A phase II/III randomized, multicenter trial of prednisone/sirolimus versus prednisone/sirolimus/calcineurin inhibitor for the treatment of chronic graft-versus-host disease: BMT CTN 0801

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Supplemental Methods

Study Design

The trial was designed as an adaptive phase II/III randomized, open label, prospective comparative study of three treatments for the treatment of chronic graft-versus-host disease (cGVHD) (Supplemental Figure 1A). Phase II included two parallel, 100-patient, randomized trials, comparing two different experimental arms prednisone/sirolimus (PDN/SRL) or prednisone/sirolimus/photophoresis (PRD/SRL/ECP) versus identical calcineurin inhibitor (CNI)-containing comparator arms prednisone/sirolimus/calcineurin inhibitor (PDN/SRL/CNI), where centers selected only one trial in which to participate. The most promising trial after considering both safety and short-term efficacy would transition to phase III. Due to slow accrual, the PDN/SRL/ECP vs. PDN/SRL/CNI phase II trial was discontinued (Supplemental Figure 1B) and a study amendment simplified the phase II/III trial to just include PDN/SRL (2-drugs) versus PDN/SRL/CNI (3-drugs). Most sites that originally identified as photophoresis (ECP)-Centers switched over to the amended non-ECP trial (Supplemental Figure 1C). In the amended protocol, phase III intended to accrue an additional 200 randomized subjects to combine with phase II subjects for a total analysis sample size of 300 across both phases (versus the original planned 400 subjects). The final (0801) protocol is available on the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Web site; https://web.emmes.com/study/bmt2/protocol/0801_protocol/0801%20cGVHD%20Protocol%20v6.pdf. Institutional review boards of participating centers approved the protocol. An independent data and safety monitoring board (DSMB) appointed by the National Heart, Lung, and Blood Institute oversaw the trial. Patients were assigned randomly 1:1 to either 2-drugs or 3-drugs using permuted blocks of random sizes with stratification by center. Patients and physicians were informed of the random assignment. An Endpoint Review Committee (ERC) included seven reviewers for the 6-month outcomes adjudication and three reviewers for the final adjudication including 2-year outcomes, blinded to treatment assignment, reviewed study data and determined the final assessment of eligibility, study deviations, and response.
Endpoints and Statistical Analysis

The primary objective of phase II was to estimate the proportion of study subjects at 6 months post-randomization with complete or partial response (CR/PR), and were alive without relapse or receipt of secondary immunosuppressive therapy (IST). Secondary IST was any systemic immunosuppressive treatment to control cGVHD. The Z-statistic for comparing CR/PR rates at 6 months between the two treatments was computed and compared to stopping boundaries for futility and efficacy. This rule determined whether the 2-drug arm was sufficiently promising for the trial to expand into phase III, during which the primary endpoint would switch to CR rate at 2 years. Pre-specified, statistically-based principles guided how to proceed at the end of phase-2 (Supplemental Figure 2). This study design, with final phase III sample sizes of 150 patients per arm, had ≥80% power to identify a 20% improvement in both 6-month CR/PR rates and 24-month CR rates between the 2-drug arm and the 3-drug arm.

Demographic and baseline characteristics were described for 2-drug and 3-drug arms using frequencies, medians and ranges. At 6 months and 2 years, the proportion of subjects with CR or CR/PR were compared using Chi-squared tests, or with treatment success (and 95% confidence interval) using Fisher’s Exact test. Patient reported, provider reported, and National Institutes of Health (NIH) cGVHD individual organ and global severity scores at each time point were described using frequencies and compared using Chi-squared tests. Steroid dose and dose reductions at 6 and 12 months were summarized using median (range) and compared between groups using the Kruskal-Wallis test.

Other endpoint definitions

Very good partial response (VGPR) was defined as response falling just short of CR due to residual trivial, asymptomatic GVHD features, while on a physiological prednisone dose (defined as ≤5 mg daily or ≤10 mg every other day) or lower. Cumulative incidence (CI) of relapse, use of secondary IST, or discontinuation of IST, treating death as a competing event, were compared using Gray’s test. Failure-free survival (FFS) was defined by absence of secondary IST, non-relapse mortality, and recurrent or
progressive malignancy during therapy. Overall survival (OS), progression-free survival (PFS), and FFS were described using the Kaplan-Meier estimate and compared using the log-rank test. Proportions of patients experiencing toxicities and infections were compared using either Chi-square test or Fisher exact test. Exploratory analysis on biomarkers and quality of life measurements were conducted using descriptive statistics and non-parametric Kruskal-Wallis test to examine the difference between arms at each time point. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute). Cumulative incidence analyses were performed with R software, version 3.3.1. Primary causes of death were reported by sites according to BMT CTN Manual of Procedures and adjudicated by the ERC.

