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**Title:** A Phase I/II study of abatacept in the treatment of patients with steroid refractory chronic Graft Versus Host Disease (cGVHD)

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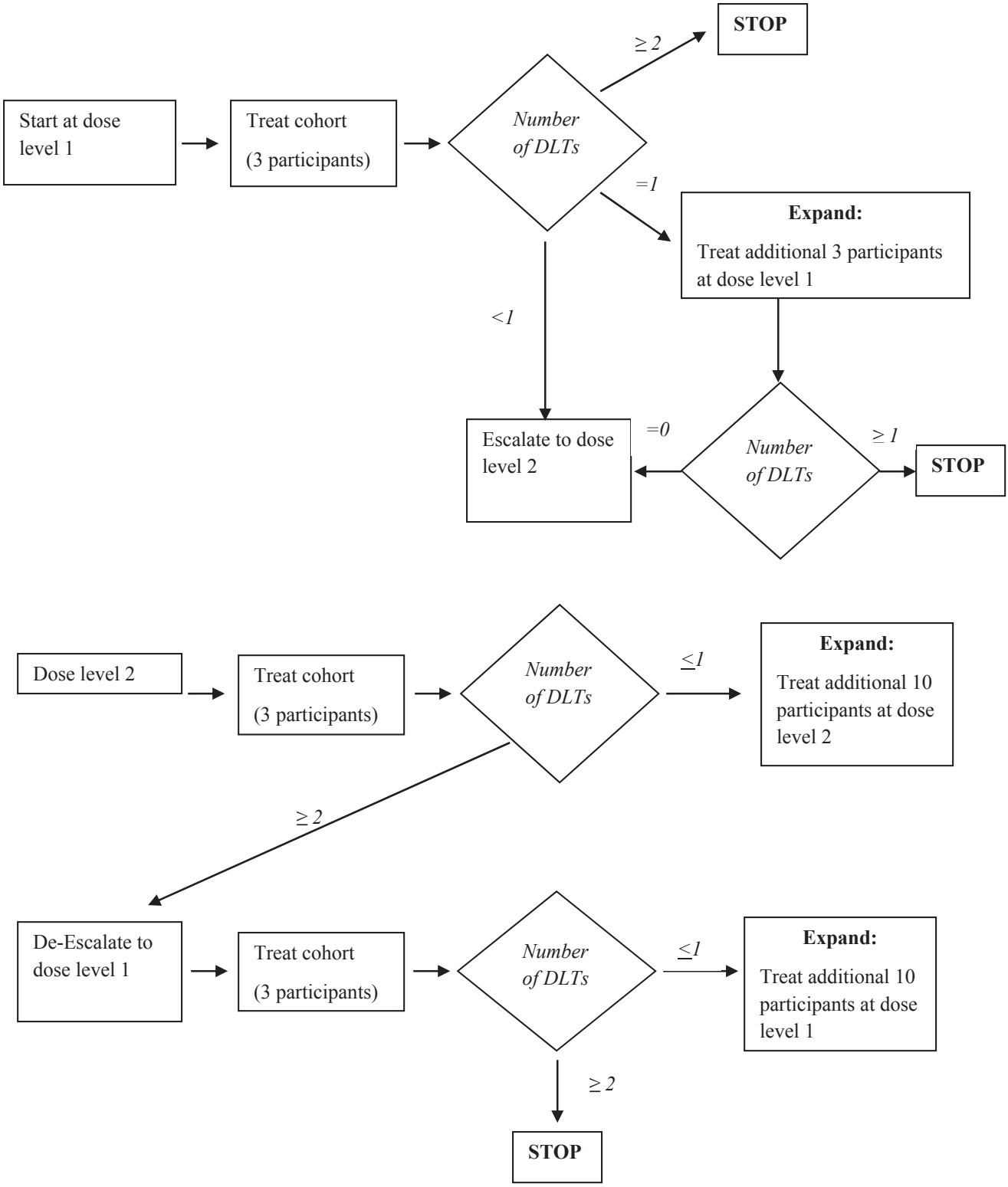
## Protocol Schema



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## LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

| Abbreviation | Term |
|---|---|
| **ACR** | American College of Rheumatology |
| **AE** | Adverse Event |
| **ALT (SGPT)** | alanine transaminase (serum glutamic pyruvic transaminase) |
| **APC** | Antigen-presenting Cells |
| **AST (SGOT)** | Aspartate transaminase (serum glutamic oxaloacetic transaminase) |
| **BUN** | Blood Urea Nitrogen |
| **cGVHD** | Chronic Graft Versus Host Disease |
| **COPD** | Chronic Obstructive Pulmonary Disease |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **CTLA4** | Cytotoxic T-Lymphocyte Antigen 4 |
| **DLT** | Dose Limiting Toxicities |
| **DF/HCC** | Dana Farber/Harvard Cancer Center |
| **DMARDS** | Disease-modifying Anti-rheumatic Drugs |
| **DSMC** | Data and Safety Monitoring Committee |
| **ECG** | Electrocardiogram |
| **ECOG** | Eastern Cooperative Oncology Group |
| **ESR** | Expedited Safety Report |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practice |
| **GVHD** | Graft Versus Host Disease |
| **HBV** | Hepatitis B Virus |

| | |
|---|---|
| **HCV** | Hepatitis C Virus |
| **HIV** | Human Immunodeficiency Virus |
| **HSCT** | Hematopoietic Stem Cell Transplantation |
| **IND** | Investigational New Drug |
| **IRB/EC** | Institutional Review Board/Ethics Committee |
| **JIA** | Juvenile Idiopathic Arthritis |
| **MTD** | Maximum Tolerated Dose |
| **NIH** | National Institute of Health |
| **PBMC** | Peripheral Blood Mononuclear Cells |
| **PET** | Positron Emission Tomography |
| **PML** | Progressive Multifocal Leukoencephalopathy |
| **QACT** | Quality Assurance Office for Clinical Trials |
| **RA** | Rheumatoid Arthritis |
| **SAE** | Serious Adverse Event |
| **SLE** | Systemic Lupus Erythematosus |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TNF** | Tumor Necrosis Factors |
| **ULN** | Upper Limit of Normal |

## 1. OBJECTIVES

Phase I portion of the Clinical Trial:

### 1.1 Primary:

- To determine the Maximum Tolerated Dose (among two dose levels) and toxicity profile of a 141 day/6 dose course of abatacept in patients with steroid refractory cGVHD.

### 1.2 Secondary:

- To determine the efficacy (in terms of cGVHD symptoms, score and steroid dose) of a 141 day/6 dose course of abatacept in patients with steroid refractory cGVHD.
- To examine the immunologic effects associated with the administration of abatacept in patients with steroid refractory cGVHD.

**Phase II Portion of the Clinical Trial**:

**1. 3 Primary Objective**:

- To evaluate the overall clinical response rate of Abatacept in patients with steroid-refractory cGVHD.

**1.4 Secondary Objectives:**

- To assess the immunologic effects of Abatacept
- To assess overall survival, progression-free survival, non-relapse mortality and relapse at 1 year after start of Abatacept.

### 1.3 Study Design

**Phase I Portion of the Clinical Trial:**

Abatacept will be administered for a total of 6 doses. Doses 1-3 will be administered at two week intervals (+/-2 days). One month following Dose 3, abatacept will be administered, and given at four-week intervals (+/-2 days) for three doses (Doses 4-6.) Patients will be followed for toxicity for 28 days following last dose of abatacept. Patients will then be seen monthly for six months following the last dose of therapy.

The study will follow a standard 3+3 design with two escalating doses of abatacept to determine the maximum tolerated dose (MTD): 3 mg/kg (dose level 1) and 10 mg/kg (dose level 2). Dose-limiting toxicities (DLTs) are defined as any Grade 3 or 4 toxicities judged to be probably or definitely related to abatacept.

A cohort of 3 evaluable patients will enter at the first dose level of 3mg/kg . If no DLT is seen in the first 3 evaluable patients and all 3 patients complete at least 8 weeks of treatment, then a dose escalation to 10mg/kg will take place. If 2 or more of the 3 evaluable patients experience DLT at 3mg/kg, the study will be terminated early. If 1 of the 3 evaluable patients experiences DLT then 3 additional evaluable patients will be treated at that dose level. If there is no DLT in the 3 additional patients then a dose escalation will take place. If 2 or more of the 3 evaluable patients experience DLT at 10mg/kg, the next cohort of 3 patients will be treated at 3mg/kg unless 6 patients have already been treated at that dose level. A minimum of six patients must be evaluated at the highest tolerated dose level, and fewer than 2 patients in 6 should experience DLT.

Once the MTD is established, an additional 10 patients will be treated at the MTD to provide a better estimate of the toxicity of abatacept.

Patients will be followed weekly until day 57 then every 2 weeks through dose 6. Peripheral blood for the laboratory immunologic studies will be obtained prior to the initiation of treatment, at each treatment visit, and four weeks following the last dose of abatacept.

