BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

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

BMT CTN PROTOCOL 0403
VERSION 5.0

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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

Co-Principal Investigators: Gregory Yanik, M.D., Kenneth Cooke, M.D.

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.

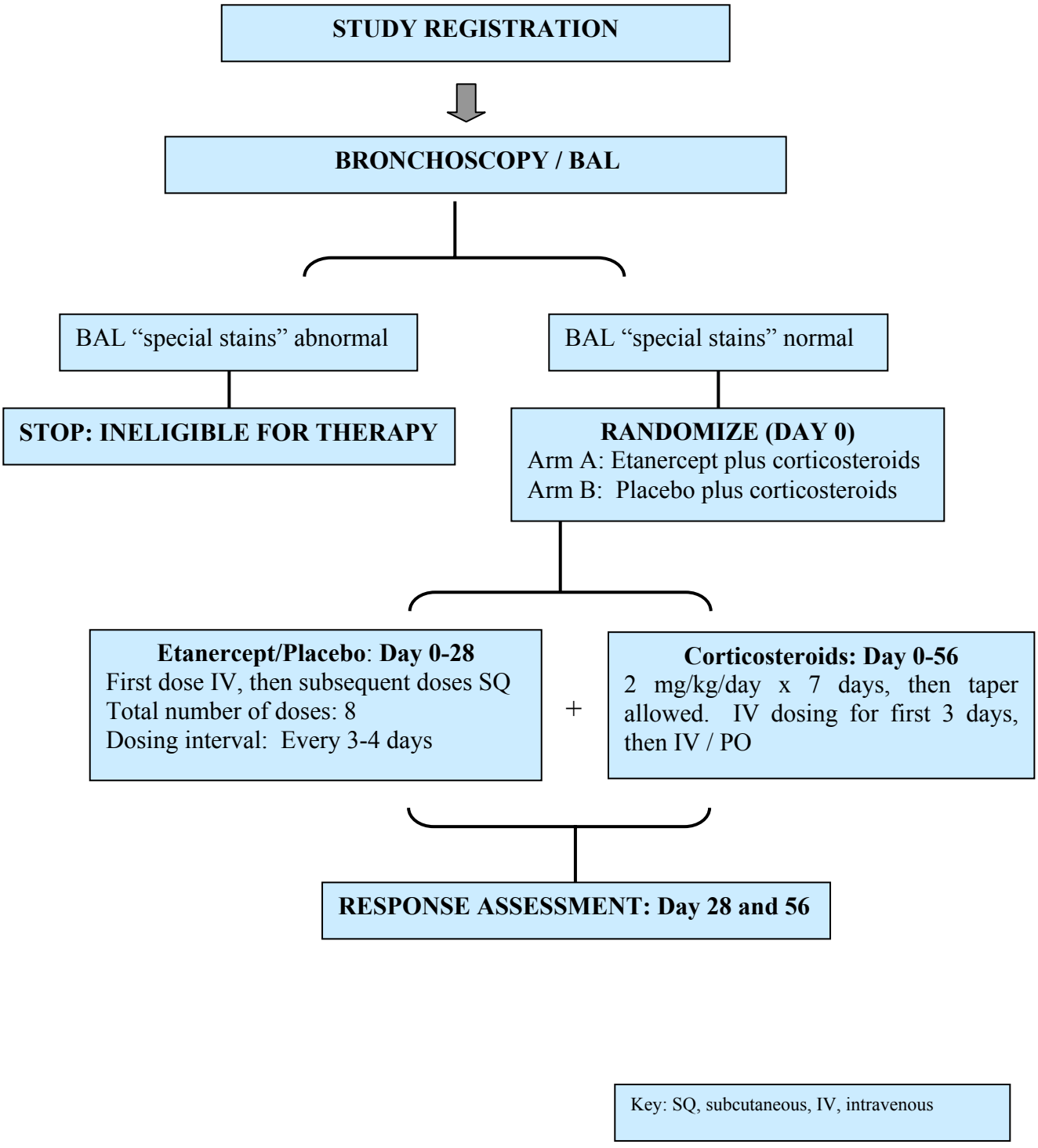
The primary study endpoint is response at Day 28, with response defined as above (see Primary Objectives). Patients who discontinue study drug therapy for any reason will still be followed for primary and secondary study endpoints.

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



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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Background

Over the last two decades, allogeneic hematopoietic cell transplantation (HCT) has emerged as an important treatment for a number of malignant and non-malignant disorders. Unfortunately, several complications, including graft-versus-host disease (GVHD) and pulmonary dysfunction, limit the utility of this aggressive form of therapy. Infectious and non-infectious lung complications occur in 25% to 55% of HCT recipients and account for up to 50% of transplant-related mortality[1,2,3,4,5,6]. In about half of affected patients, no infectious organisms are identified in the lungs. Two major types of non-infectious pulmonary injury are recognized: acute idiopathic pneumonia syndrome (IPS) and subacute lung injury (obstructive airway disease or bronchiolitis obliterans (BrOb) and restrictive lung disease). The current study will examine the use of etanercept in patients with IPS.

1.2. IPS Overview

IPS refers to diffuse, non-infectious lung injury occurring in the acute setting. In 1993, a panel convened by the National Institutes of Health (NIH) proposed a broad working definition of IPS to include widespread alveolar injury in the absence of active lower respiratory tract infection following HCT[7]. The NIH panel was careful to stress that they considered this definition to be that of a clinical *syndrome,* with variable histopathologic correlates and several potential etiologies. Diagnostic criteria of IPS include signs and symptoms of pneumonia, non-lobar radiographic infiltrates, abnormal pulmonary function and the absence of infectious organisms in the lower respiratory tract[1,7]. A variety of histopathologic findings are associated with IPS; the most frequently reported pattern is interstitial pneumonitis, a term historically used interchangeably with IPS. The time of onset for IPS ranges from 14 to 90 days after the infusion of donor hematopoietic cells. Survival after onset is poor; mortality rates of 50% to 70% are reported[1,3,5,6,7,8]. Although a recent retrospective study showed a lower incidence and earlier onset of IPS than previously reported, the typical clinical course (rapid onset of respiratory failure leading to death) was similar to historical reports, underscoring the critical nature of this transplant related problem[6]. Potential etiologies for IPS include direct toxic effects of HCT conditioning regimens, occult pulmonary infections, and inflammatory cytokines that have been implicated in other forms of pulmonary injury[9,10,11,12,13]. Additionally, immunologic factors may be important, since IPS is more frequent with allogeneic (vs. autologous or syngeneic) HCT and in patients with severe GVHD (vs. mild or absent GVHD)[1,3,5,6,8]. In many instances, acute GVHD precedes IPS, suggesting a possible causal relationship[14,15,16].

1.3. Incidence of IPS: Investigator's Experience

A retrospective review of 651 allogeneic transplants (304 unrelated donor, 347 related donor) performed at the University of Michigan Medical Center from 1996-2002 noted a 9.0%

incidence of IPS by Day 100 post-transplant. IPS was more common in recipients of unrelated donor grafts (14.1%) versus recipients of related donor grafts (4.6%). Donor-recipient HLA mismatch was also associated with higher incidences of IPS in both unrelated and related donor transplants.

Table 1.3 IPS Incidence with Donor Type

Degree of HLA Match	Incidence of IPS Unrelated Donor	Incidence of IPS Related Donor
6/6	11.0%	3.9%
5/6	34.0%	23.0%
Combined	14.6%	4.6%

Age, gender, underlying disease and pre-transplant preparative regimen did not predict for IPS in this series. The median time to onset of IPS was 15 days post-transplant (mean 22 days). Acute GVHD was present at diagnosis in 70% of IPS cases. Affected patients were treated with high dose corticosteroids and broad-spectrum antimicrobial therapy. Survival rates at 28 and 56 days post onset of IPS were 33% and 26%, respectively. Survival was not impacted by donor source (unrelated versus related donor) or underlying disease. The median time to death following the onset of IPS was 14 days.

1.4. Role of Tumor Necrosis Factor Alpha in the Pathogenesis of IPS

IPS Pathophysiology: The association between IPS and GVHD suggests a mechanistic relationship. The pathophysiology of GVHD is complex and is now known to involve donor T cell responses to host antigens, inflammatory cytokines and endotoxin[17,18,19,20,21,22,23]. Endotoxin or lipopolysaccharide (LPS) is a component of endogenous bowel flora and is a potent enhancer of inflammatory cytokine release. Translocation of LPS across a gut mucosa damaged early in the post-transplant period by the effects of conditioning and GVHD has been demonstrated after both experimental and clinical HCT[24,25,26,27]. When LPS reaches the systemic circulation, it induces the release of inflammatory cytokines from monocytes and macrophages that have been "primed" or made more sensitive to LPS via the effects of interferon **γ** (IFN**γ**) produced by donor lymphocytes. These cytokines, along with cellular effectors, contribute to GVHD target organ damage and dysfunction. During recent years, several lines of investigation have added to our understanding of how inflammatory cytokines contribute to complications of allogeneic HCT[21,28,29,30]. In particular, tumor necrosis factor α (TNFα) is an established effector of both clinical[29,30,31] and experimental[26,27] GVHD. The clinical importance of TNFα was initially suggested by studies demonstrating elevated levels of TNFα in the serum of patients with acute GVHD[32,33]. Patients with higher serum TNF levels during the conditioning regimen had a 90% incidence of grade II-IV acute GVHD (with mortality > 70% compared to a 20% mortality in patients without acute GVHD[33]. HCT recipients with a genetic polymorphism associated with high TNFα production are reported to have enhanced early mortality and an increased incidence of severe acute GVHD. TNFα appears critical for the development of early gastrointestinal

injury from acute GVHD[20,26,27]; its role in GVHD mediated damage to other target organs is less well defined[34].

Although the lung is historically not recognized as a classic target organ of GVHD, the clinical association between IPS and GVHD and the demonstration of pathologic lung changes in rodents with acute GVHD make this possibility intriguing. Pertinent to this hypothesis, elevations of TNFα are reported in the serum of patients who develop IPS[32] and in the lungs of animals with GVHD[35,36,37,38]. Furthermore, evidence for cytokine activation and LPS amplification, previously recognized in the broncho-alveolar compartment during adult respiratory distress syndrome (ARDS),[39] were recently demonstrated in patients with IPS after allogeneic HCT [40,41]. Clark and colleagues found increased vascular permeability and bronchoalveolar lavage (BAL) fluid containing IL-1, IL-12, IL-6 and TNFα and components of the LPS amplification system (LPB and CD14) in patients with IPS[2]. The investigators concluded that pro-inflammatory cytokine activation contributed to the pathogenesis of IPS and suggested that patients with this complication may be at increased risk for LPS mediated lung injury.

Murine Models of IPS after Allogeneic HCT: During the last several years, the lab of Dr. Kenneth Cooke (co-principal investigator for current study) has studied murine models of allogeneic HCT to investigate mechanisms of IPS. The majority of preliminary data has been generated using two HCT systems: B10.BR → CBA and C57BL/6 → B6D2F1. The B10.BR/CBA donor/recipient combination is matched at the MHC loci but differs at multiple minor histocompatibility (H) antigens and therefore most closely models an HCT from a matched unrelated, volunteer donor. In the C57BL/6 → B6D2F1 strain combination, donor and host differ at both major and minor H antigens. This system provides the unique opportunity to use genetically altered mice, bred on the B6 background, as donors in our experiments.

In initial studies, B10.BR donor bone marrow and T cells were transplanted into CBA recipients. Mice were killed at various time points after HCT and detailed histopathologic analysis of the lungs was performed. At 6 weeks, lungs of mice receiving syngeneic transplants maintained virtually normal histology whereas two major abnormalities were apparent in the allogeneic group[35]. First, a dense mononuclear cell infiltrate was found around both pulmonary vessels and bronchioles. Second, an acute pneumonitis involving both the interstitium and alveolar spaces was observed. Each of these histopathologic patterns closely resembles microscopic features of the nonspecific, diffuse interstitial pneumonias seen in allogeneic HCT recipients[7,15,42]. A semiquantitative index based on the severity and extent of injury present was used to score lung changes[35]. Using this system, the values for pneumonitis, periluminal infiltrate, and total index were significantly abnormal in allogeneic HCT recipients compared to syngeneic controls[35]. Identical histopathology is also observed using strain combinations across 1) other minor antigens, 2) class I or class II antigens only, and 3) major and minor H antigenic differences[43,44,45]. In each scenario, significant pulmonary pathology is first detected between weeks 2 and 4 after HCT and progresses in severity through week 6. Potential infectious etiologies of pulmonary injury were ruled out in these studies by screening sentinel mice from each group (minimum n = 5) for a broad panel of pathogenic bacteria, viruses and *Pneumocystis carinii*. No pathologic organisms were identified in any mice strongly suggesting that the lung

toxicity observed was the consequence of the histocompatibility antigen differences between allogeneic donors and hosts.

Prior to fixation of lung tissue, BAL fluid was collected from all transplanted mice and evaluated for cell count, differential and TNFα levels. Lung injury in recipients of allogeneic HCT with signs of acute GVHD was associated with a significant increase in the number of total BAL cells, lymphocytes, macrophages and neutrophils, (consistent with the mixed inflammatory alveolar infiltrates observed on histopathology) compared to syngeneic controls[35]. Cell surface staining using differences in V∃ T cell repertoires (B10 → CBA) or in CD45 alleles (B6 → B6D2F1) demonstrated that leukocytes were of donor origin.

Table 1.4. BAL Fluid Cellularity (x 10^6) and Cytokine Content 6 Weeks after HCT

Group	Pathology	Total Cells	Neutrophils	Macrophages	Lymphocytes	TNFα pg/mL
Naive CBA	0.0 ± 0.0	1.6 ± 0.3	0.01 ± 0.01	1.2 ± 0.2	0.4 ± 0.2	< 10
Syngeneic	0.3 ± 0.2	1.9 ± 0.3	0.01 ± 0.01	1.2 ± 0.2	0.6 ± 0.1	13 ± 4
Allogeneic	5.7 ± 0.5*	4.6 ± 0.5*	0.3 ± 0.13*	2.2 ± 0.5*	2.4 ± 0.5*	126 ± 24*

Table 1.4. *BAL cellularity and cytokine content is increased in mice with IPS after allogeneic HCT. CBA mice received syngeneic or allogeneic HCT as in*[35]*. Lungs were harvested and examined microscopically and BAL fluid was collected and analyzed for cell count, differential and TNFα concentrations as described. Data are expressed as mean ± standard error n = 8 to 12 per HCT group; n = 4 per naïve group. *P < .01 allogeneic versus syngeneic.*

BAL fluid protein levels of TNFα were analyzed using a standard ELISA assay and were found to be significantly elevated in animals receiving allogeneic HCT as early as week 4 (when physiologically relevant lung injury is first noted in this system) and to peak by week 6 after HCT[35]. Three-color flow cytometry (FACS) analysis (2-color cell surface markers coupled with intracytoplasmic cytokine staining) demonstrated that donor derived macrophages ($F4/80^+$; $CD11b^+$) and T cells (CD4+ > CD8+) were the producers of TNFα (data not shown). These findings are consistent with those of several other investigators who have demonstrated increases in TNFα in the lungs of allogeneic HCT recipients at early and late time points after transplantation[36,37,38].