**Study Timeline**

The first patient was enrolled in April 2010 (Supplemental Figure 1A). The ECP study closed in September 2011 due to low accrual and its 10 participants were excluded from analysis. The original cGVHD inclusion criteria were then modified to the definitions mentioned above. Specifically, “high-risk” (platelets < 100,000 x 10^9/L, extensive skin involvement > 50%, bronchiolitis obliterans syndrome, or PDN >0.5 mg/kg/day) was no longer an eligibility requirement for previously untreated cGVHD, and patients not responding between 12 to 16 weeks became eligible. Phase II enrollment finished in March 2013 and over-enrolled by 51 patients while data were compiled and analyzed. The last patient enrolled in December 2013. The ERC completed adjudication of up to 3 years of outcomes data in February 2017.
Supplemental Table 1: Primary Causes of Death

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment Arm</th>
<th></th>
<th></th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-drug</td>
<td>3-drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Malignancy Recurrence/ Persistence</td>
<td>4</td>
<td>30.8</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>GVHD</td>
<td>4</td>
<td>30.8</td>
<td>5</td>
<td>31.3</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>15.4</td>
<td>4</td>
<td>25.0</td>
</tr>
<tr>
<td>Bacterial</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fungal</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Viral</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Organ Failure</td>
<td>1</td>
<td>7.7</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Multiple Organ Failure</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-Infectious Pneumonitis</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Vascular</td>
<td>1</td>
<td>7.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>7.7</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>100.0</td>
<td>16</td>
<td>100.0</td>
</tr>
<tr>
<td>Total Accrual</td>
<td>72</td>
<td>100.0</td>
<td>66</td>
<td>100.0</td>
</tr>
<tr>
<td>Total Death (Percentage %)</td>
<td>13</td>
<td>18.1</td>
<td>16</td>
<td>24.2</td>
</tr>
</tbody>
</table>

Notes: Three participants on the 3-drug arm expired beyond 2 years are excluded from the above table. The primary causes of death as reported by sites for these three participants are recurrence/persistence on Day 836, and GVHD on days 1221 and 1463. Abbreviations: GVHD: graft-versus-host disease, 2-drug: prednisone/sirolimus, 3-drug: prednisone/sirolimus/calcineurin inhibitor
Supplemental Figure 1: Study Design, Timeline and Enrollee Distribution

A) Phase II (N=200)

- ECP Center (N=100)
  - PDN + SRL + ECP
  - Phase II Winner
  - 100 carry forward if contains the winning arm

- Non-ECP Center (N=100)
  - PDN + SRL + CNI
  - 100 end in phase II if contains the losing arm

Phase III (N=400)

- All Centers (add 300 new patients)
  - PDN + SRL + CNI
  - N=151
  - Most centers switched after Sept 2011 protocol amendment
  - Final Analysis: ineligible

B) Study timeline

- 2008: Protocol Writing
- 2009: Released to local IRBs
- 2010: 1st patient
- 2011: Unsatisfactory accrual
- 2012: Accrual caught-up
- 2013: Amend: Close ECP study
- 2014: Endpoint Response Adjudication for 6 mo, 2y, and 3y
- 2015: 3-years of follow-up after last patient
- 2016: Report primary outcomes
- 2017: Diagnostic eligibility Checklist implemented

C) Phase II study enrollees

- ECP Centers
  - PDN + SRL + CNI
  - N=10
  - Study was closed Sept 2011
  - Endpoint Response Adjudication

