_STUDY PROPOSAL SUMMARY

I. TITLE: "High-dose myeloablative conditioning (MAC) vs. Reduced-intensity conditioning (RIC) for allogeneic hematopoietic stem cell transplantation (HSCT) from HLA-identical siblings in adults with high-risk myelodysplastic syndromes (MDS) and acute myelogenous leukemia: a joint study proposal of the MDS subcommittee of the EBMT-CLWP, the acute leukemia WP of the EBMT and the MDS workpackage of LeukemiaNet"

II. SPECIFIC AIMS:

1. ***Primary aim:*** To compare **engraftment**, **non-relapse mortality (NRM)**, **relapse**, **GVHD, overall survival (OS)** and **disease-free survival (DFS)** in HLA-identical siblings receiving a RIC (including fludarabine plus intermediate-dose alkylating agent(s) +/- alemtuzumab or ATG) allogeneic HSCT or a high-dose MAC (including cyclophosphamide (100-120 mg/m^2 IV) plus high-dose TBI (≥ 8 Gy) or cyclophosphamide plus high-dose busulphan (16 mg/kg total dose by mouth or the equivalent IV dose), +/- alemtuzumab or ATG).

— ***Secondary aim:*** To compare outcomes between intermediate-intensity RICs: Alkylators +/- fludarabine; and minimal-intensity RICs: mini-TBI + fludarabine.

III. PATIENT ELIGIBILITY CRITERIA

1. *To reduce as much as possible heterogeneity in baseline patient characteristics, we propose focusing on patients with > 10% blasts in the BM at diagnosis:*

- Patients with high-risk MDS (RAEB type 2 and RAEB-t) and AML (including secondary and therapy-related AML) transplanted from an **HLA-identical sibling between January 1998 and December 2004.**
- A **RIC** will be defined as intermediate-intensity RICs and minimal-intensity RICs. Intermediate-RICs mostly consist in fludarabine plus intermediate doses of one or two alkylating agents, with or without ATG or alemtuzumab. Intermediate-doses of alkylating agents are defined as busulphan (8 to 10mg/kg orally or equivalent IV dose), IV melphalan (80 to 140 mg/m^2), IV cyclophosphamide (60 to 120 mg/m^2) and/or IV thiotepa (5-10 mg/kg) or low-dose TBI (< 400 cGy), with or without Campath or ATG. Minimal-RICs mostly include low-dose TBI + fludarabine.
- A **MAC** will be defined as regimens including cyclophosphamide (100-120 mg/m^2 IV) plus high-dose TBI (≥ 6 Gy) or cyclophosphamide plus high-dose busulphan (>10 mg/kg total dose by mouth or the equivalent IV dose), with or without other high-dose cytotoxic agents

and/or antithymocyte globulin (ATG) or alemtuzumab. Again, there will be three *types* of MAC regimens based on the use of ATG, alemtuzumab or no MoAb in the conditioning regimen.

2. Patients should have ***low tumor burden at the time of alloHSCT***. Thus, patients should be in first or second CR or PR after a first-line or salvage AML-type therapy: ***< 10% BM blasts after AML-type at the time of transplant.***

IV. DESIGN

The **outcomes** to be analyzed will be:

1. **Engraftment** of neutrophils and platelets, as well as day to complete donor chimerism in peripheral blood (100% total nucleated cells or > 95% T-cells)

2. Acute and chronic **GVHD**: incidence and time to onset. Patients at risk will be those surviving > 13 days and > 90 days post-transplant, respectively.

3. Disease **relapse or progression**.

4. **NRM.**

5. **Disease-free survival**.

6. **Overall survival**.

.....according to the number of cases, as many as possible of the following variables will be considered in univariate and multivariate analyses (the type of conditioning will be included in all analyses):

1. Disease-related variables: Disease type, biologic risk factors and phase at transplant.
2. Patient-related: Age, gender, Karnofsky score, serious comorbidities, CMV status of Do/Re, donor age and gender.
3. Transplant-related: CD34+ cell dose infused, GVHD prophylaxis (CyA/MTX vs others), T-cell depletion (ex-vivo or in vivo), SC source (BMT vs. PBSCT), route of busulphan (PO or IV).
4. Use of Alemtuzumab (and dose), ATG (type and dose) or no antibodies in the conditioning regimen. ***This information is of utmost importance for the study to be useful.***

Number of possible patients available: Estimated to be from XXX to XXX (to be confirmed exactly)