Extended-duration therapy: After completing 6 doses of abatacept and 1-3 months of follow up following the 6th dose, participants experiencing clinical benefit (complete or partial response; minor response not meeting NIH criteria for partial response) with acceptable toxicity will be permitted to continue on extended-duration abatacept treatment at the discretion of the treating physician. Participants may receive monthly doses of abatacept, at their assigned dose level, for up to a total of 12 doses of extended duration therapy.

**Phase II Portion of the Clinical Trial**:

Upon completion of the phase I dose escalation and dose expansion cohorts, the phase II portion of the study will be initiated. Thirty nine evaluable patients will be treated with Abatacept at a dose of 10 mg/kg. Abatacept will be administered for a total of 6 doses. Doses 1-3 will be administered at two week intervals (+/-2 days). One month following Dose 3, abatacept will be administered, and given at four-week intervals (+/-2 days) for three doses (Doses 4-6.) Patients will be followed for toxicity for 28 days following last dose of abatacept. Patients will then be seen monthly for six months following the last dose of therapy. Patients will be seen every 2 weeks following each dose of abatacept. Peripheral blood for the laboratory immunologic studies will be

obtained prior to the initiation of treatment, at each treatment visit, and four weeks following the last dose of abatacept.

Extended duration therapy: In the phase II portion of the trial, patients completing 6 doses of Abatacept and 1-3 months of follow up following the 6$^{th}$ dose may continue to receive extended duration therapy. In order to receive extended duration therapy, patients must experience clinical benefit (complete or partial response; minor response not meeting NIH criteria for partial response) with acceptable toxicity. Participants may receive monthly doses of abatacept at a dose of 10 mg/kg, for up to a total of 12 doses of extended duration therapy. Patients receiving extended duration therapy will be followed monthly. Deviations to the monthly schedule may be permitted following discussion with the overall PI.

## 2. BACKGROUND

### 2.1 Study Agent(s)

Abatacept is a recombinant fusion protein consisting of the extracellular domain of human CTLA4 and a fragment (hinge- CH2-CH3 domains) of the Fc domain of human IgG1 that has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity.

Abatacept is the first drug in a new class of agents termed "selective costimulation modulators." Abatacept binds specifically to the CD80 and CD86 molecules, proteins prominently displayed on the surface of antigen-presenting cells (APCs). Activation of naive T cells during an immune response requires two stimuli from APCs. The first signal is antigen-specific; antigens are presented by APCs, with the signal transmitted to the T cell through the T cell's antigen receptor. The second, or costimulatory, signal is not antigen-specific and is delivered following the engagement of a costimulatory ligand on the APC with a cognate receptor on the T cell.

A key costimulatory receptor on T cells is CD28. CD28 is constitutively expressed on resting T cells and binds to both CD80 (B7-1) and CD86 (B7-2) on the APC[1-4]. A costimulatory signal is required not only for the full activation of naive T cells, but also may be required for the survival of memory and autoimmune effector cells[5-6]. At 24 to 48 hours following T cell activation, the T cell expresses CTLA4 on its surface, which engages the CD80 and CD86 molecules on the APC surface interfering with CD28's ability to bind to its ligands on the APC; CD80 and CD86 preferentially bind to CTLA4 with a much higher avidity than with CD28. Although the precise mechanisms are as yet unclear, CTLA4 expression is associated with a decrease in T cell activation.

After the T cell activity has been dampened, the CTLA4 recycles into the T cell's cytoplasm. The CTLA4 section of abatacept binds specifically to CD80 and CD86 (B7-1 and B7-2, respectively) and down-modulates the CD28-mediated costimulation of T cells. Thus, abatacept uses a segment of a molecule that

is part of the normal immune homeostatic mechanism to suppress T cell activity involved in the immunopathogenesis of autoimmune diseases. The FC region of abatacept was engineered with several point mutations designed to inactivate it. Because of these changes, abatacept does not mediate pathways such as antibody-dependent cell cytotoxicity or complement-dependent cytotoxicity[7].

### 2.1.1 INDICATIONS AND USAGE:

#### 2.1.1.1 Summary of Results of Investigational Program

The initial efficacy and safety of abatacept (previously known as CTLA4-Ig and BMS-188667) was established in clinical studies of RA, psoriasis, and multiple sclerosis. Currently, there are no active registration studies for psoriasis or multiple sclerosis. The subsequent registration program was in juvenile idiopathic arthritis (JIA), with data being collected from the ongoing long-term extension portion.

A full development program conducted in adult RA led to regulatory approval in the United States for this indication in December 2005, in Canada in June 2006, and in Europe in May 2007. In the US, abatacept now has two indications: (1) treatment of moderate to severe active RA in adults, and (2) treatment of moderate to severe JIA in patients who have failed prior therapy with disease-modifying anti-rheumatic drugs (DMARDs).

#### 2.1.1.2 Core Efficacy Studies of Abatacept in Rheumatoid Arthritis

The RA clinical program consisted of five core studies: IM101-100, IM101-101, IM101-102, IM101-029, and IM101-031 (N=2944)[8-12]. Each study had a double-blind placebo-controlled period of 6 months or 1 year. In Study IM101-100, subjects received abatacept 2 mg/kg, 10 mg/kg, or placebo. In the other studies, subjects received abatacept 10 mg/kg or a fixed dose that approximated 10 mg/kg or placebo.

Subjects who completed the double-blind period were offered entry into an uncontrolled, open-label period, in which all subjects received abatacept (in a fixed dose that approximated 10 mg/kg). A total of 2624 subjects in the core RA studies received the approved abatacept dose (10 mg/kg or a fixed dose that approximated 10 mg/kg) in the combined double-blind and open-label periods, representing 4603 person-years of exposure[13].

The efficacy of abatacept at a weight-tiered dose approximating 10 mg/kg was demonstrated in placebo-controlled studies in adult subjects with active RA and an inadequate response to methotrexate (IM101-100, IM101-102, and IM101-043), and in one study in adult subjects with active RA and an inadequate response to at least one TNF-blocking agent (etanercept and/or infliximab; IM101-029)[8-13]. Other studies have provided additional supportive evidence of efficacy. Abatacept (10 mg/kg or a fixed dose approximating 10 mg/kg) was significantly more effective than placebo in reducing the signs and symptoms of RA, including induction of major clinical response, improving physical function, slowing the progression of structural damage, and improving the quality of life in subjects with moderately to severely active RA.

In Studies IM101-102 and IM101-029, improvement in signs and symptoms assessed by the American

College of Rheumatology (ACR) 20 response rate versus placebo was observed after administration of the first dose, as measured at Day 15, and it was maintained through the double-blind study phase and for up to 3 years (in IM101-029 and IM101-102) and up to 5 years (in IM101-100)[14-15]. In the open-label extensions of IM101-100, IM101-102, and IM101-029, durable and sustained ACR20, ACR50, and ACR70 responses have been observed through 48, 24, and 18 months, respectively, of abatacept treatment[14-16].

### 2.1.2 Adverse Events

Abatacept, a selective costimulation modulator, is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte (T-cell)-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). An intravenous (IV) formulation of abatacept is approved in several countries including the United States and in the European Union (EU) for the treatment of moderate to severe rheumatoid arthritis (RA) in adults. Based on the clinical trial experience in adults, the risks that may be associated with the use of abatacept include infections, some of which may be serious or fatal, infusion related reactions, and an increase in respiratory adverse events and infections in patients with chronic pulmonary obstructive disease (COPD). Other potential risks may include the development of malignancies or autoimmune disorders, but an increased risk of these types of events have not been observed. As with the use of any protein therapeutic, antibodies against abatacept (immunogenicity) may develop. The rate of immunogenicity has generally been low and there has not been an apparent effect on safety, efficacy, or pharmacokinetics (PK).Abatacept is also currently approved for the treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in pediatric patients 6 years of age or older in several countries including the USA for patients aged 6 - 17 years old. Abatacept was generally safe and well tolerated in subjects with JIA.

For the period from the fourth quarter of 2005 to the third quarter of 2010 inclusive, the total number of patients exposed to abatacept is estimated to be equivalent to 60,225 patient-years of exposure. During the reporting period of this IB update, no previously unrecognized AEs with abatacept have been identified. Review of the safety data from the marketed use of abatacept does not reveal any new significant safety issue. The safety profile of abatacept remains similar to the profile established during clinical trials. The overall reporting rates of events of special interest for the current period are consistent with the cumulative reporting rates. Abatacept continues to have a favorable benefit-risk profile for the treatment of patients with RA and JIA. BMS will continue to monitor suspect adverse reactions in association with the use of abatacept.

Within the clinical studies, there were no reports of progressive multifocal leukoencephalopathy (PML). In the post-marketing experience, there was 1 healthcare professional report of recurrent PML that involved a 44-year-old female with previous history of PML while receiving methotrexate (10 years ago). The patient received 6 doses of abatacept prior to hospitalization due to status epilepticus. A brain magnetic resonance image scan was atypical for PML; a cerebral spinal fluid analysis was negative for the JC virus. At the time of the report, the patient was recovering from hemiparesis and expressive

dysphasia. The overall pattern of safety reporting raises no new safety concerns.