TNFα is causally related to the development of IPS after experimental allogeneic HCT. A causal role for TNFα in the development of IPS was examined using two strategies: 1) by using TNFα knock out (TNFα -/-) mice as HCT donors and 2) neutralizing TNFα using a soluble, dimeric, TNF binding protein (rhTNFR:Fc; Immunex Corp. Seattle, WA). First, using an established parent (P) → F1 system (B6 → B6D2F1), we found that allogeneic HCT using TNFα-/- donors resulted in significantly less lung injury as measured by lung pathology and BAL cellularity compared to HCT using wild type donors (Figure 1.4a). In "mixing"

experiments using TNFα -/- bone marrow cells combined with wild type T cells and vice versa, we determined that TNFα production from both lymphoid and myeloid (accessory) cell types contributed to lung injury in this system (data not shown).

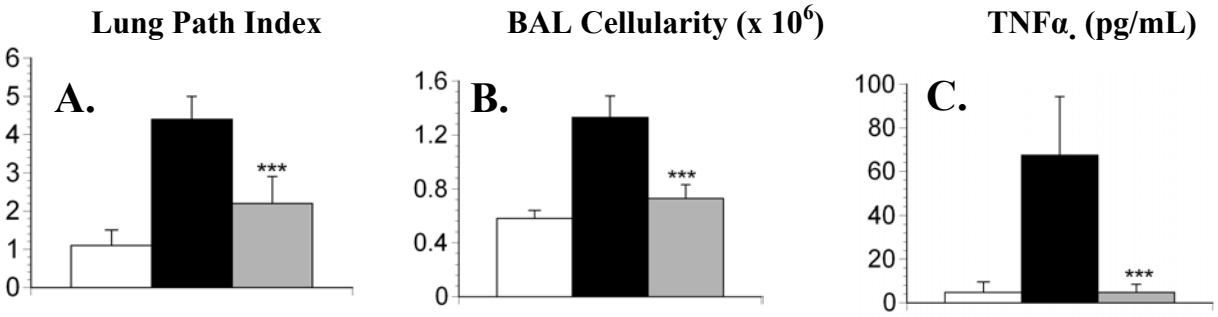

Figure 1.4a. *Allogeneic HCT with* TNFα *-/- donor cells results in a significant reduction in lung injury post-transplant. Irradiated HCT recipients received syngeneic HCT (open symbol), or allogeneic HCT from either wt donors (closed symbol) or* TNFα *-/-donors (shaded symbol) as described above. Mice were evaluated at Day 42 after HCT for pulmonary toxicity as measured by lung pathology score* ***(A),*** *BAL cellularity* ***(B)*** *and* TNFα *levels* ***(C)****. Data are expressed as mean ± standard error n = 6 to 10 per group. ***P < 0.01 (closed vs. shaded symbol).*

Secondly, in a set of translational studies, we determined whether neutralization of TNFα could effectively alter the progression of lung injury after HCT once established. In these experiments, rhTNFR:Fc or control IgG was administered to allogeneic HCT recipients beginning 4 weeks after HCT, a time point when GVHD mortality and physiologically relevant lung injury is first noted in this system[46]. Recipients of syngeneic HCT received IgG only. Neutralization of TNFα during this interval reduced GVHD mortality and prevented the progression of systemic and hepatic GVHD seen in the control group[43]. Evaluation of lung injury in surviving animals revealed that administration of rhTNFR:Fc significantly reduced the progression of lung injury during the treatment period as measured by pathology, BAL cellularity and pulmonary function (Figure 1.4b).

The reduction in lung toxicity seen at week six after HCT in these experiments may be the result of several factors. Neutralization of TNFα should decrease, at least in part, its direct toxic effects on both lung parenchyma and endothelium. TNFα is also known to be a potent chemoattractant for leukocytes both directly and indirectly by promoting CC and CXC chemokine generation by alveolar macrophages[40,41,47,48,49]. The reduction in BAL cellularity and periluminal infiltrates seen after treatment with rhTNFR:Fc support this hypothesis[43].

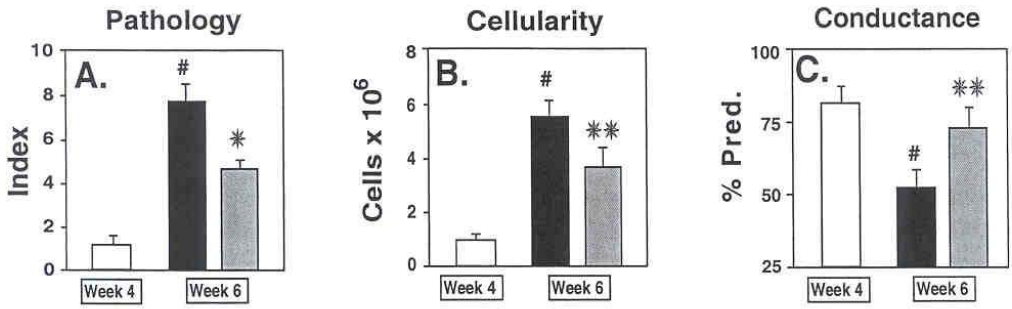

Figure 1.4b. *Administration of rhTNFR:Fc significantly reduces the development of lung injury after HCT. CBA animals received allogeneic HCT and were treated with control Ig (filled symbol) or rhTNFR:Fc (shaded symbol) from week 4 to week 6. Allogeneic animals were evaluated at week four and received no treatment (open symbol). Data are expressed as mean ± standard error, n = 8 to 15 per group and represent a combination of 2 similar experiments, #P < 0.01, filled symbol vs. open symbol; *P < 0.01, **P < 0.05 shaded symbol vs. filled symbol.*

In summary, these laboratory data correlate well with clinical reports of an association between inflammatory cytokines and IPS (see above) and with our own clinical experience (see below).

1.5. Etanercept (Enbrel, Amgen, Thousand Oaks, CA)

Normally, two distinct cell surface receptors exist for TNF: a 55 kilodalton (kd) (p55) and a 75 kd (p75) TNF receptor. Soluble TNF receptors are shed forms of the extracellular portion of the TNF receptor, occurring naturally in humans[50]. Soluble TNF receptors function by inhibiting TNF binding to the target cell surface and therefore are believed to regulate the bioavailability of TNF in the body[51]. Etanercept is a dimeric protein consisting of two soluble p75 TNF receptors fused to the Fc portion of a type I immunoglobulin (IgG1). The use of an immunoglobulin Fc region as a fusion element in the construction of the dimeric receptor imparts a longer half-life to the agent and allows alternate day dosing[52].

Clinical trials of etanercept have been conducted in healthy volunteers, patients with sepsis syndrome, rheumatoid arthritis (RA), psoriasis, HIV infection, and Crohn's disease. Injection site reactions are the most commonly reported adverse event. In the sepsis syndrome trial, etanercept was associated with increased mortality in patients treated for gram + septicemia. An increased risk of infectious complications or mortality was not noted in other clinical trials.

1.5.1. Pharmacokinetics and Pharmacology of Etanercept

The pharmacokinetics of etanercept are reported in multiple studies involving both healthy volunteers and patients with RA[53]. Pharmacokinetic parameters have been determined following intravenous (IV) and subcutaneous (SQ) administration for doses ranging from 0.125mg/m^2 to 60mg/m^2 when administered primarily as single doses. In adults, pharmacokinetic parameters

are similar between men and women, and do not vary significantly with age. In pediatric studies, the clearance of etanercept was similar, with a small reduction in clearance in children 4-8 years of age (product information, Immunex).

Etanercept is slowly absorbed after SQ injection, and has a relatively slow clearance from the body; the elimination half life is 70 hours after a single subcutaneous injection. When etanercept is administered twice weekly, steady state serum concentrations are approximately 2 times that of a single dose. When administered subcutaneously, bioavailability ranges between 25% and 60%[53]. After subcutaneous administration of 10 mg into the abdomen, etanercept reaches peak concentrations of 0.43 ± 0.2l mg/mL by 66 ± 22 hours[53]. The volume of distribution is 9.6 ± 3.3 L following IV administration and the mean clearance rates have ranged from 22-73 mL/hr/m^2. Compared to subcutaneous administration, peak concentrations are achieved earlier following IV dosing [mean time to Cmax: 0.8 hours (IV) versus 66 hours (SQ)]. Etanercept is metabolized through the reticulo-endothelial system[54] and therefore, dose adjustment is not required for patients with renal or hepatic impairment.

1.6. Clinical Trials and Adverse Events with Etanercept

Although clinical trials have been conducted in a variety of settings, most of the data come from trials in individuals with RA[55,56,57,58]. Etanercept was studied extensively in 1039 patients with RA (the disease for which etanercept is FDA approved) in 10 individual trials. In one randomized, placebo-controlled, Phase II study of patients with RA, etanercept significantly ameliorated the clinical symptoms of active RA and primary efficacy parameters showed a clear dose response[56].

In healthy volunteers challenged with endotoxin, etanercept significantly decreased release of the following inflammatory mediators: bioactive TNFα, IL-6, IL-8, G-CSF, norepinephrine, cortisol, plasminogen activator inhibitor, and tissue plasminogen activator[59]. However, a subsequent trial in patients with sepsis syndrome demonstrated increased mortality with etanercept with a dose-response relationship between the drug and mortality[60]. In this Phase II, randomized, double-blind, placebo-controlled trial compared single IV doses of etanercept (approximately 6 mg/m^2, 18 mg/m^2, or 60 mg/m^2) and placebo, which were administered during a period of 30 minutes to 141 patients with potential sepsis. Sepsis was based upon having all of the following clinical criteria at the time of study entry: temperature > 38.2° C, or < 36.0° C, heart rate > 90/minute, respiratory findings (respiratory rate > 20/minute, pCO2 < 32 mmHg, or the need for mechanical ventilation), and hypotension (systolic blood pressure < 90 mmHg, a decrease in systolic blood pressure > 40 from baseline, or the need for inotropic support above 5mcg/kg/minute of dopamine). The 28-day mortality was 30% in the placebo group and 30%, 48%, and 53% in the 6 mg/m^2, 18 mg/m^2, and 60 mg/m^2 groups, respectively. Overall, the relationship of increased mortality to increasing etanercept dose level was significant (p=0.016). Among patients who received etanercept, those infected with Gram-negative organisms had no increase in mortality rates while those infected with Gram-positive organisms had a statistically significant increase in mortality rates. Only 39% of patients in this study had documented bacteremia at the time of study entry. Patients who were neutropenic, patients receiving > 1.0 mg/kg/day of corticosteroid

equivalent, or patients < 18 years in age were also excluded from study[60]. No patients received SQ etanercept as planned in the current trial.

In placebo-controlled studies for RA with durations of 3 or 6 months, adverse events were documented for 349 patients receiving etanercept, compared to 152 patients receiving placebo. Most adverse events were mild and the proportion of patients who discontinued treatment due to adverse events was the same in both the etanercept and placebo groups (4%). Other than injection site reactions, no other adverse events occurred at increased frequency with etanercept alone or when given in combination with methotrexate compared to the control groups. All injection site reactions were described as mild to moderate (erythema and/or itching, pain, or swelling), generally occurred in the first month of treatment, and did not necessitate study drug discontinuation[61]. The mean duration of these local reactions was 3 to 5 days. No treatment was necessary in approximately 90% of cases, and those patients who required treatment received topical corticosteroids or oral antihistamines. Rare occurrences of redness at a previous injection site when subsequent injections were given have been reported but have not required treatment[61]. Upper respiratory infections ("colds") and sinusitis were the most frequently reported infections in patients receiving etanercept or placebo. The frequency of such infections was 0.68 events per patient-year in the placebo group and 0.82 events per patient-year in the etanercept group.

1.7. Etanercept/Initial Experience in Allogeneic Hematopoietic Cell Transplantation

Reports on the use of etanercept in HCT are anecdotal to date. A case report describing the successful therapy of an 11 year old with gastro-intestinal GVHD is described. There were no adverse reactions or complications with its use[62]. The use of etanercept for the treatment of 8 patients with chronic GVHD was reported in December 2000; 7 of the 8 showed symptomatic improvement using the same dosage that will be employed in this current protocol[63]. A recent study from the University of Michigan reported the use of etanercept in three children with IPS in 2000[64]. In all three patients, a pre-therapy BAL specimen was negative for infectious organisms. Each received empiric broad-spectrum antimicrobial therapy and methylprednisolone (2 mg/kg/day) prior to and during etanercept therapy. One patient required bilevel positive airway pressure (BiPAP) and two others required mechanical ventilation at the onset of therapy. The administration of etanercept was well tolerated and associated with significant improvements in pulmonary function within the first week of therapy. All three patients ceased oxygen support during their course of therapy. Response parameters are noted below (Table 1.7a, Figures 1.7a and 1.7b).

Table 1.7a Ventilatory Parameters and Clinical Response to Etanercept Administration Days after Etanercept Therapy

Patient 1	Day 0	Day 1	Day 3	Day 7
Fi02 (%)	100	100	50	Room air

Patient 2	Day 0	Day 1	Day 3	Day 7
Fi02 (%)	55	45	40	30
PIP/PEEP	29/10	26/8	22/5	22/5
MAP	14	14	8	7

Patient 3	Day 0	Day 1	Day 3	Day 7
Fi02 (%)	90	35	35	Room air
PIP/PEEP	34/9	29/9	21/5	Room air
MAP	20	16	11	Room air

Patient 1 on BiPap, patient 2 and 3 on mechanical ventilation at therapy onset. Key: FiO2: percent inspired oxygen; PIP: peak inspiratory pressure; PEEP: peak end expiratory pressure; MAP: mean airway pressure.

