PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0801

A Phase II/III Randomized, Multicenter Trial Comparing Sirolimus plus Prednisone and Sirolimus/Calcineurin Inhibitor plus Prednisone for the Treatment of Chronic Graft-versus-Host Disease

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Study Design: Combined Phase II/III, randomized, open label, multicenter, prospective comparative study of sirolimus plus prednisone versus sirolimus/calcineurin-inhibitor plus prednisone for the treatment of chronic GVHD.

Phase II Component:
A Phase II randomized trial of sirolimus + prednisone (Arm 1) versus sirolimus + calcineurin inhibitor + prednisone (Arm 2).

The intent is to enroll subjects at the start of initial therapy for chronic GVHD, or before their chronic GVHD is refractory to glucocorticoid therapy, or is chronically dependent upon glucocorticoid therapy and multiple secondary systemic immunosuppressive agents. Patients will be stratified by transplant center and will be randomized to an experimental arm of sirolimus + prednisone or the comparator arm of sirolimus + calcineurin inhibitor + prednisone in a 1:1 ratio.

Phase III Component:
The Phase II study above will proceed into the Phase III component of the protocol if the experimental arm is more efficacious than the comparator arm.

Thus, subjects that were enrolled on the Phase II will continue to be followed for the Phase III endpoints. Phase III accrual will then be completed by enrolling additional patients.

Primary Objective: **Phase II Component:**
To estimate the proportion of subjects with complete or partial responses after 6 months of therapy in both study arms using an intention to treat analysis.

Phase III Component:
To compare the proportion of subjects with complete resolution of all reversible manifestations at 24 months after starting therapy in both study arms.

Secondary Objectives:

Phase II component estimates among patients receiving SRL versus SRL +CNI: the percent reduction in the average daily dose of prednisone (or equivalent) by 6 and 12 months; the cumulative incidence of treatment failure at 1 year; the prevalence of active symptomatic chronic GVHD at 1 and 2 years; the cumulative incidence of discontinuation of all systemic immunosuppressive therapy at 1 and 2 years; the overall and cancer progression-free survival at 1 and 2 years; the candidate serum biomarkers of chronic GVHD at baseline, 2 months and 6 months; and, to evaluate NIH and other new response instruments in chronic GVHD.

Phase III component comparisons among patients receiving SRL versus SRL +CNI: percent reduction in the average daily dose of prednisone (or equivalent) at 6, 12, and 24 months; cumulative incidence of treatment failure at 1 and 2 years; prevalence of active symptomatic chronic GVHD at 1 and 2 years; cumulative incidence of discontinuation of all systemic immunosuppressive therapy at 1 and 2 years; overall and cancer progression-free survival at 1 and 2 years; candidate serum biomarkers of chronic GVHD at baseline, 2 months, and 6 months; and, to evaluate NIH and other new response instruments in chronic GVHD.

3-Year Assessments: All patients except those who are enrolled during the last 12 months of accrual will be evaluated at 3 years after beginning study therapy for the endpoints above under the Phase III component. Patients enrolled in the last 12 months will not complete 3 year assessments and will be excluded from the analysis.

Eligibility:

Inclusions:

Suitable candidates are patients with classic chronic or overlap syndrome (classic chronic plus acute) GVHD that meets NIH Consensus Working Group Guidelines in one of the following categories: [1]

a) Previously untreated (newly diagnosed) as defined by having received < 14 days of prednisone (or equivalent) before enrollment/randomization to study therapy.

b) Previously treated but inadequately responding after≤ 16 weeks of initial therapy with prednisone and/or CNI ± additional non-sirolimus agent (started at the time of chronic GVHD diagnosis).