For the period of time from January 23, 2013 to December 22, 2013 one event deemed possibly related to abatacept was observed. A 69-year-old Caucasian female with history of stress fracture of the sacrum was hospitalized and experienced significant disability due to grade 3 lumbosacral plexitis approximately 4.5 years after initiation of therapy with abatacept. The investigator and BMS assessed lumbosacral plexitis as possibly related to abatacept study therapy.

The ongoing efficacy of abatacept is robust and persistent, based on ongoing clinical study data and confirmed by clinical practice in the marketplace. The long term safety profile of abatacept, in the context of maintained efficacy, is reassuring and confirms the positive benefit/risk of abatacept in the treatment of RA.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

## 2.2 Study Disease

### Chronic GVHD

Chronic graft-versus-host disease (cGVHD) is one of the major complications of allogeneic bone marrow or stem cell transplantation. Reported incidence rates of chronic GVHD after allogeneic transplantation range from 6% to 80%. cGVHD is believed to be caused by immunologic disparities between the donor's immune cells and the host's tissues although it's exact pathogenesis is unknown. The syndrome resembles autoimmune diseases such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, bronchiolitis obliterans and immune cytopenias. Chronic GVHD may be restricted to a single organ or be widespread. Chronic GVHD is the major cause of late post-allogeneic transplantation treatment related mortality and morbidity.

## 2.3 Rationale

There are no established effective treatments for steroid refractory cGVHD, a major cause of non-disease related morbidity and mortality in patients after an allogeneic stem cell transplantation[17]. Patients are often treated with prolonged courses of corticosteroids at high doses resulting in many undesirable side-effects. There has been no generally accepted steroid sparing agent in this disease although multiple drugs have been tested in clinical trials[18].

Activated T cells have been identified as key players in cGVHD and most drugs used in the treatment of cGVHD target T cells[19]. Since T cell activation is driven by constant alloantigen

stimulation, blockade of costimulation has been considered for many years as a way to prevent and/or treat GVHD[20-21]. More importantly in a murine model blockade of costimulation with CTLA4Ig was shown to reverse cGVHD[22]. Additionally first in vivo trials with abatacept as a means for costimulation blockade has been shown to prevent acute GVHD (aGVHD) and has prompted support in conducting larger randomized phase 2 trials to study the role of abatacept in aGVHD..

Abatacept has been approved by the FDA for the treatment of Rheumatoid Arthritis and Juvenile Idiopathic Arthritis. Our hypothesis is that abatacept will be safe and effective also in the treatment of cGVHD.

As part of the trial we plan to look into the mechanism of action of abatacept in patients with cGVHD. We hypothesize abatacept will exert its clinical effects by preventing the expansion of activated alloreactive lymphocytes and favoring the expansion of inhibitory cells. This is likely to manifest as an increase in T cells secreting inhibitory cytokines such as IL-10, increased numbers of Tregs and possibly an increase in the expression of inhibitory costimulatory molecules such as PD-1. We hypothesize that these immunologic changes will be associated with improvement in clinical manifestations of cGVHD.

We believe that abatacept is very promising as potential treatment in patients with cGVHD given its relatively safe side-effect profile, the immunologic rationale and the animal data that support blockade of costimulation in a disease where there is an urgent clinical need for more effective treatments. Therefore we propose the present trial that will examine the safety and efficacy of abatacept in patients with cGVHD and try to further elucidate its immunologic mechanisms of action.

### 2.4 Summary of Phase I Cohort

17 subjects have been enrolled and treated on the phase I study. Three patients were treated at a dose of 3 mg/kg without dose limiting toxicity. Following completion of the DLT evaluation period for participant 3, the second cohort was opened. Four participants initiated treatment on cohort 2, at a dose of 10mg/kg. One participant withdrew consent following one dose of treatment and therefore is not evaluable. All three evaluable participants who were treated at a dose of 10mg/kg tolerated the treatment without DLTs observed. Ten patients were treated in the expansion cohort at a dose of 10mg/kg. 7 patients have demonstrated a Partial Response in chronic GVHD as assessed by NIH consensus criteria. In addition, the mean prednisone dose decreased by 48% from study entry to 1 month post-treatment. There was one Abatacept related SAE (grade 4 pulmonary infection). A summary of Abatacept-related adverse events is provided

in the table below.

| Adverse Event | Grade | # of events |
|---|---|---|
| PULMONARY INFECTION | 3 | 6 |
| DIARRHEA | 1 | 2 |
| FATIGUE | 1 | 2 |
| RASH | 1 | 1 |
| PAIN, SKIN | 1 | 1 |
| PAIN | 2 | 1 |
| GASTRITIS | 2 | 1 |

Given the promising results in the phase I cohort with no dose limiting toxicity and 7 patients demonstrating improvement in manifestations of GVHD, a phase II cohort is added to further assess the response to Abatacept in patients with steroid refractory GVHD.

### 2.5 Correlative Studies Background

As stated in the prior section our hypothesis is that abatacept will exert its clinical effects by preventing the expansion of activated alloreactive lymphocytes and favoring the expansion of inhibitory cells. This is likely to manifest as an increase in T cells secreting inhibitory cytokines such as IL-10, increased numbers of Tregs and possibly an increase in the expression of inhibitory costimulatory molecules such as PD-1. We hypothesize that these immunologic changes will be associated with improvement in clinical manifestations of cGVHD.

Our lab has extensive experience with characterizing in analyzing post-transplant immune reconstitution and the balance of T cell activation and tolerance in cellular immunotherapy/tumor vaccine trials[26-27]. We have demonstrated that agents such as vitamin D as well as the conditioning regimen of TLI/ATG are associated with increased Tregs and suppression of alloreactivity[28]. We plan to look at the mechanism of action of abatacept in patients with cGVHD and correlate immunologic to clinical parameters in order to identify potential disease or response markers and/or further potential therapeutic targets. The impact of abatacept on the presence of alloreactive lymphocytes, the balance of activated vs. inhibitory cells, and the ability to respond to infection will be analyzed in correlative studies in vitro.

## 3. PARTICIPANT SELECTION

### 3.1 Screening and Eligibility

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in the Schedule of Study Assessments and unless otherwise specified, must take place within 28 days prior to initiation of therapy.

In the phase I portion of the study, approximately 3-22 subjects with steroid refractory cGVHD after an allogeneic stem cell/bone marrow transplantation will be screened for enrollment and must meet the eligibility criteria below. In the phase II portion, an additional 39 subjected will be screened for enrollment and must meet eligibility criteria.

### 3.2 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.2.1 Participants must be recipients of an allogeneic bone marrow or stem cell transplantation with myeloablative or reduced intensity conditioning regimens**.**

3.2.2 Participants must be at least 100 days after the transplantation or a donor lymphocyte infusion.

3.2.3 Participants must have cGVHD (as defined by the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease)

3.2.4 Participants may have either extensive or limited cGVHD requiring systemic treatment

3.2.5 Participants must have steroid refractory cGVHD, defined as having persistent signs and symptoms of chronic GVHD despite the use of prednisone at ≥ 0.5 mg/kg/day (or equivalent) for at least 4 weeks. Patients may remain on steroids while enrolled in the study.

For the phase II portion of the study: Steroid-refractory cGVHD is defined as having

persistent signs and symptoms of cGVHD despite the use of prednisone at ≥ 0.25 mg/kg/day (or 0.5 mg/kg every other day) for at least 4 weeks (or equivalent dosing of alternate corticosteroids) without complete resolution of signs and symptoms. Patients with either extensive chronic GVHD or limited chronic GVHD requiring systemic therapy are eligible.

3.2.6 No addition or subtraction of other immunosuppressive medications for at least 4 weeks prior to starting treatment.

3.2.7 On stable immunosuppressive regimen for 2 weeks prior to enrollment. Adjustment of immunosuppressive medications to maintain a therapeutic level is permitted.

3.2.8 Age ≥18 years at the time of signing the informed consent form.

**Reproductive Status: Definition of Women of Child-Bearing Potential (WOCBP).**

WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not post-menopausal (see definition below).

3.2.8.1 Post-menopause is defined as:

- Women who have had amenorrhea for ≥ 12 consecutive months (without another cause) and who have a documented serum follicle-stimulating hormone (FSH) level > 35 mIU/mL.
- Women who have irregular menstrual periods and a documented serum FSH level > 35 mIU/mL.
- Women who are taking hormone replacement therapy (HRT).

**The following women are WOCBP:**

- Women using the following methods to prevent pregnancy: Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products

such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides).

- Women who are practicing abstinence.
- Women who have a partner who is sterile (eg, due to vasectomy).

WOCBP must be using an acceptable method of contraception to avoid pregnancy throughout the study and for up to 10 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized.

3.2.8.2 WOCBP must have a negative serum or urine pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of HCG) within 0 to 48 hours before the first dose of study drug.

3.2.8.3 Women must not be breast-feeding.

3.2.8.4 Sexually active fertile men must use effective birth control if their partners are WOCBP.

3.2.9 Life expectancy of greater than > 3 months.

3.2.10 ECOG performance status ≤2 (see Appendix *A*).

3.2.11 Laboratory test results within these ranges:

- Absolute neutrophil count ≥ 1500/mm³
- Serum creatinine ≤ 2.0 mg/dL

  OR

  Renal function assessed by calculated creatinine clearance ≥ 60ml/min by Cockcroft-Gault formula (see Appendix B: Cockcroft-Gault estimation of CrCl).
- Total bilirubin ≤ 1.5 x ULN (unless hepatic dysfunction is caused by cGVHD)
- AST (SGOT) and ALT (SGPT) ≤ 3 x ULN (unless hepatic dysfunction is caused by cGVHD).