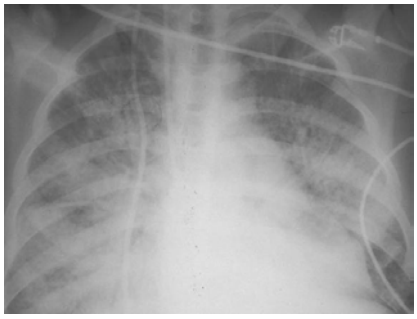

Figure 1.7a

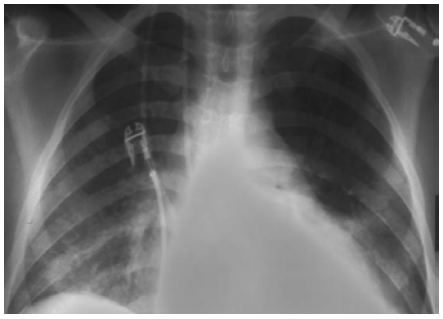

Figure 1.7b

Figures 1.7a & 1.7b: Chest Radiographs Obtained on Day 0 (Fig. 1.7a) and Day 4 (Fig. 1.7b) of Therapy with Etanercept for Patient #1

University of Michigan Trial (UMCC -0078) for the treatment of IPS:
A pilot study testing the safety and feasibility of using etanercept to treat patients with IPS was recently completed at the University of Michigan and the Dana Farber Cancer Institute / Brigham and Woman's Hospital. Fifteen patients (median 18 yrs, 1 - 60 yrs), each meeting the diagnostic criteria for IPS, were enrolled from 05/25/2001 to 02/04/2004. All patients required supplemental oxygen at therapy onset, with seven patients requiring mechanical ventilation. Etanercept was administered at 0.4 mg/kg via SQ injection, twice weekly for a maximum of 8 doses. Etanercept therapy was initiated a median of 17 days (11-87 days) post-transplant. Therapy was well tolerated overall. All patients underwent BAL prior to initiation of therapy to rule out infectious etiologies. From a safety standpoint, all patients who were intubated for the BAL procedure were extubated upon completion of the BAL. There were 17 severe adverse

events, including two episodes of bacteremia, and two admissions for acute GVHD within 56 days of study onset. One dose-limiting toxicity was noted, a grade 4 dermatologic reaction necessitating drug withdrawal. There were no episodes of septicemia and no pulmonary infections. Nine of 15 patients had a complete response, defined as the ability to completely withdraw from supplemental oxygen support within 28 days of initiation of etanercept therapy. The median time to response was 7 days (range 3-18 days) and the median time to chest radiograph normalization was 6 days (range 2-10 days). The median survival was extended from 14 days (historical controls, see above) to 67 days (range 3-822) in treated patients. Survival at Day 28 and Day 56 (from the first etanercept dose) was 73% and 60%, respectively. The duration of mechanical ventilation required prior to study onset impacted survival. Patients requiring < 48 hours of mechanical ventilation prior to study entry had a median survival of 150 days (range 46-822). In comparison, patients requiring mechanical ventilation ≥ 48 hours prior to study entry had a median survival of only 17 days (range 3–148).

In order to begin to define the biologic parameters associated with the development of IPS, we measured inflammatory cytokine levels in BAL fluid samples collected before (and when possible) after the administration of etanercept. Levels from BAL of IPS patients were compared to those obtained from untransplanted controls, from HCT recipients with subacute lung injury (discussed below), or from HCT recipients whose BAL was positive for infection.

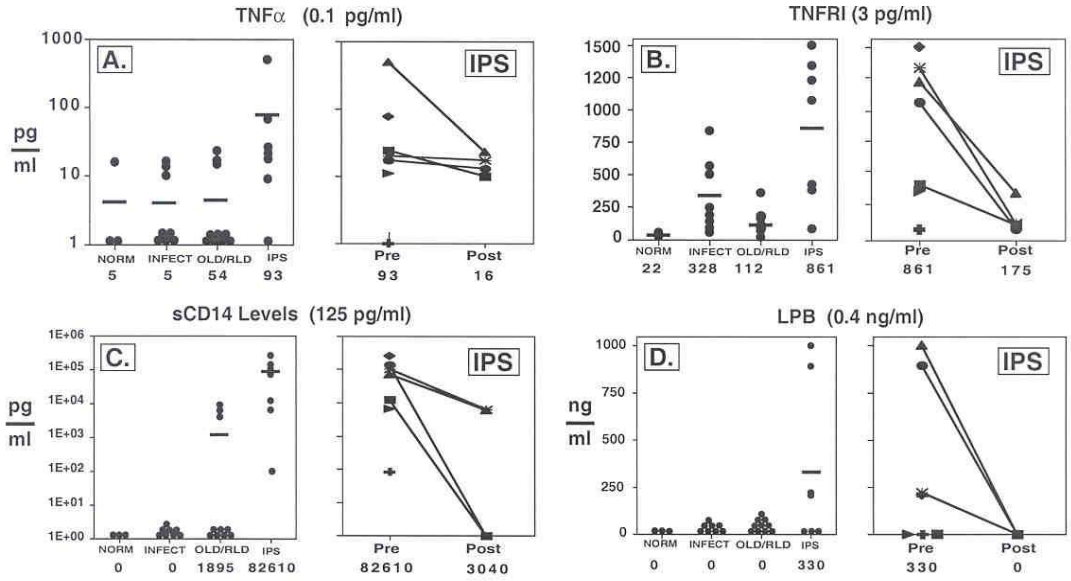

Figure 1.7c. BAL Fluid Analysis

Figure 1.7c. ***BAL fluid cytokine levels****. Patients were enrolled on protocols UMCC 0078 (IPS) or UMCC 0079 (subacute lung injury) and BAL fluid was collected at the time of study entry and at the completion of therapy. Protein levels for TNFα, TNFRI, sCD14 and LPB were measured by ELISA. Untransplanted controls n = 3; HCT recipients with infection n = 8; OLD / RLD n = 10; IPS n = 7 pre and 4 post therapy. p < 0.05 for IPS compared to OLD/RLD for all cytokines shown.*

As shown in Figure 1.7c, BAL levels of TNFα, TNFRI, soluble CD14 and LPB levels were significantly elevated in patients with IPS as compared to patients with subacute lung injury and untransplanted healthy volunteers ($p < 0.05$). These findings are consistent with those reported by Clark and colleagues in a similar subset of patients. Of note, total protein levels were also elevated in IPS patients consistent with significant endothelial damage and capillary leak that accompanies acute lung injury in other clinical and experimental settings. By contrast, levels of IL-1, IFNγ and IL-2 were not consistently elevated in any group (data not shown). Strikingly, BAL fluid protein levels decreased significantly after treatment with etanercept in the 8 patients in whom a repeat BAL was performed ($p < 0.05$ for TNFRI, sCD14 and LPB).

In summary, a pilot study at the University of Michigan employing etanercept plus corticosteroids for the treatment of IPS following allogeneic transplantation led to higher than expected survival when compared to historical controls. Survival 28 days and 56 days following the onset of etanercept therapy (Group A) or following the use of corticosteroids alone (Group B) is summarized below:

Table 1.7b Day 28 and 56 Survival

IPS Therapy	N	Day 28	Day 56
Group A: etanercept plus corticosteroids	15	73%	60%
(Historical) Group B: corticosteroids	49	33%	26%

The University of Michigan also recently completed a trial of etanercept for the therapy of subacute lung injury post allogeneic HCT. Fifteen patients with either bronchiolitis obliterans or restrictive lung injury post-allogeneic transplant were treated over a four-week period. Similar to the IPS trial, therapy was well tolerated, with no injection or local site reactions reported. One patient was documented to have aspergillus fumigatus on a post therapy BAL specimen. No other pathogens or infectious complications were identified.

Over the past year, therapy for five patients with IPS was initiated with IV etanercept instead of SQ dosing [Personal communication, G. Yanik]. Therapeutic responses were noted within 24 hours of administration of the IV dose. Pharmaco-kinetic data provided by the drug supplier (Amgen Inc.) note a marked reduction in the time to Cmax (maximal drug concentration) when etanercept has been administered IV, compared to SQ dosing (0.8 versus 66 hours). Similar drug $t_{½}$ (half lifes) have been reported comparing IV to SQ dosing (approximately 72 hours).

Overall, over thirty patients have now been treated with etanercept at the University of Michigan for either idiopathic pneumonia syndrome or subacute lung injury following allogeneic HCT. All patients were treated with 0.4 mg/kg/dose (max 25 mg) over a planned 4-week course of therapy, with over 200 doses of administered to this patient group. Infectious complications have been rare, with < 10% of patients treated coming off study therapy due to infectious issues that have arisen during therapy.

We now plan to further investigate the role of etanercept in the therapy of IPS post allogeneic HCT in a Phase III, double-blind, placebo-controlled multi-center trial.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

This is a Phase III double-blind, randomized, placebo-controlled, multi-center comparison of etanercept plus corticosteroids (Arm A) versus placebo plus corticosteroids (Arm B) for the treatment of IPS. All patients will undergo a bronchoscopy at the time of study entry, with the exception of those who are less than 30 days post transplant and the patient's clinical condition is such that a bronchoscopy is not possible to be performed. Study registration will occur prior to this bronchoscopy procedure. Following the bronchoscopy procedure, patients will be randomized to Arm A or Arm B of therapy. Randomization is not allowed until preliminary testing on the BAL fluid has been completed (see Section 2.4 for details). Randomization will be performed in a 1:1 ratio using random block sizes for the two arms. Randomization will be stratified by center. The primary study objective is to compare response rates to therapy between the two arms at Day 28 after randomization. Response is defined as survival plus the ability to completely discontinue all supplemental oxygen support for > 72 consecutive hours. Patients on the two study arms will also be followed for Day 28 and Day 56 mortality, time to discontinuation of supplemental oxygen, and for BAL fluid and plasma cytokine analysis.

2.2. Hypothesis and Specific Objectives

2.2.1. Hypotheses

Primary Hypothesis: Activation of pro-inflammatory cytokines, including TNFα contributes to the development of IPS following allogeneic HCT. The development of IPS is associated with a high mortality within 28 days of onset. Cytokine neutralization with a soluble dimeric TNFα binding protein (etanercept) will significantly improve both the survival and pulmonary status of patients with IPS.

Secondary Hypotheses: Therapy with a soluble TNFα binding protein will be well tolerated, with minimal toxicity, in patients with IPS.

Pro-inflammatory cytokine levels are elevated in the BAL fluid of patients with IPS.

2.2.2. Study Objectives

This trial is designed to compare the efficacy of etanercept plus corticosteroids versus corticosteroids alone in the treatment of patients with IPS following allogeneic HCT. The primary study objective is to determine the Day 28 response rates following therapy in the two treatment arms. Response is defined as above, the ability to survive to Day 28 plus discontinue supplemental oxygen support during that time period. Historical data indicate that IPS develops in approximately 10% of allogeneic transplant recipients, with mortality rates as high as 50-75%.

Supportive care measures plus corticosteroids are the historical mainstay of therapy. Recent animal model and human data indicate that pro-inflammatory cytokines, including TNFα, may play a key role in the pathogenesis of this disorder. The current study will examine the impact of a novel TNF inhibitor, etanercept, in the therapy of such patients.

Secondary objectives will examine response to therapy at Day 56, overall mortality post randomization, time to discontinuation of supplement oxygen support, and BAL fluid and plasma cytokines analysis.

As noted, recent evidence indicates a potential role for pro-inflammatory cytokines, including TNFα, IL-1, IL-6 and components of the LPS pathway (LPB, CD-14) in the pathogenesis of the disorder. As a secondary objective, the study will examine BAL fluid obtained prior to initiation of therapy for the expression of pro-inflammatory cytokines, LPS mediators, and chemokine expression. BAL analyses will be performed in the laboratory of Dr. Kenneth Cooke at the Case Western Reserve University Medical Center (see Appendix C). Plasma will also be obtained pre-therapy, Day 7 and Day 28 to examine similar cytokine profiles in the study population. Correlations of pre-therapy BAL fluid cytokine profiles and pre- and post-therapy plasma cytokine levels with clinical responsiveness to therapy will be examined.

2.3. Patient Eligibility - Registration

Patients must meet specified eligibility criteria to be registered on the study. Additional criteria must also be met to continue to randomization. All questions regarding eligibility criteria should be directed to the Protocol Coordinator at the Data Coordinating Center.

2.3.1. Inclusion Criteria

Patients fulfilling the following criteria will be eligible for registration onto this study:

1. Recipients of an allogeneic bone marrow, cord blood, or peripheral blood stem cell transplant. There are no restrictions based upon underlying disease, donor source, degree of HLA match, intensity of the pre-transplant conditioning regimen, or the use of a prior donor leukocyte infusion.
2. Age $\geq$ 18 years.
3. Patients with evidence of idiopathic pneumonia syndrome, based upon the presence of bilateral pulmonary infiltrates (on chest radiograph) and a supplemental oxygen requirement.
4. Patients $\leq$ 180 days post-transplant.
5. Patients who develop IPS within 180 days of a donor leukocyte infusion (DLI) are eligible, even if they are > 180 days post-transplant.

2.3.2. Exclusion Criteria

Patients with the following will be ineligible for registration onto this study:

1. Patients with uncontrolled infections, as determined by progressive radiographic findings or a persistence of positive blood, fluid or tissue cultures would be excluded from study entry. Patients who have undergone a BAL within 72 hours of study registration are ineligible if the BAL fluid is known to be positive for pathogenic microorganisms.
2. Patients with evidence of CMV infection or CMV disease, based upon an abnormal PCR assay, antigenemia assay, shell vial culture, or tissue biopsy within 7 days of study registration.
3. Patients on mechanical ventilation for > 168 hours (7 days)at study registration.Patients with evidence of congestive heart failure by clinical assessment.
4. Patients on other investigational studies (Phase I, II, or III) for the treatment of acute GVHD within 7 days of study registration. (Note: Patients enrolled on BMT CTN 0302 are ineligible for study entry.)
5. Patients who have received etanercept within the prior 14 days.
6. Patients who are pregnant or breastfeeding.
7. Patients with known hypersensitivity to etanercept.
8. Patients with a history of active tuberculosis (TB) infection.
9. Patients with a history of chronic active hepatitis B or hepatitis C infection.
10. Patients with a history of a demyelinating disorder or disease.
11. Patients on > 2 mg/kg/day of methylprednisolone equivalent for > 48 hours, within 7 days prior to study registration.
12. Patients who have relapsed or have developed progressive disease post-transplant.

2.4. Patient Eligibility - Randomization

Patients fulfilling the following criteria will be eligible for randomization onto this study:

1. BAL fluid negative for pathogenic microorganisms as assessed by gram stain and fungal stain.
2. BAL fluid negative for pathogenic microorganisms, or test result pending, as assessed by the following tests.
   a. Acid fast bacilli stain (AFB).
   b. Bacterial culture (a quantitative culture $\geq 10^4$ CFU/mL is considered positive).
   c. Viral cultures for respiratory pathogens, including (but not limited to) RSV, adenovirus, parainfluenza, influenza A and B, and CMV.
   d. Fungal and mycobacterial cultures.
   e. *Pneumocystis carinii* pneumonia (PCP) assay, by PCR, direct fluorescent antibody (DFA) stain, or cytology (per institutional guidelines).

