CENTRE HOSPITALIER
UNIVERSITAIRE DE NANTES

# ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN OF TOTAL LYMPHOID IRRADIATION AND ANTI-THYMOCYTE GLOBULIN FOR OLDER PATIENTS WITH RELAPSED LYMPHOID MALIGNANCIES

Version n° 4 : 5 juillet 2012
N° EudraCT : 2011-001940-31
Reference CPP : 2011-R24
BRD 10/6-L


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| Version et date du protocole | | |
|---|---|---|
| Version 1 du | 27 juillet 2011 | Dépôt au CPP et à l'AFSSAPS |
| Version 2 du | 24 Octobre 2011 | Réponse à l'AFSSAPS |
| Version 3 du | 23 Novembre 2011 | Réponse au CPP |
| Version 4 du | 5 juillet 2012 | Amendement n°1 |

# PROTOCOL APPROVAL

## ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN OF TOTAL LYMPHOID IRRADIATION AND ANTI-THYMOCYTE GLOBULIN FOR OLDER PATIENTS WITH RELAPSED LYMPHOID MALIGNANCIES

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# PROTOCOL AT A GLANCE/ SYNOPSIS

# ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN OF TOTAL LYMPHOID IRRADIATION AND ANTI-THYMOCYTE GLOBULIN FOR OLDER PATIENTS WITH RELAPSED LYMPHOID MALIGNANCIES

## 1. Primary Endpoint:

The primary endpoint of this phase 2 study is to evaluate the incidence of non-relapse mortality (NRM) at one year after transplantation.

## 2. Secondary Endpoints:

- To evaluate the kinetics of donor hematopoietic cell engraftment (neutrophil and platelets recovery) and chimerism.
- To document the quantitative and qualitative reconstitution of the immune system including T cell subsets, regulatory cells, NK cells and B cells.
- To evaluate the rate of relapse, overall and event-free survival and incidence of acute and chronic GVHD, at one year after transplantation.

## 3. Inclusion criteria:

- Any patient with one of the following hemato-lymphoid malignancies or syndromes in whom allogeneic stem cell transplantation is warranted. Specific disease categories include: indolent advanced stage Non-Hodgkin Lymphomas, DLBCL, Mantle Cell Lymphoma, Marginal zone lymphoma, MALT, T cell lymphoma, Chronic Lymphocytic or prolymphocytic Leukemia, Hodgkin Disease, and Waldenström macroglobulinemia. T-cell NOS, angioimmunoblastic lymphoma, HTLV1, T-gamma/delta, anaplastic lymphoma and Sezeay syndromes can be included after careful assessment by the PI and the protocol steering committee.
- Patients must be at least in partial remission (according to standard criteria) after salvage therapy and before (~one month) the start of the conditioning regimen.
- Patient age >50 and less than 66 years, or for patients <50 years of age but because of pre-existing medical conditions or prior therapy are considered to be at high risk for regimen-related toxicity associated with conventional myeloablative transplants.
- A fully HLA-identical sibling or matched unrelated donor is available (10/10 HLA match). Patients with one antigen mismatched donors (9/10 HLA match at the level of HLA-Cw) can be considered but only after discussion with the transplant team and the Principal Investigator.
- Patient must be competent to give consent.

## 4. Exclusion criteria:

The presence of one exclusion criteria makes a patient unable to enter the protocol:
- Patients with progressive hematolymphoid malignancies despite conventional therapies, and not in partial remission during the month preceding transplantation.
- Patients with cutaneous T cell lymphoma
- Uncontrolled CNS involvement with disease
- Fertile men or women unwilling to use contraceptive techniques during and for 12 months following treatment
- Females who are pregnant or female who are breast feeding
- Organ dysfunction defined as follows:
• Cardiac function: ejection fraction < 30% or uncontrolled cardiac failure (grade >=2 according to the NYHA scale)
• Pulmonary: DLCO < 40% predicted
• Renal: Serum creatinine > 1.0 mg/dL; if serum creatinine > 1.0 mg/dL, then the estimated glomerular fil-tration rate (GFR) must be >60 mL/min/1.73 m²
• Liver function abnormalities: elevation of bilirubin to > 3 mg/dl and/or transaminases > 4x the upper limit of normal
- Karnofsky performance score < 70%
- Patients with poorly controlled hypertension on multiple antihypertensives
- Patients with uncontrolled infection

- Documented fungal disease that is progressive despite treatment
- Viral infections: HIV positive patients. Hepatitis B and C positive patients will be evaluated on a case by case basis
- Psychiatric disorders or psychosocial problems which in the opinion of the primary physician or Principal Investigator would place the patient at unacceptable risk from this regimen.
- Patients with prior malignancies diagnosed > 5 years ago without evidence of disease are eligible. Patients with a prior malignancy treated < 5 years ago but have a life expectancy of > 5 years for that malignancy are eligible.
- Patients with known allergy to ATG or other allergy to rabbit-derived proteins
- Patients with known allergy or sensitivity to mycophenolate mofetil

## 5. Treatment schema:

After all pretreatment evaluations have been performed, and within four weeks of anticipated non-myeloablative transplantation, patients can be entered on study.

**Transplant Schedule**

**Week #1**

| Monday Day –11 | Tuesday Day –10 | Wednesday Day –9 | Thursday Day –8 | Friday Day –7 | Saturday Day –6 | Sunday Day -5 |
|---|---|---|---|---|---|---|
| TLI 120cGy | TLI 120cGy | TLI 120cGy | TLI 120cGy | TLI 120cGy | REST | REST |
| ATG 1.5 mg/kg | ATG 1.5 mg/kg | ATG 1.5 mg/kg | ATG 1.5 mg/kg | ATG 1.5 mg/kg | | |

**Week #2**

| Monday Day –4 | Tuesday Day –3 | Wednesday Day –2 | Thursday Day –1 | Friday **Day 0** | Saturday Day +1 | Sunday Day +2 |
|---|---|---|---|---|---|---|
| TLI 120 cGy | TLI 120cGy | TLI 120cGy | TLI 120cGy x 2 doses | Mobilized PBSCs | | |
| | Start CSA | CSA | CSA | CSA | CSA | CSA |
| | | | | Start MMF | MMF | MMF |

➔ TLI Administration: TLI is administered ten times in 120 cGy fractions on day –11 through day –7 and day –4 through day –1 according to the above delineated schedule.

➔ ATG: Thymoglobulin will be administered five times intravenously at 1.5 mg/kg/day from day –11 through day –7 for a total dose of 7.5 mg/kg. The drug will be administered by continuous IV infusion through a central venous catheter over a period of 6 hours. In case of allergy symptoms following ATG infusion, the infusion can be stopped for one hour and then resumed at a lower infusion rate (e.g. 8 to 10 hours according to local practice). ATG will be completely discontinued in case of a severe anaphylactic reaction requiring adrenaline or intensive care resuscitation measures. Cyclosporine administration will be discontinued during ATG infusion.

