PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0403

A Randomized Double-Blind, Placebo-Controlled Trial of Soluble Tumor Necrosis Factor Receptor: Enbrel (Etanercept) for the Treatment of Acute Non-Infectious Pulmonary Dysfunction (Idiopathic Pneumonia Syndrome) Following Allogeneic Cell Transplantation

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Study Design: The study is designed as a Phase III, multi-center randomized, double-blind, placebo-controlled trial investigating the use of etanercept for the treatment of acute, non-infectious pulmonary dysfunction (IPS) occurring after allogeneic hematopoietic cell transplantation (HCT).

Primary Objective: To determine the Day 28 response rate following treatment with etanercept plus corticosteroids compared to placebo plus corticosteroids for patients with IPS post allogeneic HCT. Response will be defined as (a) Survival to Day 28 of study, plus (b) Discontinuation of all supplemental oxygen support for > 72 consecutive hours by Day 28.

Secondary Objectives: To evaluate response to therapy at Day 56.

To evaluate overall mortality in patients with IPS.

To evaluate time to discontinuation of supplemental oxygen.

To evaluate pro-inflammatory markers of pulmonary disease, in both BAL fluid and plasma, in patients with IPS.

Eligibility Criteria: Eligible patients are ≥ 18 years of age and must be ≤ 180 days status post an allogeneic bone marrow, cord blood, or peripheral blood stem cell transplant. Patients must have evidence of idiopathic pneumonia syndrome, based upon the presence of bilateral pulmonary infiltrates (on chest radiograph) plus a supplemental oxygen requirement. The patient cannot have evidence for sepsis syndrome, or uncontrolled bacterial, invasive fungal or viral infections at the time of study registration. In addition, patients receiving mechanical ventilation for > 168 hours (7 days) at the time of study registration are ineligible.

Registration and Randomization:

Patients will be registered prior to undergoing a broncho-alveolar lavage (BAL) procedure. Initial diagnostic studies are then performed on the BAL fluid, and if negative, the patient is eligible for study randomization. Patients whose BAL special stains (gram stain and fungal stain) or whose initial BAL fluid cultures are abnormal are ineligible for study randomization.

BAL Procedure:

BAL samples are recommended to be collected from both the right and left sided airways and then pooled together. BAL fluid samples shall be sub-divided and distributed for the following assays: Hematology (5 mL), Microbiology (5-10 mL), Cytopathology (5 mL) and Cytokine analysis (5 mL)

All BAL fluid will be analyzed for the presence of bacterial, viral, fungal, PCP, and mycobacterial organisms as outlined in Section 4.4.2. BAL fluid will also be analyzed for inflammatory markers of disease, including but not limited to IL-1, IL-2, IL-6, TNFα, sTNFR, TGF-β, and for components of the lipopolysaccharide (LPS) activation system (LPS, LPB, and CD14). BAL fluid samples for the above biology studies (inflammatory markers) will be initially cryopreserved for subsequent analysis.

See Section 4.4.2 for full discussion of BAL procedure, Section 2.6.3 for circumstances in which the "on therapy" BAL may be waived and Appendix C for sample handling and processing.

Treatment Description:

Eligible patients will be randomized to receive one of two arms of therapy: (A) etanercept plus corticosteroids, or (B) placebo plus corticosteroids. Patients will receive a total of eight doses of study drug (etanercept/placebo) over a 4-week period. The initial dose of study drug (etanercept/placebo) will be administered intravenously on Day 0, with subsequent doses administered subcutaneously (SQ). Dosing will be administered twice weekly over 4 consecutive weeks. The placebo will be the inert diluent used for the etanercept formulation.

Additionally, patients in both arms will receive corticosteroids (2 mg/kg/day) Day 0 through Day 7, with subsequent taper as clinically indicated. Chest radiographs shall be obtained weekly through Day 28. Plasma cytokine profiles will be obtained on Days 0, 7 and 28.

If, at any point following initiation of study drug therapy, previously obtained BAL fluid cultures or other BAL fluid analysis

become positive for an infectious pathogen, study drug therapy shall be discontinued at that point, and not re-instituted. The patient will discontinue study drug therapy, but will still be followed for outcome.

The primary study endpoint is response at Day 28, with response defined as above (see Primary Objectives). Patients who discontinue study drug therapy for any reason will still be followed for primary and secondary study endpoints.

Accrual Objective: A maximum of 60 patients will be enrolled on study, 30 per arm.

Accrual Period: 5 years.

Study Duration: Patients will be followed for 1 year after randomization.

Outline of Treatment Plan