2.5. Timing of Registration and Randomization

Patients should be registered prior to bronchoscopy.

Patients will be randomized following the bronchoscopy procedure, provided that criteria for IPS, see Section 2.6, are met at that time. Patients will be stratified by center. Patients will be assigned to either Arm A (etanercept plus corticosteroids) or Arm B (placebo plus corticosteroids) in a 1:1 ratio. Day 0 is defined as the date of first administration of study drug.

Patients who are registered, but whose BAL is positive for an infectious pathogen prior to randomization, will not be randomized or followed for subsequent study endpoints and outcome.

In all cases, both the study team, physicians involved in the care and management of study subjects, and the pharmacists/Investigational Drug Pharmacy at the treating center will remain blinded to a subject's study drug therapy. Only EMMES and Amgen Inc will have access to the treatment arm assignments. Investigational Drug Pharmacies will be provided with study drug labels that do not identify which arm of treatment is being administered to a study subject. A code will be available within EMMES and Amgen, if safety concerns arise regarding a particular patient or therapy.

2.6. IPS Definition

The term IPS has been developed to describe diffuse lung injury occurring post HCT for which an infectious etiology is not identified[7]. Patients must meet the following criteria for IPS, which includes evidence of both widespread alveolar injury, and the absence of active lower respiratory tract infection defined below:

1. Evidence of widespread alveolar injury
   a. Radiographic evidence of bilateral, multi-lobar infiltrates (by chest x-ray or CT scan).
   b. Evidence for abnormal respiratory physiology, based upon a room air oxygen saturation (SpO2) $\leq$ 93%, or the need for supplemental oxygen to maintain an oxygen saturation > 93%.

2. Absence of active lower respiratory tract infection; assessed by broncho-alveolar lavage (BAL); BAL fluid negative for pathogenic bacterial and nonbacterial microorganisms. Tests to be performed include:
   a. Gram stain, fungal stain, acid fast bacilli stain (AFB).
   b. Bacterial culture (a quantitative culture $\geq 10^4$ CFU/mL is considered positive).
   c. Viral cultures for respiratory pathogens, including (but not limited to) RSV,adenovirus, parainfluenza, influenza A and B, and CMV.
   d. Fungal and mycobacterial cultures.
   e. *Pneumocystis carinii* pneumonia (PCP) assay, by PCR, direct fluorescent antibody (DFA) stain, or cytology (per institutional guidelines).

3. Other Diagnostic Issues
   a. The presence of mixed oral flora, "rare" Candida species, or Penicillium species on BAL fluid analyses (gram stain or cultures) does not exclude a patient from study, as such findings may reflect oral pharyngeal contamination.
   b. The terms diffuse alveolar hemorrhage (DAH) or peri-engraftment respiratory distress syndrome (PERDS) are included within the definition of IPS.
   c. A radiographic finding of pulmonary edema does not exclude the diagnosis of IPS, provided that the treating physician concludes that the pulmonary edema is not secondary to cardiac dysfunction or iatrogenic fluid overload.
   d. If viral cultures become positive for other potential viral pathogens not listed above, discuss with the study chair (or designee) prior to proceeding further on study.
   e. For patients < 30 days post-transplant: If the patient's clinical condition is such that a BAL is deemed "not possible to be performed" by the treating physician (or pulmonologist), then the "on study" BAL may be waived. In such circumstances, the patient may register and be randomized to study therapy without the BAL being undertaken.

      For patients not on mechanical ventilation: If a BAL is not done, appropriate virology studies on a nasal swab (or nasal washing) are required as a minimum procedure to study entry.

      For patients on mechanical ventilation: Microbiologic studies of a deep endotracheal aspirate are allowed in lieu of a formal bronchoscopy procedure. However, no protocol-specified biologic studies (see Section 4.4) will be done on these specimens.

      For patients 31-180 days post-transplant: An "on study" bronchoscopy is required in all cases.

Patients may be randomized upon completion of the BAL gram stain and fungal stain, while the remainder of BAL studies are still pending. Patients whose BAL special stains (gram stain and fungal stain) or those whose initial BAL fluid studies (including cultures) are abnormal by the criteria listed above, are ineligible for study randomization.

If a BAL has been obtained within 72 hours of study registration, the procedure need not be repeated, provided that no infectious pathogens were identified in that diagnostic specimen.

2.7. Study Treatments

2.7.1. Initiation of Study Therapy (Day 0): Arm A and Arm B

Study drug therapy (etanercept/placebo) should begin within 24 hours of randomization.

If, at any point prior to initiation of study drug therapy, cultures, special stains or analysis of BAL fluid become positive for any infectious pathogen, therapy shall not be started.

If, at any point following initiation of study drug therapy, cultures, special stains or analysis of BAL fluid become positive for any 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.

2.7.2. Corticosteroids (Day 0-28): Arm A and Arm B

All patients are required to be on methylprednisolone (or corticosteroid equivalent) at 2 mg/kg/day on Day 0 of study therapy. Corticosteroids shall be administered in divided doses, BID. While it is preferred that corticosteroids be administered by IV for the first 7 days of study enrollment, they may be given orally (PO) if deemed appropriate. If initially given IV, corticosteroids can later be changed to PO dosing when the patient is able to tolerate oral intake. Corticosteroid dosing should be based upon actual body weight.

a. Patients not on corticosteroids at the time of study registration may begin corticosteroids on Day 0, upon completion of the BAL procedure, and prior to the first dose of study drug (etanercept/placebo).

b. Patients receiving corticosteroids prior to study randomization should remain on corticosteroids, with dosing adjusted to 2 mg/kg/day of methylprednisolone equivalent.

c. No corticosteroid taper is allowed during the first 7 days of study therapy (Day 0 to Day 6). Corticosteroid taper is subsequently recommended, beginning Day 7 of therapy. Suggested guidelines for the corticosteroid taper schedule are listed below:

Table 2.7.2 Corticosteroid Taper Schedule

Therapy Date	Methylprednisolone Dose
Day 0 - 6	2 mg/kg/day
Day 7 - 20	1 mg/kg/day
Day 21 - 34	0.5 mg/kg/day
Day 35 - 48	0.25 mg/kg/day,
Day 49 - 55	0.25 mg/kg Q.O.D.
Day 56	Discontinue

Patients who require corticosteroids for concomitant therapy of acute or chronic GVHD may adjust their taper schedule as clinically indicated, beginning Day 7 of therapy. Patients whose Day 7 oxygen requirement (FiO2) has not declined from baseline (Day 0) may remain on 2 mg/kg/day of corticosteroid equivalent until response is noted, then taper as clinically indicated. Patients whose oxygen requirement improves by Day 7, but subsequently worsens following institution of the corticosteroid taper, are recommended to increase corticosteroid dosing to the prior dose level.

2.7.3. Etanercept/Placebo (Arm A and Arm B) Dosing

Patients treated on either arm A or arm B will receive a total of eight etanercept/placebo doses over a 24-day period. Etanercept/placebo therapy will be initiated following randomization. It is recommended that etanercept/placebo therapy begins within 24 hours of randomization.

Dose 1 (Intravenous): The first etanercept/placebo dose will be administered by IV infusion at 0.4 milligrams/kg/dose (maximum dose 25 milligrams). The etanercept/placebo shall be diluted in 100 mL of 0.9 NS and infused over 30 minutes. Vital signs shall be obtained immediately prior to the IV infusion, then q.15 minutes x 2 during the infusion. The etanercept/placebo may be administered via peripheral or central venous catheter.

Doses 2-8 (Subcutaneous): Subsequent etanercept/placebo doses shall be given subcutaneously (SQ) at 0.4 milligrams/kg/dose (maximum dose 25 mg), twice weekly, for a total of 7 SQ dosages. The initial SQ dose shall be given 3 days (approximately 72 hours) after the IV dose. All subsequent SQ doses shall be administered 3-4 days following the prior dose (according to Table 2.7.3). All patients should be observed for local reactions at the injection site within 30 minutes of the dose. Vital signs shall be obtained immediately prior to, then every 15 minutes x 2 following the first SQ dose.

Table 2.7.3 Etanercept/Placebo (Arm A and Arm B) Dosing

Dose	Time	Dose	Route
1	Day 0, Hour 0	0.4 mg/kg (max 25 mg)	IV
2	Day 3	0.4 mg/kg (max 25 mg)	SQ
3	Day 7	0.4 mg/kg (max 25 mg)	SQ
4	Day 10	0.4 mg/kg (max 25 mg)	SQ
5	Day 14	0.4 mg/kg (max 25 mg)	SQ
6	Day 17	0.4 mg/kg (max 25 mg)	SQ
7	Day 21	0.4 mg/kg (max 25 mg)	SQ
8	Day 24	0.4 mg/kg (max 25 mg)	SQ

For both IV and SQ dosing, no pre-medication is required. In addition, no dosage adjustment is required based upon renal or hepatic function, including hemodialysis. For patients who complete therapy as an outpatient, dosing may be adjusted by 24 hours to account for weekend scheduling. The initial IV and SQ dose of etanercept must be administered in an inpatient or outpatient medical care facility. Subsequent SQ doses may be given to the patient as an outpatient, once medically stable. Patients with refractory thrombocytopenia may receive IV dosing, in place of SQ dosing, per discretion of the treating physician.

2.7.4. Dosing Schedule Modifications

If for any reason a scheduled dose of study drug is missed or withheld, contact one of the Protocol Chairs. In such a case, study drug dose can be reinstituted or deferred after discussion with a Protocol Chair. In the event a dose is inadvertently missed on a scheduled date, it may be administered within a 24-hour period. Protocol Chairs must also be contacted. The timing of subsequent doses can be resumed.

2.7.5. Other GVHD Therapy

The institution of other therapy for the treatment of acute or chronic GVHD is allowed after enrollment, with the exception that the patient cannot be concurrently enrolled on the BMT CTN #0302.

2.7.6. Other Supportive Care Measures

All patients will receive prophylaxis against bacterial, fungal and viral infections during the peri-transplant period according to the BMT CTN MOP. CMV: monitoring and preemptive treatment strategy will be in accordance with the BMT CTN MOP and local institutional practice. Anti-fungal prophylaxis for invasive non-Candidal organisms should be considered while on study therapy.

2.7.7. Additional Therapy after Day 28

Patients who survive to Day 28 but remain on supplemental oxygen may be considered for additional therapy, including etanercept, at the discretion of the treating physician. Such patients will be deemed non-responders regardless of subsequent clinical course.

2.8. Study Drug Information: Etanercept (Enbrel)

2.8.1. Chemistry

Recombinant human etanercept is a dimer of two molecules of the extracellular portion of the p75 TNF receptor (TNFR) each consisting of 235 amino acids. The two receptors are fused to the Fc portion of human IgG1 consisting of 232 amino acids. The gene fragments encoding the truncated TNFR and the Fc portion of human IgG1 are expressed in a Chinese hamster ovary (CHO) expression vector.

2.8.2. Formulation

Etanercept is supplied as a sterile lyophilized powder containing 25 mg etanercept; 40 mg mannitol, USP; 10 mg sucrose, NF; and 1.2 mg tromethamine (TRIS), USP per vial. For parenteral administration, etanercept is reconstituted with 1 mL of sterile bacteriostatic water for injection, USP, containing 0.9% benzoyl alcohol. Investigational product, not commercially available product, will be used for this trial.

2.8.3. Reconstitution

To reconstitute, remove the plastic vial cap and swab the stopper with antiseptic. Using a syringe with a 25 gauge needle, aseptically inject 1.0 mL bacteriostatic water for injection, USP, (containing 0.9% benzyl alcohol) for a final concentration of 25 mg/mL. The water should be directed against the side of the vial and the contents gently swirled to avoid foaming during reconstitution. To avoid excessive foaming, do not shake or vigorously agitate the vial. Foaming will interfere with the ability to draw up an accurate dose. Do not filter reconstituted solution during preparation or administration. After reconstitution, draw up the prescribed dose using a 25 gauge needle.

2.8.4. Stability and Storage

Lyophilized product (25 mg etanercept): Vials of study drug should be stored refrigerated at 2-8^{o}C (36-46^{o}F). Do not freeze. Lyophilized 25 mg vials of etanercept are stable for at least 12 months at 2^{o}C to 8^{o}C.

Reconstituted etanercept: After reconstitution with bacteriostatic water for injection, the solution should be stored at 2^{o}C to 8^{o}C. Reconstituted etanercept in the original vial or a plastic syringe is stable for 28 days at 2^{o}C to 8^{o}C. Do not freeze. In the absence of compatibility and stability data, no other medications should be added to infusion solutions containing etanercept/placebo. The medication should not be prepared or administered using filtration. **Etanercept shows stability when reconstituted and diluted in 100 mL saline and stored for 24 hours at 4^{o}C.**

2.8.5. Adverse Events

Etanercept should not be administered to patients with known hypersensitivity to this drug or any of its components. Etanercept should not be administered to patients with sepsis syndrome as defined as a patient requiring dopamine > 5 mcg/kg/min or use of > one vasopressor, e.g. norepinephrine or epinephrine, or steroid prescribed with septic shock as an indication. Administration of etanercept should be discontinued immediately if a patient develops an active systemic or pulmonary infection or evidence of impending sepsis syndrome.

Parental administration of any biologic product should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Allergic reactions associated with administration of etanercept during clinical trials have been rarely reported. If any serious allergic or anaphylactic reaction occurs, administration of etanercept should be discontinued immediately and appropriate therapy initiated.

The inhibition of TNF hypothetically may be associated with malignancy, autoimmunity, or infection. Although malignancies have been reported in clinical trials, epidemiologic analyses do not support a causal relationship with etanercept. Furthermore, no patient has developed other autoimmune systemic or rheumatic diseases while on etanercept nor has there been a reported increase in frequency or severity of infections in placebo-controlled trials.

Further information related to potential adverse events, precautions, and product warnings may be found at www.enbrel.com, listed under "Important Product Information."

2.8.6. Route of Administration

Both IV and SQ route of administration have been used, with SQ administration the current approved route of administration. For subcutaneous administration, the etanercept product label suggests rotating sites of SQ injections between the thigh, abdomen, and upper arm. Use a 27-gauge needle for administration. New injections should be given at least one inch from an old site and never into areas where the skin is tender, bruised, red or hard.

2.8.6.1. Intravenous infusions

For intravenous infusion, dilute in 100 mL of 0.9 NS and administer as a 30 minute IV infusion.

Etanercept has been administered in healthy volunteers and patients with a variety of conditions (e. g., rheumatoid arthritis, sepsis, human immunodeficiency virus, and heart failure) as a single IV infusion in doses ranging from 1 to 60 mg/m^2. In these studies, etanercept was further diluted in 100 mL of normal saline and was administered as a 30-minute infusion. Data on chronic or multiple doses given by IV infusion are not available.