➔ Mobilized PBSCs: The desired cell doses (based on recipient body weight) for MRD and MUD transplants are around 4-8 x$10^6$ $CD34^+$ cells/kg.

➔ GVHD Prophylaxis: Cyclosporine (CSA) and Mycophenylate mofetil (MMF). Since CSA and MMF are routinely used in the allogeneic stem cell transplant setting, temporary or permanent discontinuation of these 2 agents should be performed **in case of side effects** according to local standard practice.

## 6. Statistical considerations:

Based on results from the literature and data from the EBMT registry, the hypothesis for the primary endpoint is an improvement in non-relapse mortality at one year after transplantation from 30% to 10%. Using a one step A'Hern procedure, 28 patients are needed. In all, 30 patients will be included (taking into account that after registration, there is a risk of dropout i.e. patients, who will not receive a transplant due to rapidly progressive disease, infection or other events occurring after identification of a donor, but before start of conditioning). If the number of patients alive at one year is 24 or more,

the hypothesis that NRM >= 0.30 is rejected with a target error rate of 0.050 and an actual error rate of 0.047. If the number of patients alive at one year is 23 or less, the hypothesis that NRM <= 0.10 is rejected with a target error rate of 0.20 and an actual error rate of 0.142.

**7. Study design:**

This is a prospective, multicenter, non-randomized Phase II study.

# Glossary of Abbreviations

| | |
|---|---|
| AE | Adverse event |
| ALL | Acute Lymphocytic Leukemia |
| Allo-SCT | Allogeneic Stem Cell Transplantation |
| ATG | Anti-thymocyte glogulin |
| ATS | Anti-thymocyte serum |
| BM | Bone Marrow |
| CLL | Chronic lymphocytic leukemia |
| CNS | Central nervous system |
| CR | Complete response |
| CRF | Case report form |
| CSA | Cyclosporine A |
| CTC | Common toxicity criteria |
| DCBCL | Diffuse large B-cell lymphoma |
| DLI | Donor lymphocyte infusion |
| EBMT | European group for Blood and Marrow Transplantation |
| ECOG | Eastern Cooperative Oncology Group |
| EFS | Event free survival |
| EMEA | European Agency for Evaluation of Medicinal Products |
| GCP | Good clinical practice |
| GMP | Good medical practice |
| G-CSF | Granulocyte - colony stimulating factor |
| GVHD | Graft Versus Host Disease |
| ICH | International Conference on Harmonization |
| MedDRA | Medical Dictionary for Regulatory Activity |
| MMF | Mycophenolate mofetil |
| MRD | Matched Related Donor |
| MUD | Matched Unrelated Donor |
| NCI | National Cancer Institute |
| NHL | Non-Hodgkin Lymphoma |
| NRM | Non Relapse Mortality |
| NST | Non-myeloablative transplant |
| OS | Overall Survival |
| PB | Peripheral Blood |
| PBSC | Peripheral Blood Stem Cell |
| RI | Relapse Incidence |
| RIC | Reduced Intensity Conditioning |
| RROT | Regimen related organ toxicities |
| SAE | Serious adverse event |
| SUSAR | Suspected unexpected Serious Adverse Reaction |
| TBI | Total body irradiation |
| TLI | Total Lymphoid Irradiation |

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# 1 Introduction

Recent advances in allogeneic hematopoietic cell transplantation (allo-SCT) have led to reduced intensity preparative regimens that are non-myeloablative and permit the development of sustained donor chimerism. As a result, regimen related organ toxicities (RROT), and consequently non-relapse mortality has been reduced. However, the incidence of acute and chronic graft-versus-host disease (aGVHD and cGVHD, respectively) has remained a major complication. Pre-clinical data, developed by the Stanford group, established that non-myeloablative conditioning with total lymphoid irradiation (TLI) combined with depletive anti-T cell antibodies protects against GVHD by skewing peripheral T cell subsets to favor suppressive regulatory T cells, specifically $CD3^+NK1.1^+$ or $CD3^+DX5^+$ T cells in C57BL/6 and BALB/c mice, respectively. In early work to date, the Stanford group has successfully translated the murine protocol to clinical transplantation and found sustained donor engraftment without GVHD, and, an increase in regulatory T cells. The current proposal will expand on this early experience and is written as a Phase II study evaluating the incidence and severity of acute GVHD following allogeneic transplantation using this novel preparative regimen of TLI combined with antithymocyte globulin (ATG). Patients with relapsed hemato-lymphoid malignancies will be considered for transplantation using donor grafts from HLA-matched related and unrelated donors. The preparative regimen of TLI combined with ATG is expected to result in high levels of sustained donor hematopoietic cell engraftment with a significantly reduced incidence of acute GVHD.

# 2 Objectives

## 2.1 Primary Objective

The primary endpoint of this phase 2 study is to evaluate the incidence of non-relapse mortality (NRM) at one year after transplantation.

## 2.2 Secondary Objectives

- To evaluate the kinetics of donor hematopoietic cell engraftment (neutrophil and platelets recovery) and chimerism.
- To document the quantitative and qualitative reconstitution of the immune system including T cell subsets, regulatory cells, NK cells and B cells.
- To evaluate the rate of relapse, overall and event-free survival and incidence of acute and chronic GVHD, at one year after transplantation.

# 3 Background

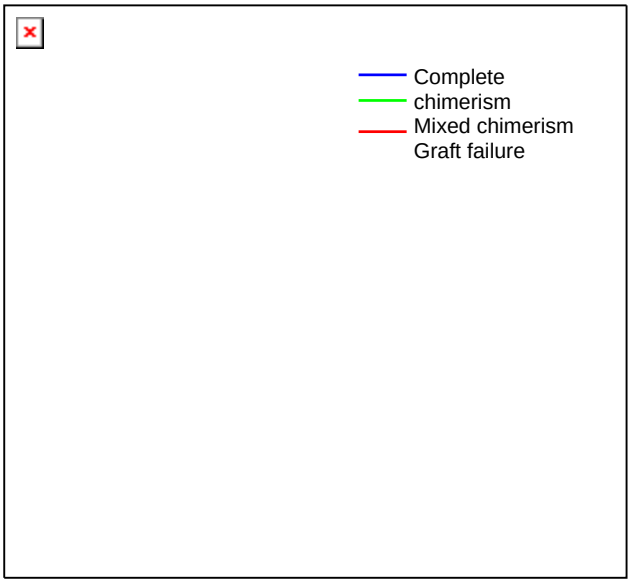
By virtue of reduced intensity conditioning (RIC), non-myeloablative allogeneic hematopoietic cell transplantation has shifted the burden of tumor eradication from chemoradiation to alloimmune graft-versus-tumor (GVT) effect.[1,2] Consequently, RIC is associated with minimal RROT, even in elderly patients or those with comorbid conditions. However, the risks of acute and chronic GVHD have remained significant post-grafting problems. In large single and multicenter studies the incidence of grade II-IV acute GVHD following RIC ranged from 20 to 50% of patients with sustained donor hematopoietic engraftment.[3-7] Although these incidences represent an improvement compared to conventional allografting, GVHD is still the leading cause of non-relapse mortality (NRM) in major studies and accounts for over 56% of the non-relapse deaths.[3,7,8] The incidence and severity of chronic GVHD is less clear as follow-up has been relatively short but it appears comparable to that observed following myeloablative allografting. In two large studies the risks of chronic GVHD were 74% and 68%, respectively, and in the EBMT report of over 900 patients the incidence of extensive chronic GVHD was 42%.[3,6,7] In addition, opportunistic fungal and viral infections complicate RIC accounting for significant non-relapse mortality.[9] Thus, despite overcoming RROT, RIC allo-SCT continues to be associated with the same medical complications that limit myeloablative allografting, specifically, acute and chronic GVHD and opportunistic infections.