3.2.12 Patients must have a negative PPD skin test and not have a positive Quantiferon

assay or TB T-spot test. Indeterminate results, due to lack of response to the mitogen control reflecting their immunocompromised state, will be permitted.

3.2.13 Must possess the ability to understand and the willingness to sign a written informed consent document.

## 3.3 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.3.1 Any serious medical condition (including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia), laboratory abnormality, or psychiatric illness/ social situation that would prevent the subject from signing the informed consent form or limit compliance with study requirements.

3.3.2 Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

3.3.3 Use of any other experimental drug or therapy within 28 days of starting treatment with abatacept.

3.3.4 Use of biologic antibody therapy for cGVHD with rituximab, alemtuzumab, or ATG within 3 months of starting treatment with abatacept.

3.3.5 Use of TNF alpha inhibitors within four weeks prior to study entry.

3.3.6 Ongoing prednisone requirement >1 mg/kg/day (or equivalent)

3.3.7 New immunosuppressive medication or ECP within 28 days of starting treatment with abatacept.

3.3.8 Donor lymphocyte infusion within 100 days prior to enrollment.

3.3.9 Active malignant disease relapse or other active malignancy with the exception of

currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix or breast.

3.3.10 Participants who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.3.11 Known seropositive for or positive viral load for HIV or positive viral loads for infectious hepatitis, type B (HBV) or C (HCV).

3.3.12 Uncontrolled intercurrent active infection. Controlled infection on long term suppressive or maintenance therapy is permissible.

3.3.13 Use of live vaccines within four weeks of starting abatacept.

## 3.4 Inclusion of Women, Minorities and Other Underrepresented Populations

The inclusion and exclusion criteria are not expected to have a negative effect on the recruitment or retention of underrepresented populations.

# 4. REGISTRATION PROCEDURES

## 4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

## 4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each**

**inclusion and exclusion criteria listed on the eligibility checklist.**

**Reminder:** Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

   **Exception:** DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

# 5. TREATMENT PLAN

## 5.1 Treatment Regimen

Abatacept will be administered for a total of 6 doses. Doses 1-3 will be administered at two week intervals (+/-2 days). One month following Dose 3, abatacept will be administered, and given at four-week intervals (+/-2 days) for three doses (Doses 4-6.) Patients will be followed for toxicity for 28 days following last dose of abatacept. Patients will then be seen monthly for six months.

Patients will be seen every two weeks following each dose of abatacept. Toxicity assessment will be performed at every visit. Efficacy assessment will be performed at every treatment visit.

Patients' chronic GVHD will be scored according to the NIH scoring system (appendix D) at study entry and every 4 weeks. In addition patients will be asked to fill out a symptom scale (Appendix E) and their steroid dose will be recorded at study entry, on days receiving treatment, and at the toxicity assessment visit.

Extended-duration therapy: After completing 6 doses of abatacept and 1-3 months of follow up following the 6th dose, participants experiencing clinical benefit (complete or partial response; minor response not meeting NIH criteria for partial response) with acceptable toxicity will be permitted to continue on extended-duration abatacept treatment at the discretion of the treating physician. Participants may receive monthly doses of abatacept, at their assigned dose level, for up to a total of 12 doses of extended duration therapy. Patients receiving extended duration therapy will be followed monthly. Participants will be reassessed after every 3 months of extended abatacept treatment to determine if abatacept therapy should continue, at the discretion of the treating physician. The reason for continuing with extended duration therapy will be documented in the medical record.

Participants on extended-duration abatacept therapy will not be evaluable for phase I toxicity endpoints. Taper of other immune suppression medications during extended-duration abatacept will be permitted at the discretion of the treating physician.

Patients will undergo disease assessment at the following time points: Screening, within 1 week prior to Dose 4, at the Toxicity Assessment visit, and at the 3 and 6 month follow-up visits. Patients who receive additional treatment as part of the expansion portion of the study will also undergo disease assessment every three months,

#### 5.1.1 Disease Assessments

Leukemia: CBC/diff. Bone marrow biopsies will be performed as clinically indicated.

Multiple Myeloma: SPEP, Quantitative Immunoglobulins (IgG, IgA, IgM), Free Kappa/Lambda Ratio, Random UPEP. Bone marrow biopsies will be performed as clinically indicated.

Lymphoma: PET/CT or CT scan as clinically indicated

## 5.2 Pre-Treatment Criteria

5.2.1 Prior to each dose of abatacept, patients meet the following criteria:

- Absolute neutrophil count ≥ 1500/mm³
- Serum creatinine ≤ 2.0 mg/dL

  OR

  Renal function assessed by calculated creatinine clearance ≥ 60ml/min by Cockcroft-Gault formula (see Appendix B: Cockcroft-Gault estimation of CrCl).
- Total bilirubin ≤ 1.5 x ULN (unless hepatic dysfunction is caused by cGVHD)
- AST (SGOT) and ALT (SGPT) ≤ 3 x ULN (unless hepatic dysfunction is caused by cGVHD).

## 5.3 Abatacept Administration

Patients will receive a defined dose of abatacept by IV infusion over 30 minutes (+/- 10 minutes.) Patients will be monitored for acute reactions through routine vital signs. Vital signs (including: blood pressure, pulse, respiratory rate, and temperature) will be obtained 0-10 minutes prior to starting the infusion, 15 minutes after the start of the infusion (+/- 5 minutes), 0-10 minutes following completion of the infusion, and 30 minutes after completion of the infusion (+/-10 minutes.) There will be two dose levels, 3mg/kg and 10mg/kg.

5.3.1 Record of administration

Accurate records will be kept in the source documents of all drug administration (including dispensing and dosing).

## 5.4 Definition of Dose-Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)

MTD will be defined as the dose cohort where dose-limiting toxicity (DLT) is observed in ≤1 patient. DLT will be defined as any Grade 3 or 4 toxicity probably or definitely related to abatacept. Infection won't be considered a DLT as infections are expected in this patient population. Patients will be monitored for the occurrence of DLTs during the first 8 weeks of treatment. Patients who experience a DLT will be taken off-study and will not receive further treatment.

A cohort of 3 evaluable patients will enter at the first dose level of 3mg/kg . If no DLT is seen in the first 3 evaluable patients and all 3 patients complete at least 8 weeks on treatment, then a dose escalation to 10mg/kg will take place. If 2 or more of the 3 evaluable patients experience DLT at 3mg/kg, the study will be terminated early. If 1 of the 3 evaluable patients experiences DLT then 3 additional evaluable patients will be treated at that dose level. If there is no DLT in the additional 3 patients then dose escalation will take place. If 2 or more of the 3 evaluable patients experience DLT at 10mg/kg, the next cohort of 3 patients will be treated at 3mg/kg unless 6 patients have already been treated at that dose level. A minimum of six patients must be evaluated at the highest tolerated dose level, and fewer than 2 patients in 6 should experience DLT.

10 additional patients will be treated at the presumptive MTD to further characterize the toxicity and efficacy of abatacept.

## 5.5 Concomitant Medications and Supportive Care

### 5.5.1 Allowed concomitant therapy

Prednisone (or equivalent steroid) and other immunosuppressive medications will be continued concomitantly. Taper of prednisone, or any other immune suppression medications, will be permitted in responders at the discretion of the treating physician.

### 5.5.2 Recommended concomitant therapy

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate.

### 5.5.3 Prohibited concomitant therapy

The following medications are prohibited throughout the entire study period:

- Any biologic antibody therapies (such as but not limited to: TNF alpha inhibitors, alemtuzumab, rituximab, ATG or any other investigational biologic drugs).
- Live vaccines.
- Use of any investigational drug other than study medication.

## 5.6 Duration of Therapy

Abatacept will be administered for a total of 6 doses. Doses 1-3 will be administered every two

weeks (+/-2 days). Doses 4-6 will be administered every four weeks (+/-2 days.) Patients will be followed for toxicity for 28 days following last dose of abatacept. Patients will then be seen monthly for six months.

Participants who receive extended-duration therapy will initiate extended-duration therapy 1-3 months following the 6$^{th}$ dose of abatacept. Participants may receive up to 12 additional doses of abatacept. For extended duration therapy, deviations to the monthly schedule may be permitted following discussion with the overall PI. Following the last dose of abatacept, participants will be seen monthly for six months.

### 5.7 Follow-Up

At completion of 6 doses of abatacept, or upon early discontinuation, subjects will undergo a safety assessment 28 (+/-2) days post the last dose of protocol therapy. Patients who complete treatment on study will be followed monthly (+/- 7 days) for 6 months. Patients who discontinue study treatment will be followed for one month (+/- 7 days) post last dose of study treatment. In addition, off-study evaluations per the Schedule of Assessments, Section 10, will be done.