The pharmacokinetic profile of etanercept was determined in a crossover study comparing two 10 mg etanercept doses administered SQ or IV (over 30 minutes) to healthy volunteers. Serum samples were collected for 21 days following SQ administration and for 14 days following IV administration. These samples were analyzed using an enzyme-linked immunosorbent assay (ELISA). The results are presented in the Table 2.8a below.

Table 2.8a. Summary of Pharmacokinetic Parameters of SQ and IV Etanercept

Parameter	SQ*	IV*
Absolute bioavailability (%)	58 (23%)	1 (-)
Maximum concentration (mcg/mL)	0.43 (48%)	2.32 (29%)
Time to maximum concentration (h)	66 (34%)	0.8 (31%)
Area under the curve (mcg·h/mL)	79 (31%)	132 (15%)
Volume of distribution (L)	17 (34%)	9.6 (35%)
Clearance (L/h)	0.137 (32%)	0.077 (17%)
Half-life (h)	92 (9%)	72 (25%)
K_a (h^{-1})	0.08 (50%)	-

** Value in parenthesis represents the coefficient of variation*
Abbreviations: K_a = absorption rate constant, h = hours

In this trial, the pharmacokinetic parameters observed are consistent with those observed in rheumatoid arthritis patients. In addition, etanercept was determined to be generally well tolerated. Side effects following IV administration were not specifically described.

An earlier safety trial of etanercept also evaluated the pharmacokinetic parameters in 14 healthy volunteers over a wide range of doses. Patients were given a single IV dose of etanercept over 30 minutes. The results are presented in Table 2.8b.

Table 2.8b. Summary of Pharmacokinetic Parameters of IV Etanercept

Parameters	Dose of Etanercept (mg/m^2)					
	1	**5**	**10**	**15**	**30**	**60**
No. of patients	2	2	2	2	2	3
Max conc. (mcg/mL)	0.4	2.1	3.8	8.8	14.3	30.6
AUC (mcg·h/mL)	44.97	158.52	305.39	585.75	1005.93	2028.30
Clearance ($mL/min/m^2$)	0.39	0.53	0.55	0.43	0.50	0.50
Half-life (h)	84.6	70.5	63.3	57.9	77.4	79.9

The authors reported that the infusion was not associated with any clinical or laboratory abnormalities. They concluded that etanercept had no acute toxic effects following IV administration to healthy volunteers and that the achievable serum levels had potent TNF inhibitory activity in vitro. No anti-etanercept antibodies were detected at 14 or 28 days.

2.8.7. Supplier

Etanercept will be supplied by Amgen Inc, and distributed through an independent contractor. Questions regarding study drug orders and study drug distribution should be directed to the trial protocol coordinator at EMMES, 301-251-1161.

2.8.8. Discard Instructions

Discard each vial, with its remaining contents, after each dose is given. At the completion of the study, unused vials should be discarded, not returned.

2.8.9. Accountability

The investigator (and/or hospital pharmacist) will ensure that all study drug is stored in a secured area under recommended storage conditions and is dispensed by qualified staff members. All study drug will be accounted for on medication inventory sheets.

The BMT CTN clinical monitor will be allowed at intervals, and upon request during the study, to check unused supplies. Accounting for the use of supplies will be by reference to each center's record of supplies received, the dispensing records for the total number of patients enrolled at each center and the unused and returned supplies.

The investigator is responsible for maintaining drug accountability records. Drug accountability records will be reviewed during monitoring visits. Each institution may use their own drug accountability log. Study drug must be administered only to patients enrolled in this study as per the protocol.

2.9. Criteria for Removal from Protocol Therapy

2.9.1. Discontinuation Criteria

Study drug therapy (etanercept/placebo) shall be discontinued and not re-instituted if any one of the following criteria are met. The patient will be taken off study drug therapy at that point, but still followed for primary and secondary study endpoints. A response assessment will be made at the time of therapy discontinuation and at subsequent defined study endpoints. The patient will not be replaced on study. In cases where a potential pathogen is identified by BAL fluid PCR analysis ONLY, the treating investigator should discuss the case with the Study Chair prior to study therapy discontinuation. Note: though the study drug will be immediately discontinued in the following circumstances, corticosteroid dosing will be tapered as clinically indicated by the treating physician. Follow-up data will be required unless consent for data collection is withdrawn.

1. If pre-therapy BAL fluid cultures, special stains or PCR analysis, become positive for any potentially infectious pathogen, study therapy will be discontinued and not re-instituted. (Exception: The presence of mixed oral flora, "rare" Candida species, or a Penicillium species on BAL fluid analysis does not warrant discontinuation of study therapy, as such findings may reflect oral pharyngeal contamination.)

2. If pre-therapy blood cultures become positive for an infectious pathogen following initiation of study therapy, study therapy will be discontinued and not reinstituted.

3. If the patient develops signs and symptoms consistent with sepsis syndrome, defined as fever plus hypotension requiring inotropic support (excluding dopamine $\leq$ 5mcg/kg/minute), study therapy will be discontinued and not re-instituted.

4. If the patient develops an invasive fungal infection, study therapy will be discontinued and not re-instituted. Patients with asymptomatic viruria may continue on therapy.

5. Regarding CMV, adenovirus and other viral infections: If during the course of study therapy, the patient develops a viral infection that in the opinion of the treating physician is not responding to conventional treatment, study drug will be held. If > 2 doses of study drug are missed, study drug therapy will be discontinued at that time and not re-instituted. The patient will still be followed for outcome.

6. If the patient develops bacteremia for > 72 hours despite antibiotic therapy for that organism, the study drug (etanercept/placebo) shall be held until the patient is no longer bacteremic. If > 2 doses of study drug are missed, study drug therapy will be

discontinued at that time and not be re-instituted. The patient will still be followed for outcome.

Persistent fever, without the presence of at least one criteria listed in 3-6 above, will not warrant discontinuation of study therapy. In addition, empiric changes in antimicrobial therapy, without change in clinical status or documented evidence of infection will not warrant discontinuation of study drug therapy.

2.9.2. Additional Discontinuation Criteria

In addition, study drug therapy shall be discontinued and not re-instituted if:

1. A patient develops hypersensitivity to the study drug injections or if any serious allergic or anaphylactic reaction occurs.

2. Refusal of further protocol therapy by patient (or legal guardian).

3. Per investigator discretion. In this circumstance, a patient will be deemed a non-responder at the time of study drug therapy discontinuation, provided the patient is within the first 28 days of study therapy. Patients who discontinue study after Day 28 will undergo the Day 28 response evaluation as described in Chapter 3.

   In the event that an investigator elects to "temporarily hold" study drug therapy to evaluate a potential toxicity issue, the patient may remain on study drug until greater than two consecutive doses of study drug are withheld. If less than or equal to two consecutive doses of study drug are withheld, the investigator may elect to continue study drug therapy. The missed doses of study drug will not be given. If three consecutive study drug doses are withheld, the patient can no longer receive study drug therapy.

CHAPTER 3

3. STUDY ENDPOINTS AND DEFINITIONS

3.1. Primary Endpoint

The primary study endpoint is the number of patients with IPS who respond to etanercept plus corticosteroids (versus placebo plus corticosteroids) at Day 28 following randomization.

Response to therapy 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.

The "time to response" will be defined as the first of 3 consecutive days in which all supplemental oxygen has been discontinued, provided that the patient survives until Day 28 of study. Patients who require re-institution of supplemental oxygen to achieve a SpO2 > 93% during this 72 hour time period will be deemed non-responders. Patients who require re-institution of supplemental oxygen support beyond the 72 hour time period will still be deemed as responders provided they meet the response criteria listed in "a" and "b" above.

Patients who are unable to completely withdraw from supplemental oxygen support or those who die from IPS or non-IPS related causes by Day 28 of therapy are defined as non-responders.

Patients who discontinue supplemental oxygen within the last 72 hours of the observation period (Days 25-28) will be classified as responders provided they survive to Day 28 and remain off supplemental oxygen for > 72 consecutive hours.

Survival duration will be the interval from the first dose of etanercept (or placebo) to the date of death or last follow-up. Patients who are treated with open-label study drug or other new therapy for lung complications before Day 28 are considered a failure for the primary endpoint.

3.2. Secondary Endpoints

a. Response to therapy at Day 56

   Response to therapy at Day 56 will be defined as the ability to survive to Day 56 of study, plus the ability to completely discontinue all supplemental oxygen support for > 72 consecutive hours during this time period.

b. Overall mortality

c. Time to discontinuation of supplemental oxygen

   The "time required to discontinue supplemental oxygen" will be measured in the number of days from study entry.

d. BAL fluid and plasma cytokine analysis

BAL fluid and plasma will be collected for cytokine analysis using standard ELISA assays. This analysis will include but be not limited to TNFα, sTNFRI, sTNFRII, LBP, IL-1, IL-6, MCP-1 and sCD14. BAL fluid will be collected at study entry only. Plasma will be collected at study entry, Day 7 and Day 28.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATION

4.1 Enrollment Procedures

4.1.1. Screening and Eligibility Procedures

Patients will be registered using the BMT CTN Advantage Electronic Data Capture (EDC)[SM] system. The following procedures should be followed:

1. Once a patient is identified with respiratory distress requiring oxygen support, an authorized user at the clinical center completes a screening form with demographic information and Segment A of the Eligibility Form (primary eligibility screening questions and date informed consent was signed).
2. If the patient is eligible, a study number is generated. A BAL must be obtained prior to initiation of study therapy.
3. An authorized user at the clinical center completes the enrollment process by entering Segment B of the Eligibility Form (eligibility for randomization) when the results of the BAL are available.
4. If the patient is eligible for randomization, a random treatment assignment is generated.

If a connection is interrupted during a randomization session, the process is completely cancelled and logged. A backup manual registration and randomization system will also be available to provide for short-term system failure or unavailability.

4.2. Study Monitoring

Criteria for Forms Submission: Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook. Forms that are not entered into the web-based data entry system within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the web based data entry system and integrated into the DCC's master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

Reporting Patient Deaths: Death information must be entered into the web-based data entry system within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in the web-based data entry system.

Center for International Blood and Marrow Transplant Research (CIBMTR) Data Reporting: Centers participating in BMT CTN trials must register pre and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during

their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Additionally, CIBMTR pre- and post- transplant Report Forms must also be submitted for all patients enrolled on this trial according to the randomization assigned to the patient at the time of initial registration with the CIBMTR. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

4.3. Adverse Event Reporting

Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system via AdvantageEDC. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 at regular intervals as defined on the Form Submission Schedule.

The Data and Safety Monitoring Board will receive summary reports of all grade 3-5, unexpected adverse experiences on an annual basis.

4.4. Patient Assessments

4.4.1. Pre-registration Studies

The following observations are to be obtained within 48 hours prior to study registration, unless otherwise noted.

1. History and physical exam including weight
2. Blood and serologic tests
   a. CBC with differential and platelets
   b. Serum electrolytes, BUN/creatinine, AST, ALT, total bilirubin
   c. Plasma cytokine analysis (1 -2 green top tubes) (see Appendix C). To be obtained within 24 hours of registration
   d. CMV assay, by PCR, antigenemia testing or shell vial culture (if not obtained within the prior 7 days)
3. Pregnancy test (if applicable). May be waived if testing done prior to admission
4. Karnofsky performance score
5. Radiographic studies: CXR (PA/lateral or portable AP)
6. Supplemental oxygen required to support a $SpO2 > 93\%$
7. Chest CT may be informative and is suggested
8. Buccal swab for recipient DNA for cytokine polymorphism analysis (see Appendix C).

4.4.2. Pre-randomization Bronchoscopy: Arm A and Arm B

All patients will undergo a bronchoscopy with broncho-alveolar lavage (BAL) at baseline, prior to randomization, unless criteria for Section 2.6.3.e are met.

The BAL procedure shall be performed, with the following guidelines: It is recommended that ≤ 2 mL/kg of sterile normal saline (max volume 150 cc) be instilled into the patient's lungs. If possible, BAL samples should be collected from both the right and left sided airways and then pooled together. BAL fluid samples shall then be sub-divided and distributed for the following assays:

1. Hematology: Recommended 5 mL (minimum 2 mL)
   a. Cell count and cytospin
2. Microbiology**:** Recommended 5 -10 mL (minimum 5 mL)
   a. Stains for bacteria, fungi, AFB
   b. Culture for bacteria (quantitative culture if available)
   c. Fungal, mycobacterial and viral cultures (as defined in Section 2.5)
   d. PCP testing by PCR, direct fluorescent antibody stain, or cytology (per local institution)
3. Cytopathology: Recommended 5 mL (minimum 2 mL)
4. BAL fluid cytokine studies: 5-10 mL in sterile container. Samples for BAL cytokine studies should be placed in a sterile container and kept on ice (or refrigerated at 4° C) until processing at the local institution. Ideally, the BAL fluid specimen should be processed (for cryopreservation) within 30 minutes of collection (see Appendix C).

If BAL fluid samples are being obtained on a weekend or holiday, and the lab is unable to process BAL fluid for required cytokine studies, please notify Study Chair (Gregory Yanik, MD at gyanik@umich.edu or Kenneth Cooke, MD at Kenneth.Cooke@uhhospitals.org).

4.4.3. Post-randomization Required Observations Arm A and Arm B

Required assessments are also shown in Table 4.4. The target day range = ± 1 day up to Day 28, and ± 7 days after Day 28, unless otherwise noted.

1. Blood and serologic tests
   a. CBC with differential and platelet count (Days 7, 14, 21, and 28, ± 2 days)
   b. Serum electrolytes, BUN/creatinine, AST, ALT, total bilirubin (Days 7, 14, 21, and 28, ± 2 days)
   c. Plasma cytokine analysis (1-2 green top tubes) Days 7 and 28
2. Radiographic tests: Chest X ray (Days 7, 14, 21, and 28)
3. Pulmonary function analysis: Record current level of supplemental oxygen support, and the duration of time (in days) that supplemental oxygen and mechanical ventilation were required (Days 7, 14, 21, 28, and 56)
4. GVHD assessment (Days 7, 14, 21, 28, and 56)

5. Toxicity assessment (Days 7, 14, 21, 28, and 56)
6. Infectious disease surveillance will be performed according to institutional guidelines

Table 4.4: REQUIRED ASSESSMENTS

	Pre-Registration	Pre-Randomization	Days Post-Randomization				
			7	14	21	28	56
History and physical exam	X						
CBC with differential and platelets[1]	X		X	X	X	X	
Pregnancy test (if applicable)[2]	X						
Karnofsky performance status	X						
Serum electrolytes, BUN/creatinine, AST, ALT, bilirubin[1]	X		X	X	X	X	
Plasma cytokine analysis[3]	X		X			X	
CMV assay[4]	X						
Chest X-Ray (PA/lateral or portable AP)	X		X	X	X	X	
Pulmonary analysis[5]	X		X	X	X	X	X
Chest CT (optional)	X						
Buccal swab	X						
BAL		X					
GVHD assessment			X	X	X	X	X
Toxicity assessment[5,6]			X	X	X	X	X

Notes:
[1] Serologic tests (including CBC, electrolytes, liver panel) should be performed within 48 hours of the indicated day.
[2] Pregnancy test may be waived if testing had been done pre-admission or at the time of admission.
[3] Plasma cytokine analysis must be performed within 24 hours of registration, Day 7, and Day 28.
[4] CMV assays are only required if the patient or donor were CMV positive pre-transplant, and if no CMV assay has been performed within 7 days prior to study registration. Study therapy may be subsequently initiated while the CMV assay results are pending. CMV assays may be performed by PCR, antigenemia, or shell vial culture.
[5] Record current level of oxygen support and the duration of time (in days) that mechanical ventilation and supplemental oxygen have been required. Record oxygen saturation (SpO2) by pulse oximetry.
[6] Includes overall survival / mortality by Day 28, Day 56 and 1 year from study onset.