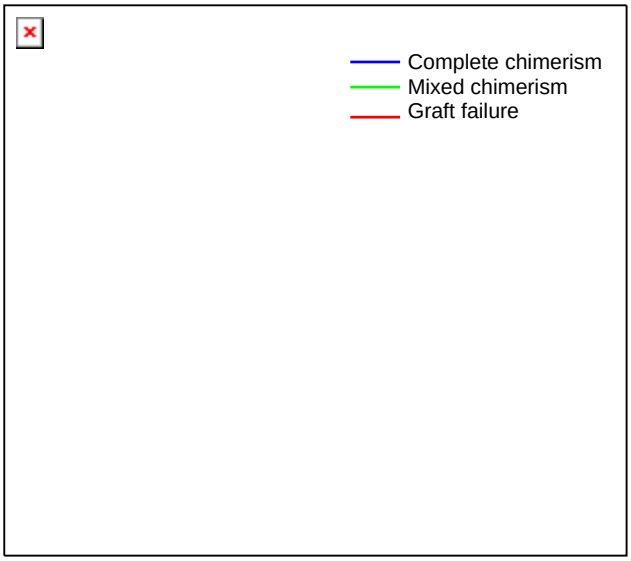
In general, established regimens for RIC can be considered as variations of any one of three themes that include: 1) purine analogue based regimens, particularly, Fludarabine based,[3,6,10-13] 2) low-dose total body irradiation (TBI) based regimens,[7] or, 3) reduced doses of myelotoxic therapy (often cyclophosphamide) combined with ATG and thymic irradiation.[8,14] A common variable is targeting of

host marrow, at least to some degree, with these non-myeloablative therapies. In contrast, the proposed protocol involves a conditioning regimen that impairs host immunity by altering peripheral T cell subsets but is unique in that it spares the marrow from direct irradiation or cytotoxic medication. Under these conditions, it is anticipated that following transplantation there will be a dramatic expansion of bone marrow derived suppressive regulatory T cells, which in mice, has been shown to protect against GVHD via an IL-4 dependent mechanism without compromising GVT effects.[15] These increases in regulatory T cells likely reflects the fact that these cells rapidly proliferate within the bone marrow in response to peripheral lymphoid depletion and do not require passage through the thymus for reconstitution, whereas conventional T cells involve a slower reconstitution and require passage through the thymus.[16]

## 4 Current results using TLI and ATG as a preparative regimen prior to allo-SCT

The Stanford group who pioneered the RIC regimen proposed in this protocol, has successfully translated the murine TLI/ATS protocol to a clinical regimen consisting of TLI/ATG with post-grafting immunosuppression of mycophenylate mofetil (MMF) and cyclosporin (CSA). The regimen proved to be well tolerated and without significant RROT. This transplantation protocol represents the translational of a preclinical model of bone marrow transplantation to a human protocol for the treatment of patients who have advanced and otherwise incurable myeloid and lymphoid malignant diseases. A publication detailing the outcomes of the first 37 consecutive patients treated with this transplant method was published in 2005.[17] In addition to the encouraging clinical results, Stanford determined that there was a highly significant increase in the percentage of regulatory T cells in all patients following transplantation. Whereas the mean value of $CD161^+CD3^+$ cells, the equivalent of mouse $NK1.1^+$ T cells, was 1.1% of all T cells before TLI/ATG, their percentages increased to a mean of 15% of all T cells by day +28 post transplant. In some cases there was a persistent elevation in the percentage of these regulatory T cells above baseline values for as long as 4 months after transplantation. Chimerism analysis of sorted regulatory T cells established that the vast majority, >85% of these cells, were donor origin by day+28. In contrast, patients allotransplanted with another NST regimen, Fludarabine/TBI, failed to demonstrate an increase in regulatory T cells (n=4; R. Lowsky; personal communication to Pr. M. Mohty).
Since the initial publication in 2005, Stanford has treated (as of Jan. 2009) over 150 additional patients using TLI and ATG as the transplantation conditioning regimen.[18] The current results suggest that the attainment of complete donor hematopoietic cell chimerism is significantly associated with improved outcomes. Complete donor chimerism is defined as the attainment of >95% donor type cells, mixed chimerism is achieving between 5-95% donor type, and graft failure is the failure to achieve >5% donor type after transplantation. In a detailed analysis of 111 patients with a median follow up of 3 years and a minimum follow up of 1-year for living patients the median OS and EFS were superior among patients achieving complete donor chimerism, 63.8 and 45.6 months, compared to patients with both mixed chimerism, 7.8 and 25.0 months (hazard ratio of 1.9 and 2.3), and primary graft failure, 0.6 and 3.4 months (hazard ratio of 6.0 and 98.0: Figures 1 and 2).




**Figures 1 and 2. Effect of chimerism on overall and event free survival.** Kaplan-Meier overall survival (A) and event-free survival (B) curve estimates among patients with non-Hodgkin's lymphoma and AML stratified by chimerism (complete, mixed chimerism or primary graft failure)

From among the 111 patients 79% achieved complete donor chimerism, 18% achieved mixed and 5% had graft failure. The data support that increasing the level of donor chimerism is a highly desirable goal. In the preclinical model the administration of increased doses of TLI resulted in a greater percentage of transplant recipients who achieved complete donor chimerism.[18]
Therefore in this protocol we will do similarly and increase the dose of TLI from the previously reported level of 800 cGy divided in ten 80 cGy fractions to ten fractions of 120 cGy for a total of 1200 cGy, to increase the percentage of patients achieving complete chimerism. The Stanford group has already extensive experience with using 1200 cGy because in two other Stanford studies involving cancer patients, they have increased the dose of TLI from 800 to 1200 cGy to promote improved engraftment and found this strategy successful and without any additional toxicity (very well tolerated outpatient treatment).

