sont en général des signes de GVHD chronique extensive.

Manifestation de GVHD chronique

Les anomalies cliniques selon les organes touchés permettant d'évaluer la GVHD chronique sont les suivantes :

Peau Erythème, sécheresse, prurit, changement de pigmentation (vitiligo, hyperpigmentation) plaques papulosquameuses, nodules, exfoliation, rash maculo-papulaire ou urticaire, sclérodermie, morphée (une ou plusieurs lésions lisses indurées et circonscrites)

Ongles Onychodystrophie, onycholyse, striés, fendus.

Cheveux Canitie prématurée (cuir chevelu, cils, sourcils), alopécie, amincissement du cuir chevelu, raréfaction de la pilosité corporelle.

Bouche Sécheresse, brûlures, gingivite, mucite, atrophie gingivale, érythème, lichen, ulcères, atrophie labiale, changement de pigmentation, contracture de la bouche, caries dentaires.

Yeux Sécheresse, brûlures, photophobie, douleur, larmoiement, sensation de grain de sable

Organes 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.

Gradation de GVHD chronique :

GVH limitée : atteinte cutanée localisée et/ou atteinte hépatique due à la GVH chronique

1. Anomalies de la cavité buccale compatibles avec une GVHD chronique, une biopsie cutanée ou labiale positive sans autre manifestation clinique de GVHD chronique.

2. Perturbation modérée du bilan hépatique sanguin avec une biopsie cutanée ou labiale positive sans autre manifestation clinique de GVHD chronique.

3. Moins de 6 plaques papulo-squameuses ou un rash cutané limité ou une dépigmentation < 20% de la surface corporelle, une biopsie cutanée positive sans autre manifestation clinique de GVHC.

4. Sécheresse oculaire (test de Schirmer ≤ 5 mn), une biopsie cutanée ou labiale positive sans autre manifestation clinique de GVHD chronique.

5. Anomalies vulvaires ou vaginales avec une biopsie cutanée positive sans autre manifestation clinique de GVHD chronique.

GVH extensive : Atteinte cutanée généralisée ou GVH chronique limitée
Plus a – hépatite chronique agressive ou cirrhose
b – atteinte oculaire (syndrome sec)
c – atteinte salivaire ou de la muqueuse buccale
d – atteinte d'un autre organe

1. Atteinte de deux organes ou plus avec des symptômes ou signes de GVHD chronique avec une biopsie contributive documentant une GVHD chronique quel que soit l'organe.

2. Perte de poids < 15 % non liée à d'autres causes, avec une biopsie contributive documentant une GVHD chronique quel que soit l'organe.

3. Atteinte cutanée plus importante que celle définie dans les GVHD chroniques limitées, confirmée par une biopsie.

4. Sclérodermie ou morphée.

5. Onycholyse ou onychodystrophie avec une biopsie contributive documentant une GVHD chronique quel que soit l'organe.

6. Diminution de l'amplitude articulaire des poignets ou des chevilles due à une fasciite causée par la GVHD chronique.

7. Contractures imputables à la GVHD chronique.

8. Bronchiolite oblitérante non liée à d'autres causes.

9. Biopsie hépatique positive. Anomalies de la fonction hépatique non liées à d'autres causes ((PA L > 2X LNS, ASAT ou ALAT > 3x LNS et bilirubine totale ≤ 1,6 mg/dl)

10. Biopsie digestive haute ou basse contributive.