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CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design

The study is designed as a Phase III, double-blind, randomized, placebo-controlled, multi-center comparison of etanercept plus corticosteroids versus placebo plus corticosteroids for the treatment of IPS. The target enrollment is 60 patients.

5.1.1. Accrual

It is estimated that five years of accrual will be necessary to enroll the targeted sample size. Over 25 centers, both Core and Affiliate Centers, will enroll patients on this study. Accrual will be reported by race, ethnicity, gender, age and donor type.

5.1.2. Randomization

All patients will be randomized following the BAL provided that the required special stains (on BAL fluid) are negative (see Section 2.6.1). Randomization will be performed in a 1:1 ratio using random block sizes for the two arms. Randomization will be stratified by center.

5.1.3. Primary Endpoint

The primary endpoint is the response rate to therapy at Day 28 after randomization defined in Section 3.0 as:

a) The ability to survive to Day 28 of study, PLUS

b) The ability to completely discontinue all supplemental oxygen support for > 72 consecutive hours by Day 28 (see Section 3.0 for details).

The primary analysis will be performed using the intent-to-treat principle, beginning at the time of study randomization, so that all randomized patients will be included in the analysis.

5.1.4. Primary Hypothesis

The primary null hypothesis of the study is that there is no difference between the response rates to etanercept plus corticosteroids compared to placebo plus corticosteroids.

$$H_{o:} \quad p_{Et} = p_{Pl}$$

$$H_{a:} \quad p_{Et} \neq p_{Pl}$$

5.2. Sample Size and Power Considerations

Response rates at Day 28 will be compared between the standard and experimental therapy arms using the binomial comparison of proportions. The primary analysis will be performed after all patients are followed for a minimum of 28 days post-randomization. At this time point, all individuals will be completely observed for the primary outcome. The sample size of 30 patients per group is sufficient to provide 80% statistical power for a two-sided test to detect an increase in the response rate from 0.3 in the placebo arm to 0.69 in the etanercept arm. While this effect size is large, it is similar to what was observed in pilot data at the University of Michigan as described in Section 1.7.

5.3. Interim Analysis and Stopping Guidelines

There will be no planned interim analyses for efficacy or futility, due to the small sample sizes planned. Monitoring of key safety endpoints will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised and if an ad-hoc meeting will be convened. Policies and composition of the DSMB are described in the BMT CTN Administrative Manual of Procedures.

5.3.1. Guidelines for Safety Monitoring

Historical data at the University of Michigan Medical Center indicate that 76% of patients with IPS die within 56 days of the onset of IPS. These data also indicated that 50% of patients with IPS required mechanical ventilation, 70% exhibited grade II-IV acute GVHD, 42% had concurrent hepatic veno-occlusive disease, and 36% were on hemodialysis at the time of their IPS diagnosis. Given the high acuity of this patient group, many patients will enter this study with both grade III-IV non-pulmonary toxicity and grade IV pulmonary toxicity already present (Common Terminology Criteria for Adverse Events, CTCAE version 3.0).

We will monitor three different toxicities separately in each treatment arm: (1) the cumulative incidence of new serious or life-threatening infections developing after Day 1 but by 28 days post-randomization; (2) the cumulative incidence of grade 4 dermatologic toxicity (CTCAE version 3.0) by Day 28 post-randomization; and, (3) the incidence of mortality by Day 28. The rationale for examining dermatologic toxicity is based upon data from the Dana Farber Cancer Institute and the University of Michigan Medical Center. Grade 4 dermatologic toxicity (rash with desquamation) was noted in 4 of 12 patients treated with etanercept at the Dana-Farber Cancer Institute, and in 0 of 40 patients treated with etanercept (for IPS or acute GVHD) at the University of Michigan Medical Center [personal communication, G. Yanik MD, V. Ho MD]. Dermatologic toxicity will now be examined in this multi-center trial, in a larger cohort of patients.

In the first two endpoints (serious infections and dermatologic toxicity), death prior to the toxicity occurring will be considered as a competing risk. Monitoring will be performed monthly until enrollment to that treatment arm is closed. Each month, the null hypothesis that the cumulative incidence of new serious infection is less than or equal to 15% will be tested

against the alternative that it is greater than 15%. Similarly, the incidence of grade 4 dermatologic reactions and mortality will be compared to a threshold of 5% and 65%, respectively.

A truncated Sequential Probability Ratio Test (SPRT) for a binomial outcome will be used for each endpoint, as described in greater detail below. Note that in the absence of censoring, the binomial proportion of patients experiencing the toxicity prior to death is equal to the cumulative incidence. This sequential testing procedure conserves type I error across all of the monthly examinations for a single toxicity endpoint, but not across two treatment arms or across the three endpoints. Thus for a single endpoint and study arm, the type I error is < 5%, and across both treatment arms and all three endpoints, the study-wide type I error is < 30%.

The rationale for not conserving type I error across multiple treatments and outcomes is twofold. First, adjusting the size of the test for multiple comparisons would reduce statistical power to detect adverse outcomes, which seems imprudent. Secondly, the procedure is a guideline for requiring additional review by the Data and Safety Monitoring Board, and is not a formal "stopping rule" that would mandate automatic closure of study enrollment.

The SPRT can be represented graphically. At each monthly interim analysis, the total number of patients enrolled is plotted against the total number of endpoints observed in those patients, (e.g., patients with new serious infection). The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring each treatment arm to protect against high incidences of new infection. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more new serious infections than predicted by the observed number of patients enrolled on study. Otherwise, the SPRT continues until enrollment to the treatment arm reaches the target goal.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_I)$. The tests to be used in this protocol were developed from the following SPRTs:

- A SPRT contrasting 15% versus 30% Day 28 incidence of new serious infection, with nominal type I and II errors of 5.6% and 20%, respectively. The common slope of the parallel lines is 0.219 and the intercept for the upper boundary is 2.997.
- A SPRT contrasting 5% versus 15% Day 28 incidence of subcutaneous reaction, with nominal type I and II errors of 6.5% and 20%, respectively. The common slope of the parallel lines is 0.092 and the intercept for the upper boundary is 2.075.
- A SPRT contrasting 65% versus 80% Day 28 mortality, with nominal type I and II errors of 5.6% and 20%, respectively. The common slope of the parallel lines is 0.729 and the intercept for the upper boundary is 3.466.

Note that since the test uses only the upper boundary, and is truncated by a finite sample size, the size of the test will be lower than the nominal level given %.

Table 5.3c demonstrates the stopping points for various numbers of enrolled patients for illustration.

Table 5.3c – Sample Stopping Boundaries for SPRT

Number of Patients Enrolled, n	Stop if Number of Events in First n Patients is ≥ x		
	Infection	Dermatologic	Mortality
5	5	3	
10	6	3	
15	7	4	15
20	8	4	19
25	9	5	22
30	10	5	26

Note that because there is a lag from randomization to complete follow up (28 days), the stopping rule may be triggered before complete follow up is available. For example, there may be 6 infection events in the first 10 patients even though the first 10 patients do not all have 28 days of follow-up. This implies that the plot of the number of patients transplanted against events observed in those patients may change for earlier accrual points as follow-up is completed, and will therefore be updated each month.

The actual operating characteristics of the truncated test, shown in Table 5.3d, were determined in a simulation study that assumed uniform accrual of 30 individuals over a five-year time period. No assumptions are made about the time to event distribution for either the toxicity event of interest or the competing event of death prior to observing that toxicity. The monitoring rule is based only on the binomial outcome of whether a patient experienced the toxicity by 28 days and prior to death. Because the simulations only use a binomial outcome, the mean month stopped is calculated based on the accrual time of the patient triggering the stopping rule + 28 days for complete follow-up. In practice, because of the potential for the stopping rule to be triggered prior to complete follow up of a particular patient, the actual mean month stopped may be earlier than shown in the simulation results. However, this is difficult to estimate because it is dependent on assumptions about the time to event distribution for both the toxicity event and the competing risk, as well as the dependence between them.

Table 5.3d – Operating Characteristics of Sequential Testing Procedure from a Simulation Study with 10,000 Replications

Serious Infection				
True 28-Day Rate	15%	25%	30%	35%
Probability Reject Null	0.028	0.287	0.500	0.722
Mean Month Stopped	60.3	53.9	48.0	40.6
Mean # Endpoints in 28 Days	4.4	6.7	7.1	7.1
Mean # Patients Enrolled	29.7	26.6	23.7	20.1

Dermatologic Reaction			
True 28-Day Rate	5%	15%	20%
Probability Reject Null	0.029	0.538	0.775
Mean Month Stopped	60.1	46.0	37.2
Mean # Endpoints in 28 Days	1.5	3.5	3.7
Mean # Patients Enrolled	29.6	22.7	18.5

Mortality				
True 28-Day Rate	65%	75%	80%	85%
Probability Reject Null	0.025	0.173	0.362	0.634
Mean Month Stopped	60.5	58.0	54.3	48.4
Mean # Endpoints in 28 Days	19.4	21.4	21.4	20.3
Mean # Patients Enrolled	29.8	28.5	26.7	23.9

For example, the testing procedure for serious new infections rejects the null hypothesis in favor of the alternative 3% of the time when the true 28-day incidence is 15%, and 72% of the time when the rate is 35%. When the true 28-day infection incidence is 35%, on average, the Data and Safety Monitoring Board will be consulted 40.6 months after opening, when 7.1 events have been observed in 20.1 patients.

5.4. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, primary disease, risk status, donor type, donor age, donor gender, donor ethnicity, donor-recipient CMV status. Between group comparisons will be performed for continuous variables via a t-test and for categorical variables, via the chi-square test.

5.5. Analysis of Secondary Endpoints

1. **Response to therapy at Day 56:** A binomial test of proportions will be computed after all patients are followed for 56 days post randomization to compare the standard and experimental treatment arms.
2. **Overall mortality:** Kaplan-Meier curves will be computed by treatment, and the groups will be compared using the log-rank test. Estimates and 95% confidence intervals will be tabulated also specifically for Day 28 and Day 56 mortality. The groups will be compared using a test based on the difference in the Kaplan-Meier estimates at a fixed point in time (Day 28 and Day 56).
3. **Time to discontinuation of supplemental oxygen support:** cumulative incidence curves will be computed by treatment, with death prior to discontinuation as the competing risk. A log-rank test will be used to compare the two arms.
4. **BAL Fluid and Plasma Cytokine Analysis:** BAL fluid and plasma will be collected for cytokine analysis using standard ELISA assays. This analysis will include but be not limited to TNFα, sTNFRI, sTNFRII, LBP, IL-1, IL-6, MCP-1 and sCD14. Measurements will be summarized with means and standard deviations for patients in each arm at each timepoint. Baseline or 7 day measurements, and the change between them, will be correlated with Day 28 response by using two-sample t-tests or nonparametric tests to compare responders vs. nonresponders. In addition, cytokine measurements over time will be correlated with time until death using Cox regression models with time-dependent covariates for the cytokine levels.

   Two-sided tests will be used throughout. A p-value of 0.05 or less will be considered statistically significant.

5.6. Safety Analysis

All entered patients will be included in the safety analysis. All reported serious adverse events potentially associated with study drug will be carefully examined with respect to the severity and relationship to study drug. Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 3.0. The incidence for each reported study drug associated adverse event will be presented for each group.

APPENDIX A

HUMAN SUBJECTS

1. Subject Consent

A conference will be held with the patient, donor and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the principle investigator or other designated physician.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

3. Participation of Women and Minorities and Other Populations

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of IPS in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

APPENDIX B

CONSENT FORMS

PATIENT INFORMED CONSENT

Informed Consent to Participate in Research

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

Your name:_____

Introduction
You are being invited to participate in a clinical trial. A clinical trial is a research study to answer specific medical questions. The information from this study may help future patients. This form tells you about the study. In addition, the study doctor (the person in charge of the research) will explain the study to you.

Please read this information and ask your study doctor about anything you do not understand. Please take your time to decide if you want to join this study. Some people find it helpful to have a family member or friend with them while learning about the study. You are being asked to join this study because you have a serious complication of transplantation affecting the lungs called Idiopathic Pneumonia Syndrome (IPS).

Before you decide whether or not to join the study, please read the information below. Feel free to ask questions. You do not have to participate in this research study - it is your choice. You and the medical staff at your transplant center will discuss other options before you make your decision.

It is important that you know:

- You will not be paid to be in this study.
- You or your insurance company will pay the bills for your medical treatment except that,
- You will not be charged for research tests or study medications.

Principal Investigator Contact Information at your Institution
Name/Title/Phone number/

Contact information for emergencies after hours or on weekends or holidays:
Name/Phone number/

Study Sponsor
The research in this study is paid for by the National Institutes of Health (NIH), which supports the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The BMT CTN will direct the research study. Some support will also be given by the Amgen Corporation, which makes the drug being tested in this study. All decisions about how the study is done are made independently by the BMT CTN and NIH.

Why is this study being done?
Pneumonia is a term that refers to the presence of fluid, congestion, or irritation or swelling in the lungs. Patients with pneumonia often have a cough and/or chest pain. They can be short of breath. Oxygen may be needed to help them breathe. In many cases, pneumonia is caused by germs such as viruses. However, sometimes patients develop symptoms of pneumonia but no germs are present. This is called Idiopathic Pneumonia Syndrome (IPS). IPS usually occurs within the first 180 days after transplant.

No one knows what causes IPS. No one knows why some patients get it and others do not. Recent studies have found that the lung fluid of patients with IPS contains certain chemicals that may directly damage the lung. One of these chemicals is called Tumor Necrosis Factor (TNF). Some recent tests suggest that TNF may be involved in causing lung damage.