# 5 Patient Selection

## 5.1 Eligibility Criteria

- Any patient with one of the following hemato-lymphoid malignancies or syndromes in whom allogeneic stem cell transplantation is warranted.
Specific disease categories include: indolent advanced stage Non-Hodgkin Lymphomas, DLBCL, Mantle Cell Lymphoma, Marginal zone lymphoma, MALT, T cell lymphoma, Chronic Lymphocytic or prolymphocytic Leukemia, Hodgkin Disease, and Waldenström macroglobulinemia. T-cell NOS, angioimmunoblastic lymphoma, HTLV1, T-gamma/delta, anaplastic lymphoma and Sezary syndromes can be included after careful assessment by the PI and the protocol steering committee.
- Patients must be at least in partial remission (according to standard criteria) after salvage therapy and before (~one month) the start of the conditioning regimen.
- Patient age >50 and less than 66 years, or for patients <50 years of age but because of pre-existing medical conditions or prior therapy are considered to be at high risk for regimen-related toxicity associated with conventional myeloablative transplants.
- A fully HLA-identical sibling or matched unrelated donor is available (10/10 HLA match). Patients with one antigen mismatched donors (9/10 HLA match at the level of HLA-Cw) can be considered after discussion with the transplant team and the Principal Investigator.
- Patient must be competent to give consent.

### 5.2 Exclusion Criteria

The presence of one exclusion criteria makes a patient unable to enter the protocol:
- Patients with progressive hemato-lymphoid malignancies despite conventional therapies, and not in partial remission during the month preceding transplantation.
- Patients with ~~DLBCL or~~ cutaneous T cell lymphoma
- Uncontrolled CNS involvement with disease
- Fertile men or women unwilling to use contraceptive techniques during and for 12 months following treatment
- Females who are pregnant or female who are breast feeding
- Organ dysfunction defined as follows:
• Cardiac function: ejection fraction < 30% or uncontrolled cardiac failure (grade >= 2 according to the NYHA scale)
• Pulmonary: DLCO < 40% predicted
Serum creatinine > 1.0 mg/dL; if serum creatinine > 1.0 mg/dL, then the estimated glomerular filtration rate (GFR) must be > 60 mL/min/1.73 m² as calculated by the Modification of Diet in Renal Disease equation where Predicted GFR (ml/min/1.73 m2) = 186 x (Serum Creatinine)-1.154 x (age in years)-0.023 x (0.742 if patient is female)
• Liver function abnormalities: elevation of bilirubin to > 3 mg/dl and/or transaminases > 4x the upper limit of normal
- Karnofsky performance score < 70%
- Patients with poorly controlled hypertension on multiple antihypertensives
- Patients with uncontrolled infection
- Documented fungal disease that is progressive despite treatment
- Viral infections: HIV positive patients. Hepatitis B and C positive patients will be evaluated on a case by case basis
- Psychiatric disorders or psychosocial problems which in the opinion of the primary physician or Principal Investigator would place the patient at unacceptable risk from this regimen.
- Patients with prior malignancies diagnosed > 5 years ago without evidence of disease are eligible. Patients with a prior malignancy treated < 5 years ago but have a life expectancy of >5 years for that malignancy are eligible.
- Patients with known allergy to ATG or other allergy to rabbit-derived proteins
- Patients with known allergy or sensitivity to mycophenolate mofetil

### 5.3 Cytoreduction Prior to Non-myeloablative Transplantation

Prior to inclusion in this protocol, cytoreduction and/or radiation therapy may be given for patients with progressive malignancies to reduce tumor bulk as determined on clinical grounds by the attending physician, and to achieve the best disease response prior to conditioning. The referring oncologists may be asked to administer this therapy. There is no minimal delay to observe between the end of salvage therapy and allogeneic transplantation. Evaluation of the impact of a specific salvage therapy prior to inclusion, is not part of the objectives of this trial.

## 6 Donor Selection/Evaluation

Only HLA identical family donors OR unrelated donors with matching in 10/10 alleles (HLA-A, B, C, DRB1, DQB1) OR maximum of one allele or antigen mismatch OR family donor with maximum one allele mismatch will be selected for the purpose of this study. After informed consent, HLA-identical family donors will undergo a clinical and biological evaluation according to the national recommendations of the «Agence de Biomedecine». Of note, donors should have no contra-indications for the mobilization of peripheral blood stem cells using G-CSF

➔ Donor selection is performed on the basis of a high resolution (4 digits) typing of HLA-A, B, C, DRB1, DQB1. The final selection of the most suitable donor is at the discretion of the transplanting physician. An HLA identical sibling donor or an unrelated donor matched in 10/10 alleles are equally considered as first choice donor. Health and age of the donor, CMV serostatus, a history of pregnancy and blood transfusion have to be considered in the donor selection process. Both family and unrelated donors up to 1 antigen or allele mismatch are acceptable.

➔ Donor mobilization with G-CSF: this will be performed according to the national recommendations of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC) and the "Agence de Biomedecine". The donor will receive 10 µg/Kg donor body weight, starting on day -5 before the planned first day of apheresis. Mobilized peripheral blood stem cells (PBSC) are the preferred type of graft. A total number of 6.0 x 10^ 6 CD34+ cells per kilogram recipient's body weight should be targeted with an acceptable minimum of 2.0 x 10^6 CD34+ cells per kilogram recipient's body weight
If bone marrow is the only stem cell source available, it will be accepted within the protocol. A total of $\geq 2x10^{8}$ mononuclear cells per kilogram recipient's body weight should be targeted.
In case of poor stem cell mobilisation or poor marrow harvest, this will be reported in the CRF, however, since this is not within the influence or responsibility of the transplant physician or the sponsor or the principle investigator of the study, this fact will not be regarded as a protocol violation.
Grafts are transfused without any further manipulation such as T-cell depletion and CD34+ selection are not permitted. Transplantation should be performed within 72 hours from start of first apheresis.

The production of PBSC or BM graft follows the standard operation procedures of the participating centers or, in case of an unrelated donor, of the donor search centers. It is the responsibility of the producing institution to perform the stem cell or bone marrow harvest according to GMP guidelines and national and international laws.

## 7 Study design

This is a prospective, multicenter, non-randomized Phase II study that will include a total number of 30 patients included over a period of 2 years (+ 1 year of follow-up; for total study duration of 3 years).

## 8 Registration and inclusion procedures

After all pretreatment evaluations have been performed, and within four weeks of anticipated non-myeloablative transplantation, patients can be entered on study. Patients are included if:

- they fulfil the inclusion the criteria
AND
- an evaluation for organ functions has not revealed any exclusion criteria as defined,
AND
- a suitable related or unrelated donor has been identified
There is no minimal delay to observe between the end of salvage therapy and inclusion in this protocol.

➔ An inclusion number will be attributed to the patient when he / she has met the inclusion/exclusion criteria and consent has been obtained.