### 5.8 Criteria for Removal from Study

#### 5.8.1 Discontinuation of Study Treatment

- Patients experiencing a DLT: Any Grade 3 or greater anaphylaxis or Grade 4 organ toxicities judged to be probably or definitely related to abatacept will be permanently discontinued from study treatment.
- Treatment discontinuation may occur at any time the study subject withdraws consent or if the investigator feels that further treatment on the protocol will endanger the patient's safety.

If study drug administration is discontinued, the reason for discontinuation will be recorded.

### 5.9 Special Handling Instructions

Reconstitution and dilution should be performed in accordance with good practices rules, particularly with respect to asepsis.

# 6. DOSING DELAYS/DOSE MODIFICATIONS

## 6.1 Dose Modifications for Adverse Events

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0 (Appendix C: NCI CTCAE v4.0) used as a guide for the grading of severity.

If there is evidence of toxicity, as determined by laboratory tests or by clinical assessment that could place the subject at increased risk in the judgment of the investigator, administration of abatacept should be interrupted and the investigator should notify BMS. Subjects may be considered eligible to continue with abatacept treatm ent only if full resolution of the adverse event is documented. (If the AE was >grade 0 at baseline, the AE grade should return to baseline in order for the patient to resume treatment.) If the adverse event completely resolves to baseline but the next dose of abatacept cannot be administered within 14 days of the target date, then that scheduled dose should be skipped. The next dose of abatacept should then be administered on the next targeted day for administration. If patients do not meet criteria for treatment on the next targeted day of therapy, they will be removed from study. Skipped doses should be given at the end of the study and at 4 week intervals (patients should receive a total of 6 doses).

Dose reductions are not permitted.

Extended Duration Therapy: If there is evidence of toxicity, as determined by laboratory tests or by clinical assessment that could place the subject at increased risk in the judgment of the investigator, administration of abatacept should be interrupted and the investigator should notify BMS. Subjects may be considered eligible to continue with abatacept treatment only if full resolution of the adverse event is documented. (If the AE was >grade 0 at baseline, the AE grade should return to baseline in order for the patient to resume treatment.) If the adverse event completely resolves to baseline but the next dose of abatacept cannot be administered within 14 days of the target date, then that scheduled dose should be skipped. The next dose of abatacept should then be administered on the next targeted day for administration. If patients do not meet criteria for treatment on the next targeted day of therapy, they will be removed from study. Skipped doses will not be made up.

## 6.2 Management of Possible Acute Hypersensitivity Reactions to Abatacept

Hypersensitivity or acute allergic reactions may occur as a result of the protein nature of abatacept. The following information is provided to assist in the recognition of hypersensitivity reactions and in the management of those reactions should they occur during or after the administration of abatacept. Care should be taken to treat any acute toxicities expeditiously, should they occur.

Signs and management of potential acute hypersensitivity reactions:

| Sign | Management |
|---|---|

| | |
|---|---|
| **Symptomatic Hypotension** | Discontinue the abatacept infusion. Place the subject in the Trendelenburg position and administering IV fluid. Administer epinephrine, glucocorticoids, antihistamines, and pressor agents as indicated. |
| **Dyspnea** | Discontinue the abatacept infusion. Observe the subject for worsening of the event and for the appearance of additional signs and symptoms of anaphylaxis. Administer antihistamines, epinephrine, and glucocorticoids as indicated. |
| **Acute Pain in Chest, Back or Extremities** | These are potential signs of anaphylaxis. Follow the same treatment regimen as is used to treat dyspnea. |
| **Chills, Fever, Urticaria, or Generalized Erythema** | These may be signs of an allergic reaction to protein products. Treat by administration of acetaminophen and antihistamines. |

Patients will not receive prophylactic premedications to prevent hypersensitivity reactions. If a patient experiences a reaction, prophylactic premedication with acetaminophen 500-1000mg PO, diphenhydramine 25-50mg PO or IV, and hydrocortisone 25-50mg IV will be administered 15-60 minutes prior to subsequent infusions.

Patients who experience grade 3 or 4 anaphylaxis at any point on the study will be permanently discontinued from treatment and removed from the study.

## 7. ADVERSE EVENT REPORTING REQUIREMENTS

### 7.1 Definitions

#### 7.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if

they induce clinical signs or symptoms or require treatment or further diagnostic tests.

### 7.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- Specific Events Requiring Reporting as SAEs:
    - Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.
    - Although pregnancy, overdose and cancer (though not always serious by regulatory definition) these events must be handled as SAEs
    - Potential drug induced liver injury (DILI) is also considered an important medical event

- Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.
- Potential drug induced liver injury is defined as

    1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

    AND

    2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

    AND

    3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

### 7.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

#### 7.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Appendix F for a listing of expected adverse events associated with the study agent(s).

7.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

7.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

## 7.2 Expected Toxicities:

7.2.1 Because abatacept has immunomodulatory activity, subjects may be at increased risk of infectious complications. Significant infectious complications should be treated appropriately. Study medication should be withheld, and restarted only when the infection is clinically resolved. For a complete list of expected toxicities please refer to Appendix F and the Investigator's Brochure.

## 7.3 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study starting after initiation of study drug.

All AEs and SAEs whether reported by the participant, discovered during questioning,

directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

All pregnancies, regardless of outcome, must be reported to BMS, including pregnancies that occur in the female partner of a male study subject. All pregnancies must be followed to outcome.

## 7.4 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to BMS as described below.

### 7.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria

outlined in Section 7.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Jacalyn Rosenblatt, MD

Tel: 617-667 9920

Fax: 617-667 9922

Jrosenb1@bidmc.harvard.edu

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

### 7.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

### 7.4.3 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

### 7.4.4 Expedited reporting by investigator to the FDA

For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on

MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

SAEs will also be reported to the FDA in compliance with 21 CFR 312.32.

### 7.4.5 Expedited reporting by investigator to the BMS

Serious adverse events, whether related or unrelated to abatacept, must be recorded on the SAE page and reported within 24-hours to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs should be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If the investigator believes that an SAE is not related to the investigational product but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the potential relationship should be specified in the narrative section of the SAE report.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent within 24 hours to BMS. As follow-up information becomes available it should be sent within 24 hours using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

## 7.5 Adverse event updates/IND safety reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (i.e. not previously described in the Investigator Brochure). In the European Union, an event meeting these criteria is termed a Suspected Unexpected Serious Adverse Reaction (SUSAR). BMS will send investigators an expedited safety report (ESR) to notify them of such an event.

Other important findings that BMS may report as ESRs include increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (e.g. animal) study, important safety recommendations from a study data monitoring committee, or the decision by BMS to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, BMS will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, BMS will report suspected serious adverse reactions (whether expected or unexpected) to the relevant health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

## 7.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

## 7.7 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

# 8. DRUG FORMULATION AND ADMINISTRATION

## 8.1 Abatacept Description

Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons.

Abatacept is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the solution of abatacept is clear, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial of abatacept provides 250 mg abatacept, 500 mg maltose, 17.2 mg monobasic sodium phosphate, and 14.6 mg sodium chloride for administration.single-use vial of abatacept provides 250 mg abatacept, 500 mg maltose, 17.2 mg monobasic sodium phosphate, and 14.6 mg sodium

chloride for administration.

Abatacept will be supplied to the study site by Bristol Myers Squibb (BMS) from commercial supply. The site research pharmacy will reconstitute, dilute, and prepare abatacept for administration per the instructions below and in the Investigator Brochure.

### 8.2 Storage and Stability

Abatacept for infusion should be stored refrigerated at 2°C to 8°C (36°F to 46°F) with protection from long-term exposure to light. Do not use beyond the labeled expiration date of the

The diluted solutions of abatacept for injection may be stored at either refrigerated, 2°C to 8°C (36°F to 46°F), or room temperature, 15°C to 25°C (59°F to 77°F). The abatacept infusion solutions must be completed within 24 hours of dilution.

### 8.3 Compatibility

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Abatacept should not be infused concomitantly in the same intravenous line with other medicinal products. Abatacept should NOT be used with siliconised syringes

### 8.4 Handling and preparation

Reconstitution and dilution should be performed in accordance with good practices rules, particularly with respect to asepsis.

Use aseptic technique.

Abatacept is provided as a lyophilized powder in preservative-free, single-use vials. Each

Abatacept vial provides 250 mg of abatacept for administration. The abatacept powder in each vial must be reconstituted with 10 mL of Sterile Water for Injection, USP, using ONLY the SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL and an 18-

to 21-gauge needle. After reconstitution, the concentration of abatacept in the vial will be 25 mg/mL. If the abatacept powder is accidentally reconstituted using a siliconized syringe, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

If the SILICONE-FREE DISPOSABLE SYRINGE is dropped or becomes contaminated, use a new SILICONE-FREE DISPOSABLE SYRINGE from inventory. For information on obtaining additional SILICONE-FREE DISPOSABLE SYRINGES, contact Bristol-Myers Squibb 1-800-ABATACEPT.

During reconstitution, to minimize foam formation in solutions of abatacept, the vial should be rotated with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present. The solution should be clear and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.