Currently, there is no proven treatment for IPS. Patients may receive oxygen to help with breathing. They may receive medications (called diuretics) to remove fluid from their lungs. Patients often receive steroids to decrease some of the irritation and swelling in the lungs. Despite these treatments, many patients with IPS do not get better.

Etanercept is a drug approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (joint disease) and psoriasis (skin disease). We know that TNF is responsible for the damage caused to the joints or skin in patients with these diseases. Etanercept blocks the effects of TNF. Since we think that TNF may cause some of the lung damage in patients with IPS, it is possible that etanercept will help this disease too. In a previous small study of etanercept in patients with IPS, no serious side effects were seen. Some of the patients got better.

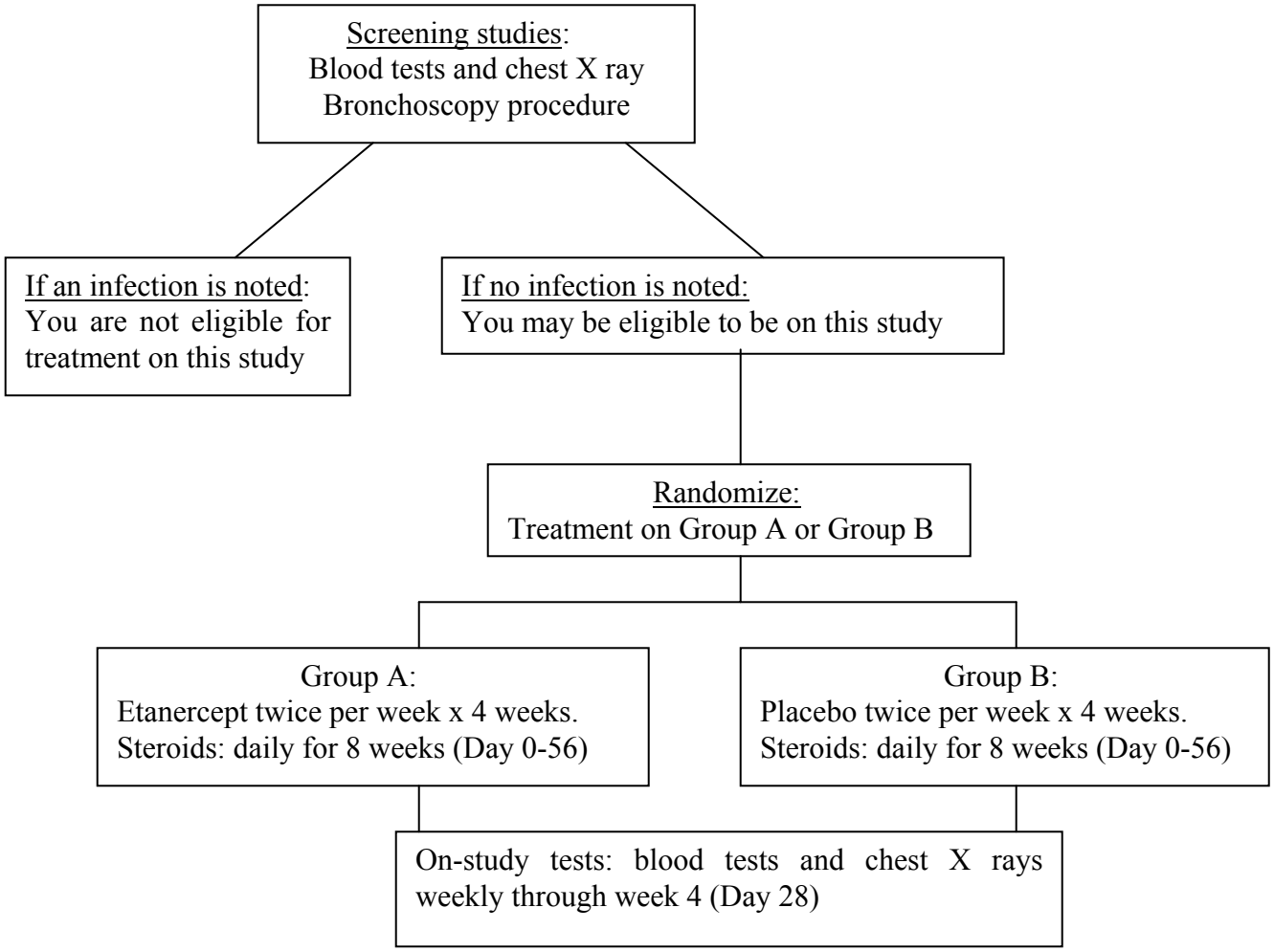
The purpose of this study is to find out whether adding etanercept to a commonly-used treatment for IPS (steroids) is more effective in treating IPS than steroids alone. Patients will receive either “etanercept and steroids” (Group A) or “placebo and steroids” (Group B). The placebo has no good or bad effect on IPS. Thus patients in Group B are actually receiving only steroids to treat IPS.

Steroids are the most common treatment for IPS.

Doctors want to know if giving etanercept plus steroids is better, the same or worse than giving steroids alone. The study will also see whether side effects result from adding etanercept to the commonly-used steroids. The study may help doctors make better treatment choices for future patients with IPS.

How many people will take part in the study?
A total of 60 patients will participate in this study. Thirty patients will be assigned to each group. This study will be done at more than 25 different medical centers in the United States, including [Center Name/Location].

What will happen if I take part in this research study?
The diagram below outlines the research study (the details follow the diagram). Start reading at the top and read down the list following the lines.



Screening studies:
You will need to have the following tests or procedures to find out if you are eligible for this study. We refer to these as "screening studies." These screening studies are often part of regular care, and may be done even if you do not join the study.

- *Chest X ray*
- *Blood tests*
- *Bronchoscopy*

Bronchoscopy: A bronchoscopy is a procedure performed by lung specialists. A small flexible tube is inserted into your nose (or mouth), and passed into your lungs. The tube has a light on one end that allows doctors to see into your lungs. The doctors will take out a sample of fluid from your lungs. This lung fluid will be tested for the presence of germs. If any germs are found, you can not be on this study but will receive treatment for the specific germs found. A portion of the fluid will also be tested for research purposes. The research will look for the presence of chemicals such as TNF.

During the bronchoscopy, you may or may not be put to sleep. In some cases, your doctor may place you on a breathing machine (called a mechanical ventilator). This will make sure you get enough oxygen during the procedure. At the end of the procedure, the breathing tube is usually removed. In some cases, however, the breathing machine may need to remain in place longer.

If you have had a bronchoscopy in the past 3 days, this procedure will not need to be repeated as long as no germs were found.

In some cases, your physician may choose not to do the bronchoscopy procedure. If your medical condition is such that a BAL is deemed "not possible to be performed" by your treating physician, then the "on study" BAL may be waived (not done). In this circumstance, you may enroll and still be randomized to study therapy without the BAL being undertaken.

Randomization:
If the results of tests and procedures show that you can be in the study, you will be "randomized" into one of the study groups described below. Randomization is done by a computer. Randomization puts you into a group by chance, much like flipping a coin. You will have an equal chance of being placed into either group. You will not be able to choose which group you are assigned. Neither you nor your doctors will know your group.

- If you are in Group A, you will receive treatment with etanercept plus steroids.
- If you are in Group B, you will receive treatment with steroids plus a placebo. The placebo will be a salt solution without medication.

You will not be able to tell the etanercept from the placebo, as both will look the same. Once you start treatment, you may not change to therapy in the other group while on this study.

Study Treatment:
The etanercept (or placebo) may begin within 24 hours after the bronchoscopy procedure. You will receive either etanercept or the placebo two times per week, for 4 weeks (see Table below).

There will be a total of 8 doses given. You will receive the first dose of etanercept (or placebo) as a 30-minute intravenous (IV) infusion. You will receive the second dose of etanercept (or placebo) as an injection under the skin (SQ) 3 days after the first dose. You will receive the remaining etanercept (or placebo) doses as injections under the skin approximately 3-4 days after the previous dose. The dosing plan is provided below.

GROUP A

Etanercept Dose	Time	How Administered
1	Day 0	IV
2	Day 3	SQ
3	Day 7	SQ
4	Day 10	SQ
5	Day 14	SQ
6	Day 17	SQ
7	Day 21	SQ
8	Day 24	SQ

GROUP B

Placebo Dose	Time	How Administered
1	Day 0	IV
2	Day 3	SQ
3	Day 7	SQ
4	Day 10	SQ
5	Day 14	SQ
6	Day 17	SQ
7	Day 21	SQ
8	Day 24	SQ

Key: IV, intravenous; SQ, injection under the skin

In addition to the etanercept (or placebo), you will also be given steroids (such as prednisone, Medrol, or Solumedrol). The steroids may be given to you by IV or by mouth. The dose of steroids you receive varies according to your weight. If you are getting better (requiring less oxygen to breathe) by Day 7 of treatment, the dose of steroids may be decreased.

If you continue to get better (requiring less oxygen to breathe), the steroid dosage will be decreased further over a 2-month period. In some cases, the steroids will be continued for a longer period of time (after 2 months).

Required tests while you are on the study:

Day:	Process:
Tests within 24 hours of study registration	Blood tests Chest X ray
Day 0	Bronchoscopy
Week 1	Blood tests Chest X ray
Week 2	Blood tests Chest X ray
Week 3	Blood tests Chest X ray
Week 4	Blood tests Chest X ray

Weekly blood tests will be obtained through week 4 (Day 28). Tests will include routine measurements of blood counts and electrolytes. Research tests will measure levels of certain chemicals called cytokines (including TNF) in the blood.

How long will I be in this study?
You will be treated on this study for 8 weeks. You will be given etanercept (Group A) or placebo (Group B) over 4 weeks, and steroids over about 8 weeks. Your participation on this study will last for one year as we follow how you are doing through regular visits with your transplant doctor. Follow-up for your transplant will last as long as you require care. However, we would like to keep track of your medical condition for the rest of your life. We will do this by contacting you and the doctor providing your regular medical care by phone or mail once a year. Keeping in touch with you and checking on your condition every year helps us know whether there are any unexpected long-term side effects of treatment. Many transplant centers include this type of long-term follow-up as part of their regular care.

Can I stop being in this study?
Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

If you have any questions about your rights as a study subject, you may contact the Institutional Review Board (IRB) office at /number/.

Can the Principal Investigator withdraw me from this research study?
The study doctor may stop you from taking part in this study at any time if he/she:

- Believes it is in your best interest;

- If you do not follow the study rules; or,
- If the study is stopped.

You can be taken off the study (with or without your consent) for any of these reasons:

- If, after undergoing the bronchoscopy procedure, lab testing indicates that germs were present in your lungs. Your study treatment will be stopped. No further study treatment will be given.
- If you develop a severe side effect from the study treatment.
- You need treatment not allowed in this study.
- You do not follow directions that are important to being in the study.
- The study is cancelled.
- Other study-specific reasons, for example, if study doctors determine the study should be closed early because of side effects found in other patients.
- If your physician feels it is in your best interest to stop.

What side effect or risks can I expect from being in the study?
There are risks involved in this study. There may be side effects from the drugs or study procedures. The side effects **we know about now** are described below. Side effects can range from mild to severe. Some side effects may last only a short time (hours – days). Others may last longer.

Please talk with your doctor about possible side effects. If you want to read more about the drugs used in this study, please ask your doctor. We have grouped side effects according to how likely they are to happen:

Likely Side Effects	What it means: This type of side effect is expected to occur in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely Side Effects	What it means: This type of side effect is expected to occur in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare Side Effects	What it means: This type of side effect does not occur very often – in fewer than 2% of patients – but is serious when it occurs. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect.

I. Risks related to the bronchoscopy procedure:

Bronchoscopy is a standard procedure for evaluating patients with pneumonia. You will be given a separate consent form to sign that explains the risks and discomforts.

II. Risk of steroids:

All patients on this trial will receive steroids. This is the most commonly used treatment for IPS. The following table shows expected side effects of steroids.

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients)*	• Difficulty sleeping • Increased susceptibility to infections • Weight gain, especially around the face/cheeks, shoulders, belly or legs • Muscle weakness • Pimples/acne • Increase in appetite • Increase in blood pressure • Increased levels of glucose (sugar) in the blood • Mood swings • Upset stomach (heartburn or gastritis)
Less Likely *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients)*	• Red face • Slow healing of cuts or other wounds • Slowed growth • Stretch marks and easy bruising of the skin • Abnormal electrolyte (salt) levels in the blood • Increased pressure in the eyes • Weakened bones (due to lower calcium levels in the bones) • Cataracts (thickening of the lens of the eye) • Headache • Dizziness • Infections
Rare, but Serious *(These possible risks have been reported in rare occurrences, typically < 2% of patients. They may be serious if they occur)*	• Joint damage, which can cause pain and loss of motion in that joint • Irritation of the pancreas (pancreatitis) • Irregular heart beat • Stomach and intestinal bleeding ulcers • Increased pressure in the brain, which can lead to difficulty seeing and headache • Bone fractures • Serious changes in mood, personality and/or severe depression

III. Risks related to etanercept: (this applies if you are assigned to Group A therapy)

Etanercept has been studied in both children and adults with a number of other conditions. These conditions include rheumatoid arthritis (a joint disease), psoriasis (a skin disorder), Crohn's disease, AIDS, heart failure, or serious infections. Infections, some serious, have been reported in these studies. Many infections occurred in patients who already had diseases that tended to weaken their body's ability to fight infection. In all cases, the occurrences of these side effects were rare. Also it is unclear whether or not etanercept was the cause. In patients with rheumatoid arthritis or psoriasis, the number of infections in patients treated with etanercept did not differ from the number in patients treated with a placebo. This included serious infections.

We cannot determine how etanercept may affect your risk of getting cancer. To date, the incidence of cancer in patients receiving etanercept has been similar to the risk in untreated people.

A small number of people receiving etanercept have formed antibodies *(proteins that attack foreign matter)* against etanercept. Although these antibodies do not appear to decrease the effect of the drug, it is a possibility that it may in some patients. The effects of a person developing antibodies to etanercept are not known. Your chances of developing antibodies are believed to be very low, < 5%.