THIS NUMBER WILL BE AUTOMATICALLY GENERATED BY CONNECTING TO THE ELECTRONIC CRF USING THE CAPTURE SYSTEM SOFTWARE ACCESSIBLE FROM THE **HTTPS://WWW.DIRC-HUGO-ONLINE.ORG/CSONLINE** WEB SITE

## 9 Treatment Plan

**Transplant Schedule**
**Week #1**

| Monday<br>Day –11 | Tuesday<br>Day –10 | Wednesday<br>Day –9 | Thursday<br>Day –8 | Friday<br>Day –7 | Saturday<br>Day –6 | Sunday<br>Day -5 |
|---|---|---|---|---|---|---|
| TLI 120cGy | TLI 120cGy | TLI 120cGy | TLI 120cGy | TLI 120cGy | REST | REST |
| ATG 1.5 mg/kg<br>+<br>Premedication | ATG 1.5 mg/kg<br>+<br>Premedication | ATG 1.5 mg/kg<br>+<br>Premedication | ATG 1.5 mg/kg<br>+<br>Premedication | ATG 1.5 mg/kg<br>+<br>Premedication | | |

**Week #2**

| Monday Day −4 | Tuesday Day −3 | Wednesday Day −2 | Thursday Day −1 | Friday Day −0 | Saturday Day +1 | Sunday Day +2 |
|---|---|---|---|---|---|---|
| TLI 120 cGy | TLI 120cGy | TLI 120cGy | TLI 120cGy x 2 doses | Mobilized PBSC | | |
| | Start CSA | CSA | CSA | CSA | CSA | CSA |
| | | | | Start Oral MMF | MMF | MMF |

(A) TLI Administration: TLI is administered ten times in 120cGy fractions on day −11 through day −7 and day −4 through day −1 according to the above delineated schedule. The TLI schedule may be adjusted based on availability of the radiation therapy department. The radiation field (four fields—two anterior and two posterior) will include all major lymphoid organs including the thymus, spleen and lymph nodes. A radiation oncologist will evaluate patients prior to conditioning to determine blocks and radiation ports. Since TLI can cause nausea, anti-emetics will be given prior to TLI.

(B) ATG: Thymoglobulin will be administered five times intravenously at 1.5 mg/kg/day from day −11 through day −7 for a total dose of 7.5 mg/kg. Premedication for thymoglobulin will include solumedrol 1.0 mg/kg/day, paracetamol and anti-histaminics. The drug will be administered by continuous IV infusion through a central venous catheter over a period of 6 hours. In case of allergy symptoms following ATG infusion, the infusion can be stopped for one hour and then resumed at a lower infusion rate (e.g. 8 to 10 hours according to local practice). ATG will be completely discontinued in case of a severe anaphylactic reaction requiring adrenaline or intensive care resuscitation measures. Cyclosporine administration will be discontinued during ATG infusion.

(C) Mobilized PBSC: The desired cell doses (based on recipient body weight) for MRD and MUD transplants are around 4-8 x10^6 CD34+ cells/kg.

(D) ABO incompatibility: ABO incompatibility between donor and host will require red cell depletion only if bone marrow is used as the hematopoietic source.

(E) Post-Transplant Growth Factors: Patients should not receive post-transplant growth factors while receiving MMF particularly during the first month off MMF taper. Growth factors should not be given unless severe neutropenia develops or persists past day 27 post-transplant (ANC < 100/ml for > five days).

(F) Cyclosporine (CSA): Cyclosporine A alone (3 mg/Kg IV from day-3); CSA will be usually tapered after the day +56, and the patient is without evidence of GVHD. The CSA will be tapered at 6% every week. Modifications of the taper schedule may be indicated if significant disease progression occurs early post-transplantation or the patient develops GVHD. Tacrolimus may be used if patient does not tolerate cyclosporine. Tacrolimus is administered according to current standards of care.

(G) Mycophenylate mofetil (MMF): MMF 500 mg x 4/ jour PO from day 0. MMF will be stopped on day +28 for matched related donors and for one antigen mismatched or unrelated donors beginning day +56 MMF will be tapered by 10% weekly till off, typically by day +96. If there is nausea and vomiting at any time preventing the oral administration of MMF, MMF should be administered intravenously.

Guidelines for MMF dose adjustment:
If in the clinical judgment of the investigator, there is documented toxicity related to MMF administration, a dose adjustment will occur. Based on previous solid organ transplantation

studies, dose adjustments are likely to occur because of hematopoietic or gastrointestinal adverse effects. Dose adjustments will not be made for hematopoietic toxicities unless severe neutropenia develops or persists until day +21 post-transplantation (ANC <1000/µl for >5 days). In the event of gastrointestinal toxicity that requires medical intervention including medication for control of persistent vomiting or diarrhea that is considered to be due to MMF, a 20% dose reduction or the drug will be given i.v. For severe gastrointestinal toxicity related to MMF (severe refractory diarrhea or overt gastrointestinal bleeding), MMF may be temporarily stopped.

(H) Graft infusion at day 0: Peripheral Blood Stem Cells are the preferred stem cell source.

(I) Supportive care: will be performed according to each participating centre usual practice

In general, since CSA and MMF are routinely used in the allogeneic stem cell transplant setting, temporary or permanent discontinuation of these 2 agents should be performed **in case of side effects** according to local standard practice.

## 10 Post-transplant follow-up

See Appendix 5.

➔ **Clinical:** The incidence, severity and extent of acute and chronic GVHD will be monitored and scored according to standard criteria (see Appendix 1). As well, documented and presumed post-transplant infectious complications, rate of relapse, event-free and overall survival and transplant related mortality will be recorded.

➔ **Chimerism:** Chimerism of the CD3 peripheral blood cell fraction will be performed on days +14 (or at time of neutrophil recovery whichever occurs earlier), +28, +56, +96, +120, +180, +270 and yearly to evaluate the degree of donor hematopoietic cell engraftment. For the purpose of this protocol, mixed chimerism will be defined as detection of donor T cells ($CD3^+$), as a proportion of the total T-cell population, of >5% and <95% in the peripheral blood. Full donor chimerism is defined as >95% donor $CD3^+$ T cells. Increasing donor chimerism is defined as an absolute increase in 20% of $CD3^+$ T cells over the chimerism evaluation of the previous month. Decreasing donor chimerism is defined as an absolute decrease of 20% of $CD3^+$ T cells over the chimerism of the previous month. Decreasing donor T cell chimerism after day +28 may indicate that graft rejection is occurring. These cases should be discussed with the Principal Investigator, as they may be eligible for a second salvage non-myeloablative HCT procedure.

➔ **Monitoring Immune Reconstitution**: Evaluation of immune reconstitution will be studied in the peripheral blood post-transplantation. Immune recovery analyses will be performed prior to transplantation, and on days +28, +96, and +180 after transplantation. (see Appendix 6)

Immunological evaluations are centralised at CHU de Nantes. The whole blood samples of patients (except for patients included at Nantes Hospital) will be shipped within 24 hours to the CHU de Nantes, at room temperature by a carrier.

➔ **Assessment of Disease Response:** Since the diseases treated on this protocol are heterogeneous, appropriate disease specific studies will be performed to evaluate response to transplant. As a guideline for investigators, disease assessment will be performed on days +96, +180, +270 and yearly after transplantation. Responses will be classified as continued complete remission (CCR), achieved complete remission ($CR_a$), partial response (PR), progressive disease (PD), or no response (NR). Disease response will be according to accepted criteria. All cases of progressive disease should be discussed with the Principal Investigators. If patients show evidence of progressive disease then they may be candidates for DLI.

