PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0402

A Phase III Randomized, Multicenter Trial Comparing Sirolimus/Tacrolimus with Tacrolimus/Methotrexate as Graft vs. Host Disease (GVHD) Prophylaxis After HLA-Matched, Related Peripheral Blood Stem Cell Transplantation

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Study Design: The study is designed as a Phase III, randomized, open label, multicenter, prospective, comparative trial of sirolimus and tacrolimus versus tacrolimus and methotrexate as GVHD prophylaxis after HLA-matched, related peripheral blood stem cell transplantation in patients with hematologic malignancies. Recipients will be stratified by transplant center and will be randomized to the sirolimus/tacrolimus or tacrolimus/methotrexate arms in a 1:1 ratio.

Primary Objective: The primary objective is to compare the rates of 114-day Grades II-IV acute GVHD free survival between patients in the two study arms from the time of randomization using an intent-to-treat analysis.

Secondary Objectives: Patients randomized to the two study arms will be compared for the following endpoints: time to neutrophil and platelet engraftment, the incidence of Grades III-IV acute GVHD, mucositis severity, time to first hospital discharge after transplantation, all infections, CMV reactivation and thrombotic microangiopathy incidence and VOD during the 100 days post-transplantation, malignant disease relapse and 1-year relapse-free and overall survival.

Eligibility Criteria: Eligible patients are between 2 and 60 years of age, have acute leukemia, myelodysplasia, chronic myeloid leukemia, adequate organ function, a serologic (or higher resolution) 6/6 Class I HLA-A and B and molecular Class II DRB1 matched sibling donor, and are able to give signed informed consent prior to enrollment.

Treatment Description: Patients will receive one of two conditioning regimens described in the protocol, at the discretion of the transplant physician. The transplant physician must choose among these regimens prior to GVHD prophylaxis assignment by randomization. Conditioning regimens will vary by center but at each center will be the same for patients randomized to either GVHD prophylaxis regimen. Stem cell donors will donate peripheral blood stem cells according to local institutional practices. Peripheral blood stem cells will not be manipulated or T-depleted prior to administration. Standard post-

transplant care will be administered. Patients will be randomized to one of two GVHD prophylaxis regimens and will be followed for the endpoints of interest.

Accrual Objective: Patients who are candidates for transplantation of G-CSF-mobilized peripheral blood stem cells from HLA-matched, related donors will be targeted for accrual. Approximately 156 patients will be accrued per study arm (total of 312 patients).

Accrual Period: The estimated accrual period is three years.

Study Duration: Patients will be followed for 114 days post randomization for evaluation of the primary endpoint, with additional follow-up to two years after transplantation for evaluation of secondary endpoints.

TREATMENT SCHEMA