1) To reconstitute the abatacept powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Rotate the vial with gentle swirling until the contents are completely dissolved.
2) Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present. After reconstitution, each milliliter will contain 25 mg (250 mg/10 mL).
3) The reconstituted abatacept solution must be further diluted to 100 mL as follows. From a 100 mL infusion bag or bottle, withdraw a volume of 0.9% Sodium Chloride Injection, USP, or 5% dextrose injection (D5W), equal to the volume of the reconstituted abatacept solution required for the patient's dose. Slowly add the reconstituted abatacept solution into the infusion bag or bottle using the same SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL. Gently mix. DO NOT SHAKE THE BAG OR BOTTLE. The final concentration of abatacept in the bag or bottle will depend upon the amount of drug added, but will be no more than 20 mg/mL. Any unused portions in the vials must be immediately discarded.
4) Prior to administration, the abatacept solution should be inspected visually for particulate matter and discoloration. Discard the solution if any particulate matter or discoloration is observed.
5) The entire, fully diluted abatacept solution should be administered over a period of 30 minutes and must be administered with an infusion set and a STERILE, NONPYROGENIC, LOW-PROTEIN-BINDING FILTER (pore size of 0.2 μm to 1.2

μm).

6) The infusion of the fully diluted abatacept solution must be completed within 24 hours of reconstitution of the abatacept vials. The fully diluted abatacept solution may be stored at room temperature at 15ºC to 25ºC (59ºF to 77ºF), or refrigerated at 2ºC to 8ºC (36ºF to 46ºF) before use.

7) Abatacept should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of abatacept with other agents.

### 8.5 Supplier(s)

Bristol-Myers Squibb Company will supply abatacept to study participants at no charge.

### 8.6 Dosage form

250 mg single-use vial

## 9. CORRELATIVE/SPECIAL STUDIES

Research blood (4 green top tubes containing 3-10cc each) will be obtained at every treatment visit and at discontinuation. Research blood will not be drawn during extended-duration treatment. The research blood will be taken to and the experiments will be performed in Dr Avigan's lab in the CLS building adjacent to the medical center.

We plan to look at the mechanism of action of abatacept in patients with cGVHD and correlate immunologic to clinical parameters in order to identify potential disease or response markers and/or further potential therapeutic targets. The impact of abatacept on the presence of alloreactive lymphocytes, the balance of activated vs. inhibitory cells, and the ability to respond to infection will be analyzed in correlative studies in vitro. The following experiments will be performed based on the availability of samples and reagents before treatment initiation and then every 4 weeks until the discontinuation visit.

PBMCs will be isolated prior to each dose of abatacept and at 1 and 3 months after completion

of therapy. The relative presence of CD4+ and CD8+ naive (CD45RA/CCR7+), central memory (CD45RO/CD62L+/CCR7+) and memory effector cells (CD45RO/CD62L-/CCR7-) will be quantified by multichannel FACS analysis. T cells will undergo further phenotypic analysis to determine the percentage of activated (CD4/CD25low, CD4/CD25/CD69) T cells and the level of expression of the inhibitory costimulatory molecule PD-1 by T cells. T cell expression of Th1 (IFNγ, IL-2) as compared to Th2 (IL-10, IL4) cytokines will be quantified. Expression of the cytolytic markers granzyme B and perforin will be assessed for CD8+ T cells.

The ratio of activated dendritic cells (DC1) to suppressive (DC2 ) cells has been associated with the risk of GVHD. The presence of DC1 and DC2 cells will be determined by quantifying DR+/CD11c+/lineage- and DR+/CD123+/lineage- cells.

The functional capacity of T cells with respect to alloreactivity, T cell inhibition, and response to mitogens and individual antigens will be assessed. DCs will be generated by culturing adherent mononuclear cells with GM-CSF and IL-4 for 1 week and then matured with TNFa. Alloreactive responses to patient derived and third party DCs will be measured by coculturing T cells with donor derived DCs and in a mixed lymphocyte assay. T cell responses to nonspecific stimuli will be determined by measuring proliferation and cytokine expression following exposure to anti-CD3/CD28 and PHA. Response to tetanus toxoid and influenza peptide will be determined to measure responses to recall antigens.

Regulatory T cells will be quantified by measuring CD4/CD25high and CD4/CD25/FOXP3+ T cells and low expression of CD127. Similarly, when cell yields allow, the CD25high population will be quantified. Functional characteristics of circulating T cells, including the ability to respond to mitogens (PHA) and recall antigens such as tetanus will be assessed. The ability of circulating T cell populations to function as regulatory T cells will be assessed by their ability to suppress, in a dose dependent fashion, 3rd party T cell responses to mitogens, tetanus and allogeneic dendritic cells.

## 10. STUDY CALENDAR

**Phase I and Phase II:**

Abatacept will be administered for a total of 6 doses. Doses 1-3 will be administered at two week intervals (+/-2 days). One month following Dose 3, abatacept will be administered, and given at four-week intervals (+/-2 days) for three doses (Doses 4-6.) Patients will be followed for toxicity for 28 days following last dose of abatacept. Patients will then be seen monthly for six months.

Patients will be seen every two weeks following each dose of abatacept. Toxicity assessment will

be performed at every visit. Efficacy assessment will be performed at every treatment visit.

Extended-duration therapy: After completing 6 doses of abatacept and 1-3 months of follow up following the 6th dose, participants experiencing clinical benefit (complete or partial response; minor response not meeting NIH criteria for partial response) with acceptable toxicity will be permitted to continue on extended-duration abatacept treatment at the discretion of the treating physician. Participants may receive monthly doses of abatacept, at their assigned dose level, for up to a total of 12 doses of extended duration therapy. Patients receiving extended duration therapy will be followed monthly. Deviations to the monthly schedule may be permitted following discussion with the overall PI. Participants will be reassessed after every 3 months of extended abatacept treatment to determine if abatacept therapy should continue, at the discretion of the treating physician. The reason for continuing with extended duration therapy will be documented in the medical record.

Participants on extended-duration abatacept therapy will not be evaluable for phase I toxicity endpoints. Taper of other immune suppression medications during extended-duration abatacept will be permitted at the discretion of the treating physician.

### Schedule of Study Assessments

| **Procedure** | **Screening** ≤ 28 days from First day of drug administration | **Treatment day (+/-2 days)** | **Follow-up Day (+/-2 days)** (Every 2 weeks) | **Toxicity Assessment Visit (+/-2 days)** (28 days after last dose) | **Monthly Follow-Up[0] (+/-7 days)** |
|---|---|---|---|---|---|
| Informed consent | X | | | | |
| Record prior medications, treatments | X | | | | |
| Record prior anti-cancer therapies | X | | | | |
| Physical examination, height[1] and weight | X | X | X | X | X |
| Vital Signs[2] | X | X | X | X | X |
| ECOG performance status (App.A) | X | X | X | X | X |

| | | | | | |
|---|---|---|---|---|---|
| GVHD scoring (App D ) | X | X | | X | X |
| GVHD Survey (App E) | X | X | | X | |
| ECG | X | | | X | |
| PFTs[3] | X | | | X | |
| Hematology[4] | X | X | X | X | X |
| Serum chemistry[5] | X | X | X | X | X |
| HIV, Hepatits B and C Serologies | X | | | | |
| Pregnancy testing | X | | | | |
| PPD and Quantiferon or TB T-spot | X | | | | |
| Disease Assessments[6] | X | X | | X | X |
| Research blood[7] | | X | | X | |
| Record adverse events | | X | X | X | X |
| Record concomitant therapies/procedures | X | X | X | X | X |

0. Participants who only receive 6 doses of abatacept will be evaluated monthly for 6 months following the toxicity assessment visit. Participants who receive extended-duration therapy will be evaluated monthly for 6 months following the last dose of treatment.

1. Height is only required at screening visit.

2. Vital signs (including: BP, pulse, RR and temperature) will be obtained 0-10 minutes prior to starting the infusion, 15 minutes after the start of the infusion (+/- 5 minutes), 0-10 minutes following completing of the infusion, and 30 minutes after completion of the infusion (+/-10 minutes.)

3. For patients with lung GVHD

4. To include CBC and differential

5. To include Na, K, Chl, CO2, BUN/Creat, Glu, Total Protein/Albumin, AST, ALT, Total Bilirubin, Calcium, Magnesium, Phosphorus

6. Patients will undergo disease assessment at the following time points: Screening, within 1 week prior to Dose 4, at Toxicity Assessment Visit, and at 3 and 6 month follow-up visits. Patients who receive additional doses of abatacept will undergo disease assessment at Dose 9 and 12. Please see Section 5.1.1 for details.

7. Four green top tubes (3-10cc each). Study bloods are not required during extended-duration therapy.

## 11. MEASUREMENT OF EFFECT

Patients' GVHD will be scored according to the NIH scoring system at study entry and every treatment visit. Figure 1 in Appendix D shows the consensus scoring system for individual organs. Organ sites considered for scoring include skin, mouth, eyes, GI tract, liver, lungs, joints and fascia, and the female genital tract. Each organ or site is scored according to a 4-point scale (0-3), with 0 representing no involvement and 3 reflecting severe impairment. Performance status is captured on a 0 to 3 scale, and check boxes note the presence or absence of other specific manifestations.