Etanercept given by injection under the skin may cause local pain, bleeding, bruising, and rarely, an infection at the site of injection. A summary of the possible risks of etanercept is shown below:

Likely *("Likely" refers to a side effect that is expected to occur in more than 20% of patients)*	• Pain at the site of the injection
Less Likely *("Less likely" refers to a side effect that is expected to occur in 20% or fewer patients)*	• Increased risk of infections. Some of these infections may be serious or even life threatening • Irritation, itching, bruising, swelling or redness at the site of the etanercept injection • Hyper or hypothyroidism, where the thyroid gland produces too little or too much thyroid hormone • Belly pain, nausea and/or vomiting • High blood sugar levels • Blurred vision • Headache, or dizziness • Runny nose, sore throat

Rare, but Serious *(These possible risks have been reported in rare occurrences, typically < 2% of patients, but may be serious if it occurs. In most cases it is unclear whether or not etanercept was the cause.)*	• Severe allergic reactions during the infusion or injection • Severe rashes which can affect the skin and mouth, leading to pain, peeling of the skin and increased risk of infections • Headaches, seizures, strokes • Onset of multiple sclerosis or muscle weakness • Decreased blood counts, such as – A low number of white blood cells, which can make it easier to get infections – A low number of red blood cells, which can make you feel tired and weak – A low number of platelets, which causes you to bruise and bleed more easily • A relapse of one's cancer, or the development of a new cancer such as leukemia or lymphoma. Patients with Wegener's granulomatosis, a known immune system disorder, have had an increased risk of developing lymphoma. • Weakened heart muscle which may make you feel tired, weak, or short of breath • Recurrence of certain viral infections, such as the hepatitis B virus, which can lead to severe liver damage or liver failure • Recurrence of tuberculosis, if you have been previously infected with tuberculosis • Development of proteins (called antibodies) that react against your own body tissue. Collectively, these are called auto-immune reactions. They are often associated with rashes and fever. • Blood clots, or bleeding problems

There may be other, as yet unknown, side effects of etanercept.

IV. Reproductive risks: The effects of etanercept on your ability to get pregnant is not known. Its risks to an unconceived, unborn or newborn child are also unknown. Because the drugs in this study may affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse a baby while on this study. Women or men of child-bearing potential are not allowed to be in the study unless they use birth control (which may include abstinence).

V. Risks related to the placebo: (this applies if you are assigned to Group B therapy)
The treatment with placebo is anticipated to have few side effects. Pain at the site of the injections of the placebo may be noted in > 20% of patients receiving the placebo injections.

Are there benefits to taking part in the study?
Being in this study may or may not lead to any direct benefit for you. We also hope that information gathered in this study will help future patients with IPS.

What other choices do I have if I do not take part in this study?
If you do not take part in this study, you will be followed and treated according to the usual practice at your transplant center. This may include, for example:

- Bronchoscopy.
- Supportive care such as oxygen, or medications to remove fluid from your lungs.
- Steroid medications to treat IPS.
- Etanercept to treat IPS (this etanercept is the same as the study drug, but it would be given to you not as part of this study).

You should know about your treatment choices before you decide if you will take part in this study.

What are the costs of taking part in this study?
You or your insurance company will pay for all standard care relating to your transplant and IPS. This includes (but not limited to) routine blood tests, chest X-rays, and bronchoscopy procedures.

You will not be billed for tests that are only done for research purposes. These include the cost of the etanercept or placebo, and the cost of laboratory studies to measure chemicals called cytokines, such as TNF.

You will not be paid to be in this study.

Amgen, the company that makes etanercept, is providing funds for some of the costs of this study. However, Amgen did not plan or design this clinical trial. Amgen will also not have a part in analyzing the results of this study.

Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What if I am injured as a result of being in this study?
In the event that this research activity results in an injury, treatment will be available. This treatment includes first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed to your insurance company. If you think you have suffered a research related injury, let the study doctors know right away. Unexpected side effects or accidents might result in your getting sicker than anticipated. All available medical care will be provided to you, but you and your insurance company are responsible for the costs of all such care.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you. You will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information that may effect your health or your willingness to stay in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Will my medical information be kept private?
Your participation in this research study will be kept private and confidential. All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

<u>Organizations with access to your research and medical records:</u>

- /Institution/
- The National Institutes of Health (NIH)
- The National Heart, Lung, and Blood Institute (NHLBI)
- The National Cancer Institute (NCI)

- Office of Human Research Protection (OHRP)
- The Food and Drug Administration (FDA)
- Institutional Review Boards (IRBs) responsible for this study
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation who are coordinating the studies of the BMT CTN
- Representatives of Amgen, Inc. (drug supplier for the etanercept used in this study)
- Study investigators

Scientific and medical findings resulting from a study may be presented at meetings. They may be published so that the information can be useful to others. You will not be identified in these presentations and publications.

Information related to or resulting from your transplant will be reported to the CIBMTR. The CIBMTR is a voluntary organization of basic and clinical scientists working together to gather results of stem cell and marrow transplants. This information is used to guide clinical decisions and identify ways to improve transplant outcomes. Scientific data or medical information (not identifiable with you) that could be useful to others may be presented at meetings and/or published in medical journals.

For questions about access to your medical records, please contact /name/ at /number/.

HIPAA[1] authorization to use and disclose individual health information for research purposes

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *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.*

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior

1 HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

treatment), physical examination findings, and laboratory test results obtained at the time of work up and after transplantation (e.g., blood tests, biopsy results).

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from:

(list hospitals, clinics or providers from which health care information can be requested)

_____

_____

_____

d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff at the University of Michigan
- Staff/laboratories identified in the protocol for the evaluation of other laboratory samples
- National Heart, Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), including the Center for International Blood and Marrow Transplant Research (CIBMTR), the National Marrow Donor Program (NMDP) and the EMMES Corporation who are coordinating the studies of the BMT CTN
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.
- Others:

_____

_____

_____

e. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health

information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

g. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. This authorization does not have an expiration date.

****

Is there an expiration date for keeping my records?
Study records will be kept indefinitely by the transplant center for re-analysis and follow-up. If you have questions about the keeping of your research records or access to your files, please call /name/ at /number/.

Will researchers benefit from me being in this research study?
Your doctors have no money invested and will not get any financial gain from this study. Presenting research results may help the career of a doctor. Therefore, the doctors running this research study may benefit when the results are presented at scientific meetings or in the scientific press.

****

BLOOD AND LUNG FLUID FOR FUTURE RESEARCH:

Please note: This section is about future research studies. These studies will be done using blood and lung fluid samples. You may give samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to allowing these samples to be used for future research studies. Please mark your choice at the end of this section.

The study investigators ask your permission to store and use any remaining blood or lung fluid for future research. If your blood/lung fluid has already been collected, any remaining blood/lung fluid will be used for research, if you agree. These future studies may help researchers learn more about IPS and your response to treatment. Researchers may also perform genetic studies to determine whether there are correlations among your genetic make-up, the risk of developing IPS, and your response to treatment. This new research will be unlinked to your private personal information or other medical history. The doctors involved in running this study will not give other researchers your name, address, phone number, or any other information that will let the researchers identify you. Data generated from your blood/lung fluid will be entirely investigational. Reports about research done with your blood/lung fluid will not be given to you or your doctor. These reports will not be put in your health record.

Your blood/lung fluid may be distributed to the researchers in the BMT CTN and other qualified researchers interested in IPS or other transplant-related complications. As noted above, the researchers will be given these samples without any potentially identifying information. Information gained from research on your blood/lung fluid may be used for the development of diagnostic procedures or new treatments for lung complications after transplant. Your blood/lung fluid will not be sold to any person, institution, or company for financial gain or profit. Moreover, neither you nor your heirs will gain financially from discoveries made using the information and/or specimens that you provide.

In some cases, you may have already given consent to your treating institution or the National Marrow Donor Program (if you were the recipient of stem cells from an unrelated donor) for the collection of blood samples prior to your bone marrow transplant. If this has occurred, your treating institution (or the NMDP) will also be requested to, when possible, supply a portion of these samples for research purposes. In addition, you will be asked to provide a tissue sample that could be collected by rubbing a cotton swab on the inside part of your cheek.

Things to Think About: The choice to let us use these samples for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood/lung fluid can be kept for research, you can change your mind at any time. If you change your mind, we ask that you tell [the study Principal Investigator] in writing; his/her mailing address is on the first page of this form. Tell your doctor that you do not want us to use your blood or lung fluid. Then any blood/lung fluid that remains will no longer be used for research.

Benefits: You may not get any direct benefit for providing blood/lung fluids for this study, but the research performed with these samples may help us learn more about what causes IPS and other complications after transplantation, and how to prevent and/or treat them.

Risks: The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private and secure. The chance that this information will be given to someone else is very small.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Making Your Choice: Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

- ❑ I agree to allow my blood, lung fluid and cheek swab used to be used for future research.

- ❑ I do not agree to allow my blood, lung fluid and cheek swab to be used for future research.

_____ _____
Signature *Date*

Who can I contact if I have questions or problems?
If you think you have suffered an injury as a result of this study, or have any other problems, you may contact (INSERT CONTACT INFORMATION). If it is after normal business hours or a weekend, you may contact (INSERT CONTACT INFORMATION).

If you have any questions about this study, you may contact the study Principal Investigator listed on the first page of this form.

If you have questions about your rights as a research participant, you may contact (INSERT CONTACT INFORMATION).

Consent for Treatment:

I have been informed about this study's purpose, procedures, possible benefits and risks. I have been given a chance to ask questions and have had them answered to my satisfaction. I understand that I can ask more questions at any time.

I voluntarily agree to participate in this study.

By signing this consent form, I have not given up any of the legal rights which I otherwise would have as a subject in a research study.

_____ _____
Signature of Subject *Date*

_____
Print Name of Subject

_____
Signature of Legally Authorized Representative *Date*

Certification of Counseling Healthcare Professional

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this study have been explained to the above individual and that any questions about this information have been answered.

_____ _____
Counseling Healthcare Professional *Date*

Use of an Interpreter: Complete if the subject is not fluent in English and an interpreter was used to obtain consent:

Print name of interpreter: _____ Date: _____

Signature of interpreter: _____

An oral translation of this document was administered to the donor in _____ (state language) by an individual proficient in English and _____ (state language). See the attached short form addendum for documentation.

APPENDIX C

LABORATORY PROCEDURES

C-1 CYTOKINE AND INFLAMMATORY MARKERS

BAL fluid and plasma specimen will be analyzed for a panel of cytokine and inflammatory markers (listed below) in the laboratory of Dr. Kenneth Cooke, Case Western Reserve University Medical School. BAL fluid samples will be obtained at study entry and plasma will be collected at study entry, Day 7 and Day 28 of study, as outlined below:

Table C.1 Sample Collection Summary:

Study Date	Sample	Sample Volume
Pre-randomization	BAL	5-10 mL in sterile container
Day 0	Plasma	5-10 mL in green top tubes
Day 7	Plasma	5-10 mL in green top tubes
Day 28	Plasma	5-10 mL in green top tubes

I. Processing of BAL fluid sample (at Local Institution):
A minimum of 5 mL (range 5-10 mL) of BAL fluid is required for the cytokine studies. Upon completion of the bronchoscopy procedure, the BAL fluid should be placed in a sterile container and kept on ice (or refrigerated at 4^{o} C) until processing. Ideally, the BAL fluid specimen should be processed within 30 minutes of collection. Specimen should be spun at 400x g for 5 minutes in order to separate supernatant from the cell pellet. Supernatant will be extracted and divided into 1-2 mL aliquots in five sterile cryovials and frozen at -80^{o}C. The samples will remain cryopreserved until later shipment to the laboratory of Dr. Kenneth Cooke (see below).

II. Processing of serum samples (at Local Institutions):
Five to ten mL of peripheral blood should be obtained in green top tubes on Day 0, 7, and 28 of study. The initial plasma sample should be obtained prior to the first dose of study drug on Day 0 of study. Samples should be separated within 30 minutes of sample acquisition. Samples should be centrifuged a 400x g for 10 minutes, the supernatant separated from the cell pellet, aliquoted into two sterile cryovials, and frozen at -80^{o}C. The samples will remain cryopreserved until later shipment to the laboratory of Dr. Kenneth Cooke.

III. Sample shipping:
The BAL and plasma samples should be kept frozen until Day 28, then batched and collectively shipped with all samples for a patient overnight on dry ice.

IV Cytokine analysis:
BAL fluid and plasma will be analyzed in the laboratory of Dr. Kenneth Cooke for the following cytokines using commercially available ELISA kits that have no cross-reactivity with other related cytokines/chemokines.

Pro-inflammatory proteins to be analyzed:
TNFα, TNFR I and II, LPS, LBP and CD14, and IFNγ.

Pro-fibrotic panel of proteins to be analyzed:
IL-1ra, TGFβ, IL-6, IL-8, and MCP-1.

Additionally, plasma samples will be analyzed by mass spectroscopy for proteomics analysis.

C-2 CYTOKINE GENE POLYMORPHISM

To assess recipient cytokine genes, if available, pre-transplant recipient blood collected in an ACD-A anticoagulant-containing tube or an EDTA tube for DNA will be used. In addition, a buccal swab will be collected for recipient DNA.

The buccal swab should be allowed to dry at room temperature. Remove the tip of the swab and store in a 1.8 mL cryovial. Freeze cryovial at -80° C.

The pre-transplant blood and buccal swab samples should be kept frozen until Day 28, then batched and collectively shipped with all samples for a patient overnight on dry ice.

TABLE C.2 LABORATORY SCHEDULE

TEST	TYPE OF SAMPLE (Collection Container)	TYPE OF STORAGE	DATES SAMPLES OBTAINED	SHIPPING SPECIFICATIONS	LOCATION OF TEST PERFORMED
Cytokine and Inflammatory Markers – BAL	5-10 mL BAL fluid (sterile container).	Keep on ice (or refrigerate at 4 ^{o} C) until processing. Centrifuge at 400 x g for 5 minutes. Aliquot supernatant into 1-2 mL aliquots into five sterile cryovials and freeze at -80^{o} C.	Prior to randomization.	Batch ship on dry ice with all samples for one patient.	Dr. Kenneth Cooke's Laboratory.
Cytokine and Inflammatory Markers – Plasma	5-10 mL peripheral blood (green top tube).	Centrifuge at 400 x g for 10 minutes. Aliquot the plasma into five sterile cryovials and freeze at -80^{o} C.	Day 0 (prior to first dose of study drug), Day 7, Day 28.	Batch ship on dry ice with all samples for one patient.	Dr. Kenneth Cooke's Laboratory.
Cytokine Gene Polymorphism – Buccal Swab	Buccal Swab allowed to dry at room temperature and transferred into a 1.8 mL cryovial.	Frozen at -80°C	Day 0.	Batch ship on dry ice with all samples for one patient.	Dr. Kenneth Cooke's Laboratory.
Cytokine Gene Polymorphism – Pre Transplant Blood Sample (If Available)	3 mL pre-transplant peripheral blood (preferable collected in ACD-A or anticoagulant yellow top tube or EDTA purple top tube) aliquoted into two 1.8 mL cryovials.	Frozen at -80°C	Pre-transplant (if available).	Batch ship on dry ice with all samples for one patient.	Dr. Kenneth Cooke's Laboratory.

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APPENDIX D

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