Definition of Disease Progression

| Disease | Progression |
|---|---|
| CLL, NHL & Hodgkin's disease | New sites of lymphadenopathy or increase of ≥ 25% in lymph node size (as assessed by CT scans); or increase of ≥ 25% of bone marrow or blood involvement (if lymphocyte count > 50,000/ml) with clonal B cells (CLL). |

➔ **Monitoring of infectious complications:** Since the different drugs used in this protocol are already widely used in the allogeneic stem cell transplant setting. Thus, appropriate monitoring will be performed according to standard practice. As a guideline for investigators, it is standard of care to monitor routinely after transplant and usually within the first 3 months (or beyond in case of active GVHD) viruses reactivation such as CMV and EBV. In case of viral reactivation, appropriate therapeutic and symptomatic measures should be delivered according to standard practice.

# 11 Therapeutic Interventions for Disease Progression

(A) Early discontinuation of cyclosporine immunosuppression (<day +120)

This should be considered the first therapeutic maneuver; however, neither MMF nor cyclosporine should be stopped prior to reviewing chimerism results. If the donor T cell chimerism is ≥ 50%, and there is < grade II GVHD, MMF is to be stopped (if still being taken), and CSA tapered over two weeks. Bone marrow aspirate and blood chimerism studies will be performed when off immunosuppression after two weeks.

(B) Donor Lymphocyte Infusion (DLI)

All decisions to infuse DLI should be discussed with the Principal Investigator prior to DLI infusion. If disease progression shows limited or no response after stopping immunosuppression and donor T cell chimerism has not decreased below the level of 50% and GVHD is < grade II then patients will receive DLI as outlined below. However, if after discontinuation of immunosuppressives there is a ≥20% increase in T cell donor chimerism patient should be observed for an additional two weeks and then chimerism studies repeated.

(C) Intercurrent treatment with chemotherapy or radiation:

Conventional chemotherapy or radiation should be considered in the setting of life threatening disease progression. After therapy is completed chimerism should be evaluated and administration of DLI off protocol considered.

# 12 Donor Lymphocyte Infusions

## 12.1 Criteria for DLI infusions

Patients will be given DLI if:

- They have >50% donor $CD3^+$ cells in their peripheral blood and GVHD is <grade II.
- They have completed routine taper of immunosuppression and they have progressive disease at ≥ two weeks off immunosuppression. Assessment of disease progression is outlined above.
- They have undergone early discontinuation of immunosuppression and have progressive disease at ≥ two weeks off immunosuppression.
- They have undergone early discontinuation of immunosuppression with disease response, but there is incomplete response after 6 weeks off immunosuppression.

### 12.2 Dose and Administration of DLI

The following describes a plan for collection and sequential administration of DLI. Two or more doses of DLI can be used**,** depending on disease and patient characteristics.

| DLI | $CD3^+$ cells/Kg (recipient weight) | Timing of DLI |
|---|---|---|
| Dose 1 | $1.0 \times 10^6$ | Must be off immunosuppression for $\geq$2 weeks with no evidence of GVHD, have $\geq$50% donor $CD3^+$ chimerism and evidence of progressive disease (see Section s 11.5 and 12.0) |
| Dose 2 | $1.0 \times 10^7$ | Same as above<br>Or<br>If disease progression and no GVHD at day >28 after DLI #1<br>Or<br>Stable persistent disease and no GVHD at day 45 after DLI #1 |

## 13 Drugs and Devices

For specific information relating to drugs used in this protocol, please refer to Appendix 10.
Side effects related to **Total Lymphoid Irradiation (TLI) are summarized below:**

- Nausea and vomiting are seen in almost all patients. This toxicity varies in degree with most patients experiencing some intermittent nausea and a minority having mild emesis; this usually resolves in 24 hours. Patients will be premedicated as necessary prior to starting radiation and thereafter q 4-6 hours prn, with care to avoid oversedation and risk of aspiration.
- Uric acid nephropathy may be seen depending upon the tumor burden. Measures to be taken include administration of allopurinol, hydration, alkalinization of urine to pH 7-7.5 and furosemide as needed to maintain adequate urine output.
- Diarrhea of variable severity may occur starting in the first week, and will be managed symptomatically.
- Neutropenia and thrombocytopenia are likely to occur with a nadir of 1,200-2,000 WBC/$mm^2$ and 50-100,000 $mm^3$.
- Late effects of TLI include risk of a second malignancy, including lung cancer in smokers and skin cancer. Secondary hematologic malignancy risk is less than two-fold. Hypothyroidism risk is increased. Viral infections have an increased risk within two years, including herpes zoster. The combined use of TLI and ATG increase the risk of secondary lymphoproliferative disease and CMV infection.

## 14 Statistical considerations, termination of study and safety committee

Based on results from the literature and data from the EBMT registry, the hypothesis for the primary endpoint is an improvement in non-relapse mortality at one year after transplantation from 30% to 10%. Using a one step A'Hern procedure, 28 patients are needed. In all, 30 patients will be included (taking into account that after registration, there is a risk of dropout i.e. patients, who will not receive a transplant due to rapidly progressive disease, infection or other events occurring after identification of a donor, but before start of conditioning). If the number of patients alive at one year is 24 or more, the hypothesis that NRM >= 0.30 is rejected with a target error rate of 0.050 and an actual error rate of 0.047. If the number of patients alive at one year is 23 or less, the hypothesis that NRM <= 0.10 is rejected with a target error rate of 0.20 and an actual error rate of 0.142.

Every effort will be made to keep the number of missing values for all parameters to a minimum. Missing data on overall survival is assumed to be 0 and on event free survival to be below 10 % as patient care after transplantation is very close.

Every patient included in the study will be taken into account at time of data analysis. A descriptive analysis will be conducted on the following parameters:
- The characteristics of donors and patients
- Primary and secondary endpoints

Qualitative data will be described in frequency and percentage and will be represented using histograms or diagrams of distribution. They will be compared using the X2 test or Fisher exact test. Quantitative data will be described using the calculations of average, standard deviation, median, and extreme values, and will be compared with the Mann & Whitney nonparametric test.
The toxicities rate will be calculated and will be given with their 95% confidence intervals.
The probabilities of survival will be estimated by the Kaplan-Meier method and by calculating the cumulative incidences for relapse/progression, GVHD and non-relapse mortality incidence.
All tests will be bilateral, and the level of significance is 0.05.

**Stopping Rules:**
All patients regardless of diagnosis will be considered in the evaluation of stopping the study prematurely. If at any point during the study the incidence of clinically significant acute GVHD (grade ≥ 2) is above 50%, or the rate of graft failure is above 20%, or the transplant related mortality rate is above 25%, or any other transplant related complication develops in excess of expected (i.e. veno-occlusive disease of the liver, interstitial pneumonitis, opportunistic viral and fungal infections) then the trial will be stopped and re-evaluated due to safety concerns.
In addition to the above stopping rules, a **premature discontinuation** is defined when a patient selected in a trial ceases its participation before the end of study. The criteria for premature discontinuation of the study are:
- Patient's refusal to continue the study
- Interruption of the study as per the sponsor's decision or per the regulatory agencies
- Cancellation of allo-SCT

In case of premature discontinuation during the selection period, the patient will be replaced and his data will not be taken into account for analysis. However, monitoring of patients who have undergone allo-SCT will be pursued, even if they have ceased their participation in the trial.