Exclusions:

a) Patients with late persistent acute GVHD or recurrent acute GVHD only.

b) Inability to begin prednisone therapy at a dose of ≥ 0.5 mg/kg/day (or equivalent).

c) Receiving sirolimus for treatment of chronic GVHD (sirolimus for prophylaxis or treatment of acute GVHD is acceptable).

d) Already receiving sirolimus (for prophylaxis or treatment of acute GVHD) with prednisone at ≥ 0.25 mg/kg/day (or equivalent) ± additional agents.

e) Receiving therapy for chronic GVHD for more than 16 weeks.

f) Invasive fungal or viral infection not responding to appropriate antifungal or antiviral therapies.

g) Creatinine clearance < 50 mL/min/1.73 m^2 or a serum creatinine based on the Cockcroft-Gault formula (adults) or Schwartz formula (age ≤ 12 years).

h) Inability to tolerate oral medications.

i) Absolute neutrophil count < 1500 per microliter.

j) Requirement for platelet transfusions.

k) Receiving any treatment for persistent, progressive or recurrent malignancy.

l) Progressive or recurrent malignancy defined other than by quantitative molecular assays.

m) Known hypersensitivity to sirolimus.

Treatment Description:

Arm 1: Sirolimus + Prednisone
Arm 2: Sirolimus + Calcineurin Inhibitor + Prednisone

Prednisone is administered initially as a single early morning dose of 1 mg/kg/day [or equivalent (Adults: maximum dose 100 mg, for age < 17 years, the use of adjusted body weight as per institutional guidelines should be considered to calculate doses for patients who weigh > 110% of ideal body weight)].

If prednisone at a dose of 1 mg/kg/day (or equivalent) is contraindicated (e.g. poorly controlled diabetes, hypertension, osteoporosis, avascular bone necrosis, major mood disturbance) patients may begin prednisone between 0.5 -1 mg/kg/day.

Prednisone therapy continues at the initial dose until there is objective evidence of improvement in manifestations of chronic GVHD.

The initial taper of prednisone from the starting dose of 0.5-1 mg/kg/***every day*** (or equivalent) is attempted within 2 weeks after the

first evidence of improvement in GVHD and takes place over 4-8 weeks to achieve a dose of 0.5-1 mg/kg/***every-other-day***.

Once an alternating-day prednisone (or equivalent) regimen is achieved, the dose of prednisone should be held constant for 10-12 weeks until all reversible manifestations of chronic GVHD resolve, after which a second taper is attempted. The tempo of this second taper may follow individual institutional guidelines but it is recommended that the extent of the taper be approximately calibrated to the magnitude of an individual patient's alternating-day prednisone dose. For example, a patient whose prednisone dose has been stable at 0.5 mg/kg/every-other-day may attempt to taper prednisone completely. However, a patient whose prednisone dose has been stable at 1.0 mg/kg/every-other-day is recommended first to taper over 4-8 weeks to 0.5 mg/kg/every-other-day, followed by 2-3 months of further observation before attempting a complete taper.

Calcineurin inhibitor therapy continues at a dose which achieves the following trough serum levels (HPLC/TMS):

a) Tacrolimus: 5-10 ng/mL
b) Cyclosporine: 120-200 ng/mL

Sirolimus therapy begins at 2 mg orally per day (1 mg/m^2 per day if < 40 kg) to target a trough serum level of 3-12 ng/mL.

Supportive care will follow institutional guidelines that reflect reasonable standard practices appropriate to the patient with chronic GVHD as outlined by the Ancillary Therapy and Supportive Care Working Group Report of the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD.[2]

Accrual Objective:

Phase II Component: One hundred subjects will be randomized 1:1 across the Phase II study (50 per arm).

Phase III Component: If the Phase II is successful, then 100 patients from the Phase II study continue on the Phase III. Two hundred additional subjects will be randomized 1:1 across the Phase III (100 per arm) for a combined Phase II/III total of 300 subjects.

Accrual Period: The estimated accrual period is 3 years for the Phase II, and 4 years for the Phase III.

Study Duration: The estimated study duration is 3.5 years for the Phase II, and 6 years for the Phase III.

STUDY DESIGN SCHEMATIC