- Non-ECP Centers
  - PDN + SRL + CNI
  - N=151
  - Final Analysis: ineligible

*Reverse example could also occur where the ECP study contains the losing arm*
Supplemental Figure 2: End of Phase II Decision Making Considerations. (A) Prednisone/sirolimus, (PDN/SRL) is inferior to comparator prednisone/sirolimus/calcineurin inhibitor (PDN/SRL/CNI) and the trial ended at Phase II. Underlying assumptions include: an overall response rate for the comparator arm of approximately 40%; and, overall response rates in the PDN/SRL arm < 40% are not of interest to pursue further. (B) The PDN/SRL arm might be of sufficient interest to continue into a future Phase III trial, but Phase II short term outcome data does not warrant proceeding directly to Phase III. In this scenario, both arms would have similar complete or partial response (CR+PR) rates higher than the estimated 40% benchmark for the (PDN/SRL/CNI) arm. In this situation, how to proceed may require more information on longer-term endpoints. Considerations would also include, in rank order, toxicity, convenience and cost of both study arms, as well as Blood and Marrow Transplant Clinical Trials Network (BMT CTN) priorities and other available therapies at the time. (C) In this scenario, PDN/SRL is superior to the comparator (PDN/SRL/CNI) and has a CR+PR rate of at least 40%, such that the study proceeds to Phase III as intended. (D) In this example, while the comparator arm(PDN/SRL/CNI) exceeds the 40% benchmark, the experimental arm (PDN/SRL) is considered sufficiently more superior over (PDN/SRL/CNI) that proceeding directly to Phase III with (PDN/SRL) versus PDN/SRL/CNI may not be justified. The Data and Safety Monitoring Board (DSMB) would advise whether (PDN/SRL) and PDN/SRL/CNI should be tested head-to-head in Phase III or if (PDN/SRL) should be tested against a novel therapy of interest. Considerations would also include, in rank order, toxicity, convenience and cost of all study arms, as well as BMT CTN priorities and other available therapies at the time. Note: the star on the graph is theoretical and is not the actual data point. The actual 6-month CR/PR rates for the first 50 evaluable patients at each arm was 51% in the (PDN/SRL) arm versus 50% in (PDN/SRL/CNI), which fell within scenario B, and led to the DSMB recommendation of suspending the study accrual of phase III.
BMT CTN 0801 Eligibility Chronic GVHD Diagnosis Checklist

To satisfy the NIH consensus working group guidelines for chronic GVHD diagnosis the patient needs either:

1) At least one diagnostic manifestation from the following list. Check all that apply:
   - None
   - Skin: lichen-planus like
   - Skin: poikiloderma
   - Skin: sclerotic-type
   - Skin: lichen-sclerosis like
   - Skin: morphea-like
   - Mouth: lichenoid lesions
   - Mouth: hyperkeratotic plaques
   - Mouth: restricted oral opening from sclerosis
   - Genitalia: lichenoid lesions
   - Genitalia: vaginal scarring or stenosis*
   - GI tract: esophageal web*
   - GI tract: strictures or stenosis (mid to upper third)*
   - Lung: BOS with lung biopsy
   - Fasciitis
   - Joint stiffness due to sclerosis or fasciitis
   - Contractures due to sclerosis or fasciitis
   - Other?

   Notes:
   * Requires confirmation by GIN exam or, endoscopy or contrast radiology as appropriate
   + Please send supporting documentation to EMMES and the protocol chairs (see bottom of form)

   OR

2) At least one distinctive manifestation from the following list that is supported by biopsy, radiology or some other lab test (e.g., Schirmer's). Check all that apply:
   - None
   - Skin: depigmentation**
   - Skin: vitiligo**
   - Nails: dystrophy**
   - Nails: onycholysis**
   - Nails: pterygium unguis**
   - Scalp: alopecia and/or scarring**
   - Scalp: scaliness with/without alopecia**
   - Scalp: papulosquamous lesions**
   - Mouth: xerostomia*
   - Mouth: mucoceles*
   - Mouth: mucosal atrophy*
   - Mouth: pseudomembranes*
   - Eyes: new onset dry, gritty, painful*#
   - Eyes: cicatrical conjunctivitis***
   - Eyes: keratoconjunctivitis sicca***
   - Eyes: confluent punctate keratopathy***
   - Genitalia: erosions
   - Genitalia: fissures
   - Genitalia: ulcers
   - Lungs: BOS*** based on PFT# and radiology#
   - Muscles: polymyositis with +ve biopsy
   - Muscles: myositis + elevated CPK or aldolase
   - Muscles: myositis with +ve biopsy
   - Other*

   Notes:
   # Requires absence of infection and FEV1/FVC<0.7 and FEV1<75% predicted plus RV>120% or HRCT showing air trapping or small airway thickening/bronchiectasis
   ## Requires Schirmer's test <5mm OU or mean values of 6-10 mm plus positive slit lamp examination for KCS.
   *** Must also have 1 other distinctive manifestations in a separate organ
   ** Requires positive skin biopsy or positive biopsy in other organ (may include liver)
   + Requires positive lip biopsy or positive biopsy in other organ (may include liver)
   + Please send supporting documentation to EMMES and the protocol chairs

If your patient meets none of the aforementioned criteria and you still believe that they are a suitable study candidate for 0801 please contact:

- Maita Arora
- Paul Carpenter
- Moira Lewis

A completed version of this form must be sent (via email) to Maita Arora, Paul Carpenter and Moira Lewis and approval will be given to the site before a patient can be enrolled/randomized on to the BMT CTN 0801 cGVHD protocol.