**An independent safety committee** (composed of experts in the field) will be established by the sponsor to assess at regular intervals the progress of the trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop the trial.
During the study, meetings or teleconferences of the Independent Data Monitoring Committee will be organised periodically (i.e. on inclusion of five, 10, 15, and 24 patients),
The members of this committee are listed below:

| Name | Speciality | Address | E-mail |
|---|---|---|---|
| Pr Blaise Didier | Hematologist | Institut Paoli-Calmettes (Marseille) | blaised@marseille.fnclcc.fr |
| Dr Peffault de la Tour Régis | Hematologist | Hôpital Saint Louis (AP-HP) | regis.peffaultdelatour@sls.aphp.fr |
| Dr Fegueux Nathalie | Hematologist | Hôpital Lapeyronie (Montpellier) | n-fegueux@chu-montpellier.fr |

The members of the Independent Committee agree to participate in safety committee by signing a participation agreement.

# 15 Evaluation criteria

## 15.1 Primary endpoint

Evaluation of the cumulative incidence of non-relapse mortality at one year after transplantation

## 15.2 Secondary endpoints

- Incidence of engraftment defined as the first day of neutrophil (>500/µl for 3 consecutive days). Engraftment failure is defined as neutrophil <500/µl at day+42 after allo-SCT.
- Evaluation of overall and progression-free survival at one year after transplantation

- Disease response rate (remission status) at day +90, 6, 12 and 12 months after allo-SCT
- Cumulative incidence of relapse, death from disease at 12 months after transplantation
- Cumulative Incidence and severity of acute and chronic Graft-versus-Host disease

# 16 Safety aspects and adverse events

## 16.1 Adverse Event (AE)

An adverse event (AE) is any noxious, unintended, or untoward medical event occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of the medical condition such as relapse or progression of the hematological disease, this should not be considered as an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome. All AEs will be recorded by the Investigator(s) from the time of signing the informed consent until the end of the designated follow-up period.

## 16.2 Serious Adverse Event (SAE)

A serious adverse event is any event occurring irrespective of the dose (including overdose) and that:

- Results in death
- Is life-threatening(1)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity(2)
- Is a congenital anomaly or birth defect
- Is an important medical event(3)

1"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
2"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
3"Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

## 16.3 adverse drug reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

## 16.4 Definition of an expected adverse event (AE-E)

An "expected" adverse event is one, the nature or severity of which is consistent with information already available in the relevant source document(s).
A serious adverse event fulfils with seriousness definition as mentioned previously.

The expected adverse events in this study can be summarized as follow:

- related to desease = disease symptoms in relation with relapse or progression

- related to study products (Thymoglobuline, CSA, MMF) according to the drug brochures (please see appendices). The most frequent events are those:
  - Linked to immunosupression such as infectious complications (candidosis, herpes-zoster, pneumonia, bacteremia, septicemia, septic choc,...)
  - Linked to hematological toxicity (anemia, leuco-neutropenia with or without fever, thrombocytopenia, aplasia..)
  - Linked to toxicity on the mucosal and cutaneous tissues: mucositis, rash, dermatitis, alopecia...
  - Linked to digestive toxicity (nausea, vomiting, anorexia..)
  - Linked to renal impairement (increase of serum creatinine, renal failure..)
  - Linked to liver (increase of ASAT, ALAT, serum bilirubin)

  All adverse events not previously described in the drug brochures should be considered as unexpected AEs.
- Related to the allogeneic transplantation procedure itself such as the use of TLI, acute GVHD, aplasia, etc.
- Related to other concomitant treatments (e.g. growth factors, analgesic drugs, anti-emetic drugs, immunosuppressive therapy): declaration of AEs related to such treatments will be left at the discretion of the attending physician (mainly with respect to possible interaction)

### 16.5 Definition of an unexpected adverse event (AE-U)

An "unexpected" adverse event is one, the nature or severity of which is not consistent with information already available in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction. As part of this protocol, serious adverse events that will be considered are those > grade 3. Except for death, AE related to disease progression or to the allogeneic transplant procedure itself will not be communicated to the sponsor irrespective of their severity.

### 16.6 Classification of severity

For both adverse events (AE) and severe AE (SAE), the investigator(s) must assess the severity of the event. The severity of the AEs will be graded on a scale going from 1 to 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE). The NCI CTCAE V4.0 can be viewed on-line at the following NCI web site: http://ctep.cancer.gov/reporting/ctc.html. If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade the event :

| Grade | Definition |
|---|---|
| 1 | **Mild** Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities |
| 2 | **Moderate** Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic manoeuvres |
| 3 | **Severe** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required |
| 4 | **Life-threatening** Immediate risk of death; requires hospitalization and clinical intervention. |
| 5 | **Death** |

### 16.7 Classification of relationship/causality of adverse events (SAE/AE) to study drug

The investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as "Not suspected" or "Suspected" as defined below:

- Suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
- Not suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

The sponsor of the trial shall determine the causality using the WHO method.

### 16.8 Procedure in case of a serious adverse event (SAE)

The declaration should be made within 24 hours by fax to 02 53 48 28 36 using the specific declaration form in appendix 9.

Département Promotion de la Recherche Clinique

CHU de Nantes, 5 allée de l'Ile Gloriette,
44093 NANTES Cedex1

Fax : 02 53 48 28 36

Tel: 02 53 48 28 35

### 16.9 Serious Adverse Event Reporting

Reporting of Adverse Events to Regulatory Authorities and the Ethics Committee. The sponsor will inform relevant all relevant regulatory authorities and the ethics Committee according to mandatory rules :

- of all relevant information about serious unexpected adverse events suspected to be related to the study medication that are fatal or life threatening as soon as possible, and in any case no later than seven days after being aware of such a case. Relevant follow-up information for these cases will subsequently be submitted within an additional eight days.

- of all other serious unexpected events suspected to be related to the study medication as soon as possible, but within a maximum of fifteen days of first knowledge by the sponsor.

### 16.10 Annual safety report

A safety report will be produced annually at time of the anniversary of the clinical trial authorization issued by the competent authority. This report comprises three parts: report on patient safety, "line-listing" of SAE and comprehensive summary of study status. The report is produced by the sponsor of research in collaboration with the principal investigator. This report will be submitted to the relevant authorities by the sponsor within 60 days from the above anniversary date.

## 17 Quality assessments

### 17.1 Good Clinical Practice

The study will be performed according to the Guidelines for Good Clinical Practice (ICH Harmonised Tripartite Guideline for Good Clinical Practice, (17.01.1997)).