Participants will have the response of GVHD to abatacept classified according to the standardized cGVHD assessment per NIH guidelines, summarized below:

Complete response: Organ response: resolution of all reversible manifestations related to cGVHD in a specific organ; Overall response: resolution of all reversible manifestations in each organ or site of cGVHD involvement. Depending on relevant organ system involvement, patients will undergo repeat detailed assessment of ocular, oral, cutaneous, musculoskeletal and pulmonary systems.

Partial response –Organ response: at least 50% improvement in the scale used to measure disease manifestations related to cGVHD (e.g. a 50% decrease in skin rash from 80% BSA to 40% BSA), with a minimum of 25% improvement in the full scale as opposed solely to a percentage of the starting value. Overall response: improvement in measure at least one organ or site, without progression in measures at any other organ or site. Of note, for global ratings and categorical scales, a 1- point change in a 3- or 7- point scale or a 2- to 3- change on a 0- to 10- point scale (0.5 SD change) would be considered clinically meaningful. Additionally, the hallmark for response to therapy for bronchiolitis obliteraans syndrome (BOS) is stabilization of lung function with no further decrease in FEV1 during a 3-month period.

Non-responders (e.g.,minor response,stable disease): no changes in cGVHD meeting NIH criteria for partial response or disease progression.

Progressive disease: Organ progression: an absolute increase of at least 25% in the scale used to measure disease manifestations related to cGVHD. Of note, for global ratings and categorical scales, a 1-point change in a 3- or 7- point scale or a 2- to 3- change on a 0- to 10- point scale (0.5 SD change) would be considered progression. Additionally, 'clinical worsening of cGVHD' is not synonymous with progressive cGVHD per NIH criteria, as patients may experience worsening symptoms that do not meet objective NIH criteria for progression. If so, they still have the option of discontinuation of Abatacept.

In addition, patients will be asked to fill out a standardized symptom scale to self report symptoms using the validated GVHD Symptom Scale (Appendix E). Steroid dose will be recorded.

## 12. DATA AND SAFETY MONITORING

### 12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

| **Form** | **Submission Timeline** |
|---|---|
| Eligibility Checklist | Complete prior to registration with QACT |
| On Study Form | Within 14 days of registration |
| Baseline Assessment Form | Within 14 days of registration |
| Treatment Form | Within 10 days of the last day of the cycle |
| Adverse Event Report Form | Within 10 days of the last day of the cycle |
| Response Assessment Form | Within 10 days of the completion of the cycle required for response evaluation |
| Off Treatment/Off Study Form | Within 14 days of completing treatment or being taken off study for any reason |
| Follow up/Survival Form | Within 14 days of the protocol defined follow up visit date or call |

### 12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this trial. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed with the Principal Investigator, statistician and study team members. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the trial.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual, treatment regimen information, adverse events and serious adverse events reported by category, summary of any deaths on study, audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

## 12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related

activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

# 13. REGULATORY CONSIDERATIONS

## 13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

## 13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent

document must be retained in the medical record or research file.

### 13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

    - Title 21 Part 56 – Institutional Review Boards
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

    - Title 21 Part 312 – Investigational New Drug Application
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

### 13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the

study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

### 13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

# 14. STATISTICAL CONSIDERATIONS

This section reflects the design change made in May 2016, to incorporate a phase II portion, given the promising results observed in the phase I portion of the study. In the phase I portion of the study, dose escalation was completed with no DLTs observed. As of May 2016, 7 of the 16 evaluable patients demonstrated partial responses (2/3 in the 3mg/kg cohort and 5/13 in the 10mg/kg cohort).

## 14.1 Study Design/Endpoints

Phase I Portion

The primary endpoint of the phase I portion of the study is to determine the maximum tolerated dose (MTD) of abatacept. Dose-limiting toxicities (DLTs) is defined as any Grade 3 or 4 toxicity judged to be probably or definitely related to abatacept.

This is a standard 3+3 design with two escalating doses of abatacept to determine the MTD: 3 mg/kg (dose level 1) and 10 mg/kg (dose level 2). A cohort of 3 eligible patients will entered at each dose level. Patients will be considered unevaluable for the determination of MTD if they require removal from the study for reasons unrelated to therapy (i.e. lost to follow-up, patient withdrawal, relapse of disease) or die within 28 days of starting treatment without developing DLT and cause of death is unrelated to therapy. Additional patients can be added at that dose level in such events. All patients who receive any amount of abatacept will be evaluated for toxicity.

A cohort of 3 evaluable patients will enter at the first dose level of 3mg/kg . If no DLT is seen in the first 3 evaluable patients and all 3 patients complete at least 8 weeks of treatment, then a dose escalation to 10mg/kg will take place. If 2 or more of the 3 evaluable patients experience DLT at 3mg/kg , the study will be terminated early. If 1 of the 3 evaluable patients experiences DLT then 3 additional evaluable patients will be treated at that dose level. If there is no DLT in the 3 additional patients then a dose escalation will take place. If 2 or more of the 3 evaluable patients experience DLT at 10mg/kg, the next cohort of 3 patients will be treated at 3mg/kg unless 6 patients have already been treated at that dose level. A minimum of six patients must be evaluated at the highest tolerated dose level, and fewer than 2 patients in 6 should experience DLT.

Table 14.1 shows the probability of escalation under various true DLT rates. With this design, there is a 91% probability of escalation if the true rate of DLT is 10% and a 17% probability of escalation if the true DLT rate is 50%.

**Table 14.1: Probability of dose escalation**

| True Rate of DLT | 10% | 20% | 30% | 40% | 50% | 60% |
|---|---|---|---|---|---|---|
| Prob. of Escalation | 0.91 | 0.71 | 0.49 | 0.31 | 0.17 | 0.08 |

Once the MTD is established, an additional 10 patients will be treated at the MTD to provide a better estimate of the toxicity of abatacept. With 10 evaluable patients, the 90% confidence interval of the toxicity rate will be within +/- 28%. The MTD defined in this study will then be used to plan a larger multi-center phase II study.

Phase II Portion

The primary endpoint in the phase II portion of this study is the overall response rate (CR or PR) of using abatacept in treating chronic GVHD in this patient population. Given that the response rate in this patient population is currently estimated to be 20-30%,for the purpose of statistical design, the null hypothesis is that the response rate will be 25% and the alternative hypothesis is that the response rate is 45%

Based on data observed in the phase I portion, abatacept is safe and tolerable. Here, a one -stage design is considered, with accrual goal of 39 evaluable patients. Patients who start at least one dose of abatacept will be considered as evaluable. In the analysis, the following decision rule will be used to determine whether the agent will be worthy of further evaluation. Of the 39 evaluable patients, if the total number of patients with a response (CR or PR) is 14 or more, then this agent will be deemed as worthy of further evaluation for the treatment of chronic GVHD. Conversely, if the total number of responders is 13 or fewer, then this agent will be deemed as not worthy of further evaluation. With this design, the power is at least 0.90 under the alternative hypothesis of a response rate 45% or higher, with a type I error rate 0.09.

## 14.2 Secondary Objectives

Secondary endpoints include the efficacy of abatacept and immunologic effects of abatacept. Due to the exploratory nature and limited sample size, all secondary endpoints will be primarily descriptive. Our hypothesis of this trial is that abatacept will exert its clinical effects by preventing the expansion of activated T cells and favoring the expansion of inhibitory cells. To elucidate the immunologic effects of abatacept, in the laboratory correlative studies, we will

examine the changes of T cells (particularly, CD4 CD8, Treg, CD 28, memory T-cells), intracellular and serum cytokines, inhibitory costimulatory molecule PD-1, and dendritic cells pre and post treatment. If the sample size permits, we will also attempt to associate these immunologic changes with the clinical response to chronic GVHD. Overall survival and Progression-free survival will be estimated using the Kaplan-Meier curves. Non-relapse mortality and time to relapse will be estimated using cumulative incidence curves using each other as competing risks. Point estimates at 1-year after start of abatacept for the time to event outcomes will also be computed along with 90% confidence intervals.

### 14.3 Sample Size/Accrual

The sample size for the phase I portion will range from 3-22 evaluable patients, depending on the number of dose levels which are tested. For the phase II cohort, the sample size is 39 evaluable patients. DFCI and BIDMC are taking part in the study, and as such, accrual is anticipated to be be at least 50 patients per year and thus complete the accrual within a year.

Early Stopping rules for the phase I portion

If 2 or more DLTs are observed at the first dose level (3mg/kg) then the accrual will stop and the study will be terminated early.

## 15. PUBLICATION PLAN

The results from this trial will be submitted for publication to a peer reviewed journal.

