BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

PROTOCOL #0802 aGVHD
FREQUENTLY ASKED QUESTIONS (FAQs)

1. Why is a Phase III study needed in acute GVHD?

Corticosteroids have served as the primary therapy for acute GVHD for almost four decades. The long term response rate to single-agent corticosteroid therapy, when analyzed in large retrospective reviews is less than 50%. Therefore it is clear that new strategies that help to control GVHD with as little toxicity as possible are needed.

2. Why was mycophenolate mofetil chosen for this Phase III trial?

Based on the results of BMT CTN 0302 (a Phase II multi-center trial of etanercept, mycophenolate mofetil, denileukin diftitox and pentostatin for the primary therapy of acute GVHD) we selected mycophenolate mofetil as the most promising agent to proceed in a Phase III trial combined with steroids vs. steroids with placebo. The primary objective of that study was to estimate the complete response rate at Day 28 for each of the four agents and evaluate secondary outcomes pertinent to the best agent for testing in a planned follow up Phase III trial against steroids alone.

- The proportion of complete responses at Day 28 were: mycophenolate mofetil (60%), denileukin diftitox (53%), pentostatin (38%) and etanercept (26%), and Day 56 complete plus partial response rates were 78%, 68%, 71% and 59%, respectively.
- Six month chronic GVHD (cGVHD) incidence was: denileukin diftititox (29%), mycophenolate mofetil (25%), pentostatin (24%) and etanercept (21%).
- Overall survival at 6 months was mycophenolate mofetil (71%), denileukin diftitox (63%), etanercept (59%), and pentostatin (55%) respectively.

These results support the selection of mycophenolate mofetil as a promising agent for testing in a Phase III trial.

3. What is the justification for the primary end point and the many secondary endpoints?

The primary purpose of the study is to define the GVHD free survival by Day 56 without the need of further therapy in both arms. Besides obtaining information on complete responses, it is very important to review other safety and efficacy parameters (the secondary endpoints). This is relevant as we are interested in finding an effective therapy for GVHD but without excessive

rates of the anticipated complications of infection, GVHD flare, chronic GVHD or early mortality.

4. Is our accrual goal feasible?

Yes. We carefully analyzed BMT CTN data on the past acute GVHD study (BMT CTN 0302) from both Core and Affiliate centers and supplemented this with a separate survey of Core Centers to determine willingness to participate.

5. Is there a need for a multi-center network to meet the objectives?

Yes. Although GVHD is a common diagnosis for transplant centers and the most common post-transplant complication, no single center treats sufficient numbers of patients to complete this study in a reasonable timeframe.

6. What are the proposed plans for data acquisition, transfer, management and analysis?

A web-based data entry platform will be used for all BMT CTN supplemental forms. Data are transmitted encrypted using secure socket layer (SSL) technology. SSL is the standard used by banks in their electronic transactions. This platform includes online missing forms reports as well as other reports as deemed useful by the transplant centers. A User's Guide and Data Management Handbook will be developed for reference and training of clinical research associates (CRAs).

Missing forms reports are updated daily. Queries will be developed to check for missing and inconsistent data. Queries will be distributed to the centers at least monthly.

Analysis files will be prepared prior to each Data and Safety Monitoring Board (DSMB) meeting. Most analyses will be conducted using SAS and following the statistical analysis plans outlined in each protocol.

7. Are there any specific study training plans necessary to accomplish the research goals (e.g. workshops, study certification)?

CRAs will be certified for data submission by the DCC after participating in an in person meeting or in a training session conference call with the protocol coordinator. No other certifications or workshops will be required for this study.

8. Accrual estimates – See separate summary of Accrual Estimates.