### 17.2 Auditing

To guarantee a high quality of treatment for the patients within the present study, the sponsor will insure that the participating centers fulfils the following criteria:

- fulfilling of legal requirements
- experience of the principle investigator of the entire study and the respective center with respect to study conduct
- ICH/GCP knowledge and certifications

### 17.3 Monitoring

Regular monitoring is an essential part of the study conduct. It will be performed by the sponsor of the trial. After the initiation visit, the frequency of monitoring visits will depend on the course of the study, and recruitment. It is the monitor's responsibility to make the local investigators and all the stuff who is involved into the study or the care of the patients familiar with the protocol. During the course of the study, the monitor will control the progress of the study, the commitment to the protocol, the documentation and careful usage of the study medication, and the maintenance of GCP guidelines and legal obligations. Problems as well as changes in reported data will be worked out in collaboration with the local investigator, who is obliged to cooperate with the monitor and to allow access to the patients' charts. Source data verification is performed by the monitor. In terms of Risk for patients, the protocol has been classified at Class C. Therefore, 100% source data verification will be performed in about 40% of the patients. In contrast, inclusion criteria will be verified in 100% of patients. The monitor will have to respect that the data she/he comes into contact with are highly confidential. A monitoring report will be provided for each visit.

## 18 Final report and publications rules

At the end of the study evaluation the principle investigator presents a final report, containing the clinical report, single tables, and the final conclusions.
Publication of the results is realized independently from the outcome of the trial. The study or parts of the study should be published by the writing committee only which consists of the persons in charge of the study as mentioned on the front page. According to the EBMT rules, co-authors will be offered to the local PI of participating centers, the order depending on the number of patients included by the respective centers, or depending on their contribution to the protocol or the realisation of the study. Other investigators will be mentioned in the addendum. All publications and/or communications related to this trial should at least mention the PI of the trial and the sponsor.

## 19 Regulatory aspects

The study will be conducted according to the European Union directive (ICH Harmonised Tripartite Guideline for Good Clinical Practice, (17.01.1997)). The study has to be conducted in compliance with the protocol, GCP and all applicable regulatory requirements:

- Helsinki declaration from1964, revised in Washington in 2002,
- GCP of the International Harmonization Conference (ICH–E6, 17/07/96),
- European Directive (2001/20/CE) on the conduct of clinical trials,
- French law n° 2004-801 dated 6 August 2004,
- French bioethics law n° 2004-800 dated 6 August 2004.

Accordingly, investigating physicians, have to provide direct access to study documents to monitoring, audits, institutional internal control, external authorities, and the members of the ethical committee. Written informed consent by the patient is mandatory.
The co-ordinating investigator and all investigators will be given an up-to-date investigator's brochure containing full details of the status of the pre-clinical and clinical knowledge of the study medication. As soon as new information is obtained, an updated version will be supplied or an amendment added to the existing investigator's brochure.

### 19.1 Regulatory Authorities Approval (CPP and AFSSAPS)

No patient may be included in the study before the respective requirements of the national health authorities are fulfilled. The trial will begin only after the positive vote of the responsible Ethics Committee (CPP) and after the approval by the appropriate national health authority (AFSSAPS).
The protocol has to be followed strictly, protocol violations have to be documented and the reason has to be given (e.g. emergency measures). Any changes in the protocol can only be performed by the principle investigator or the protocol writing committee. Any subsequent changes will be reported or submitted for approval to the ethical committee and to local and national authorities.

### 19.2 Informed consent

Written informed consent is obtained by each patient before inclusion into the study. Using patient information sheets, as well as personal oral explanation by a local investigator at the patient's transplant center, the patient will be informed of the aims and the investigational nature of the study, the exact procedures that will be done during treatment and evaluation, the possible risks and side effects, and of alternative treatment options. They will be informed as to the strict confidentiality of their patient data, but that authorised individuals other than their treating physician may review their medical records for trial purposes. Further, the patient will be informed, that their anonymzed data will be scientifically analysed and published. It will be emphasised that the participation is voluntary and that consent can be withdrawn by the patient at any time without explanation of the reason. The patient is allowed to refuse further participation in the protocol, whenever he/she wants. The patient's further treatment will not be influenced by this decision.

### 19.3 Responsibilities

In collaboration and according to the SOP of the sponsor (CHU de Nantes), a detailed list of delegation of responsibilities has been established. It is held by the sponsor, who is finally responsible for the correct performance of delegated responsibilities by the respective persons or institutions. A copy of this list will be delivered to the participating institutions.
The investigator of each institution undertakes to conduct the trial according to the protocol which was approved by the ethics (CCP) and health authorities (AFSSAPS). The investigator must not make any changes to the protocol without the permission of the sponsor and without the CCP has given a favourable opinion on the proposed amendments.
It is the responsibility of the investigator responsible for the trial in the participating center:

- To provide his curriculum vitae as well as co-investigators,
- Identify team members, who will participate in the trial and define their responsibilities,
- To start recruiting patients after authorization of the sponsor,
- Try to include the required number of patients within the period of recruitment.

**It is the responsibility of each investigator:**

- To obtain the informed consent dated and signed personally by the patient before any selection process specific to the trial
- To fill in a CRF for each patient included in the trial and allow direct access to source documents to validate CRF data,
- Correct, sign and date the correction of the CRF for each patient enrolled,
- Notify the sponsor of any serious adverse events within the time required
- To accept regular monitoring visits and possibly those of auditors mandated by the sponsor or inspectors from authorities.

All documentation on the study (protocol, consents, notebooks observation, file investigator, etc.), And original documents (laboratory results, x-rays, minutes of consultations, review reports, etc..) must be kept in a safe place and considered confidential material. The data archiving will be under the responsibility of the investigator and, as required by law. Data will be kept for a minimum of 15 years after the end of the study.

### 19.4 Sponsor responsibilities

It is the responsibility of the sponsor to:

- Subscribe insurance to cover its liability for the harmful consequences of research,
- Provide the investigators with all information necessary to conduct the research,
- Pay any charges in relation with the submission of this protocol to health authorities,
- Apply for authorization from a relevant CPP,
- Apply for authorization from AFSSAPS,
- Inform the Directors and Pharmacists of health facilities,
- Inform AFSSAPS, CPP and EMEA of any serious incidents that may be due to research.

### 19.5 Protocol amendments

Any amendment to this protocol must be agreed to by the sponsor. Written verification of CPP and AFSSAPS approval will be obtained before any amendment is implemented.

### 19.6 Protocol deviations

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

### 19.7 Biocollections

Biological samples collected for the immunological assessment will be stored in a biocollection. The patient's informed consent will be collected and the samples will be stored in one of the biocollections of CHU de Nantes : biocollection on "hematologic malignancies". This biocollection and the procedure for obtaining informed consent were reported to Ethics Committee located at Angers.

## 20 REFERENCES

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# 21 APPENDICES (in french)

ANNEXE 1 : Echelle de cotation de la GVH
ANNEXE 2 : Evaluation de l'état général en fonction de la classification de Karnofsky et de l'échelle de valeur de l'ECOG.
ANNEXE 3 : Formulaires d'information et de consentement destinés au patient
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