## 16. REFERENCES

1. Azuma, M., et al., *B70 antigen is a second ligand for CTLA-4 and CD28.* Nature, 1993. **366**(6450): p. 76-9.
2. Freeman, G.J., et al., *Cloning of B7-2: a CTLA-4 counter-receptor that costimulates human T cell proliferation.* Science, 1993. **262**(5135): p. 909-11.
3. Linsley, P.S., et al., *Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors.* Immunity, 1994. **1**(9): p. 793-801.
4. Peach, R.J., et al., *Complementarity determining region 1 (CDR1)- and CDR3-analogous regions in CTLA-4 and CD28 determine the binding to B7-1.* J Exp Med, 1994. **180**(6): p. 2049-58.
5. Oliveira-dos-Santos, A.J., et al., *CD28 costimulation is crucial for the development of spontaneous autoimmune encephalomyelitis.* J Immunol, 1999. **162**(8): p. 4490-5.
6. Skak, K., et al., *TNF-alpha impairs peripheral tolerance towards beta-cells, and local costimulation by B7.1 enhances the effector function of diabetogenic T cells.* Eur J Immunol, 2003. **33**(5): p. 1341-50.
7. Davis, P.M., et al., *Abatacept binds to the Fc receptor CD64 but does not mediate complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity.* J Rheumatol, 2007. **34**(11): p. 2204-10.
8. Genovese, M.C., et al., *Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition.* N Engl J Med, 2005. **353**(11): p. 1114-23.
9. Kremer, J.M., et al., *Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial.* Arthritis Rheum, 2005. **52**(8): p. 2263-71.
10. Kremer, J.M., et al., *Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial.* Ann Intern Med, 2006. **144**(12): p. 865-76.
11. Kremer, J.M., et al., *Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig.* N Engl J Med, 2003. **349**(20): p. 1907-15.
12. Weinblatt, M., et al., *Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study.* Arthritis Rheum, 2006. **54**(9): p. 2807-16.
13. Abatacept(BMS-188667), *Summary of Clinical Safety.* BMS Document Control No. 930013008, 2005.
14. Kremer J, e.a., *Long-term efficacy and safety of abatacept through 3 years of treatment in*

*rheumatoid arthritis patients in the AIM and ATTAIN trials.* Arthritis Rheum, 2007. **56(9S):S300**.

15. Westhovens, e.a., *Maintained efficacy and safety of abatacept in rheumatoid arthritis patients receiving background methotrexate through 5 years of treatment.* Arthritis Rheum, 2007. **56(9S):S395**.
16. Genovese, M.C., et al., *Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy.* Ann Rheum Dis, 2008. **67**(4): p. 547-54.
17. Barton-Burke, M., et al., *Graft-versus-host disease: a complex long-term side effect of hematopoietic stem cell transplant.* Oncology (Williston Park), 2008. **22**(11 Suppl Nurse Ed): p. 31-45.
18. Joseph, R.W., D.R. Couriel, and K.V. Komanduri, *Chronic graft-versus-host disease after allogeneic stem cell transplantation: challenges in prevention, science, and supportive care.* J Support Oncol, 2008. **6**(8): p. 361-72.
19. Ferrara, J.L., et al., *Graft-versus-host disease.* Lancet, 2009. **373**(9674): p. 1550-61.
20. Taub, D.D., et al., *Induction of alloantigen-specific T cell tolerance through the treatment of human T lymphocytes with wortmannin.* J Immunol, 1997. **158**(6): p. 2745-55.
21. Wallace, P.M., et al., *CTLA4Ig treatment ameliorates the lethality of murine graft-versus-host disease across major histocompatibility complex barriers.* Transplantation, 1994. **58**(5): p. 602-10.
22. Via, C.S., et al., *Differential effect of CTLA4Ig on murine graft-versus-host disease (GVHD) development: CTLA4Ig prevents both acute and chronic GVHD development but reverses only chronic GVHD.* J Immunol, 1996. **157**(9): p. 4258-67.
23. Korhonen, R. and E. Moilanen, *Abatacept, a novel CD80/86-CD28 T cell co-stimulation modulator, in the treatment of rheumatoid arthritis.* Basic Clin Pharmacol Toxicol, 2009. **104**(4): p. 276-84.
24. Maxwell, L.J. and J.A. Singh, *Abatacept for rheumatoid arthritis: a Cochrane systematic review.* J Rheumatol. **37**(2): p. 234-45.
25. Mease, P., et al., *Abatacept in the treatment of patients with psoriatic arthritis: Results of a double-blind, randomized, placebo-controlled phase 2 trial.* Arthritis Rheum.
26. Avigan, D. and D. Tzachanis, *Cancer vaccines in hematologic malignancies: advances, challenges and therapeutic potential.* Expert Rev Vaccines. **9**(5): p. 451-4.
27. Rosenblatt, J., et al., *Generation of tumor-specific T lymphocytes using dendritic cell/tumor fusions and anti-CD3/CD28.* J Immunother. **33**(2): p. 155-66.

28. Rosenblatt, J., et al., *Immunomodulatory effects of vitamin D: implications for GVHD.* Bone Marrow Transplant. **45**(9): p. 1463-8.

## 17. Appendix A

### ECOG Performance Status Scale

| SCORE | DESCRIPTION |
|---|---|
| **0** | Fully active, able to carry on all pre-disease performance without restriction. |
| **1** | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. |
| **2** | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| **3** | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| **4** | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| **5** | Dead. |

## 18. Appendix B

**Cockcroft-Gault formula for Estimated Creatine Clearance**

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

## 19. Appendix C

# NCI CTC Version 4.0

**Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (http://ctep.cancer.gov). All appropriate treatment areas have access to a copy of the CTC Version**

## 20. Appendix D

Diagnosis of chronic GVHD requires the presence of at least 1 diagnostic clinical sign of chronic GVHD (e.g., poikiloderma or esophageal web) or the presence of at least 1 distinctive manifestation (e.g., keratoconjunctivitis sicca) confirmed by pertinent biopsy or other relevant tests (e.g., Schirmer test) in the same or another organ. Furthermore, other possible diagnoses for clinical symptoms must be excluded. No time limit is set for the diagnosis of chronic GVHD. The broad category of chronic GVHD includes (1) classic chronic GVHD (without features or characteristics of acute GVHD) and (2) an overlap syndrome in which diagnostic or distinctive features of chronic GVHD and acute GVHD appear together

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **PERFORMANCE SCORE:** ☐ **KPS ECOG LPS** | ☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%) | ☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%) | ☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%) | ☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%) |
| **SKIN** *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐ | ☐ No Symptoms | ☐ <18% BSA with disease signs but **NO** sclerotic features | ☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch) | ☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus |
| **MOUTH** | ☐ No symptoms | ☐ Mild symptoms with disease signs but not limiting oral intake significantly | ☐ Moderate symptoms with disease signs **with** partial limitation of oral intake | ☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake |
| **EYES** Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done | ☐ No symptoms | ☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca | ☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment | ☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca |
| **GI TRACT** | ☐ No symptoms | ☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%) | ☐ Symptoms associated with mild to moderate weight loss (5-15%) | ☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation |
| **LIVER** | ☐ Normal LFT | ☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN | ☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN | ☐ Bilirubin or enzymes > 5 x ULN |

**Figure 1.** Organ scoring of chronic GVHD. *AP may be elevated in growing children, and not reflective of liver dysfunction. †Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS)

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| LUNGS* FEV1 ☐ DLCO ☐ | ☐ No symptoms | ☐ Mild symptoms (shortness of breath after climbing one flight of steps) | ☐ Moderate symptoms (shortness of breath after walking on flat ground) | ☐ Severe symptoms (shortness of breath at rest; requiring $0_2$) |
| | ☐ FEV1 > 80% **OR** LFS=2 | ☐ FEV1 60-79% **OR** LFS 3-5 | ☐ FEV1 40-59% **OR** LFS 6-9 | ☐ FEV1 <39% **OR** LFS 10-12 |
| JOINTS AND FASCIA | ☐ No symptoms | ☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL | ☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL | ☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.) |
| GENITAL TRACT | ☐ No symptoms | ☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam | ☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam | ☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum |

**Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)**

| | | |
|---|---|---|
| Esophageal stricture or web___ | Pericardial Effusion___ | Pleural Effusion(s)___ |
| Ascites (serositis)___ | Nephrotic syndrome___ | Peripheral Neuropathy___ |
| M yasthenia Gravis___ | Cardiomyopathy___ | Eosinophilia > 500µl___ |
| Polymyositis___ | Cardiac conduction defects___ | Coronary artery involvement___ |
| Platelets <100,000/µl ___ | Progressive onset___ | |

OTHERS: Specify:_____

**Figure 1 (continued).** is preferred, but if DLCO is not available, grading using FEV1 should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established [29]. The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: >80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; <40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12. GVHD indicates graft versus host disease; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, Martin P, Chien J, Przepiorka D, Couriel D, Cowen EW,Dinndorf P, Farrell A, Hartzman R, Henslee-Downey J, Jacobsohn D, McDonald G, Mittleman B, Rizzo JD, Robinson M,Schubert M, Schultz K, Shulman H, Turner M, Vogelsang G, Flowers ME.
National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report.

Biol Blood Marrow Transplant. 2005 Dec;11(12):945-56.

## 21. Appendix E

*Please let us know whether you have been bothered by any of the following problems in the past month.*

| | Not at all | Slightly | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|
| **SKIN:** | | | | | |
| a. Abnormal skin color | 0 | 1 | 2 | 3 | 4 |
| b. Rashes | 0 | 1 | 2 | 3 | 4 |
| c. Thickened skin | 0 | 1 | 2 | 3 | 4 |
| d. Sores on skin | 0 | 1 | 2 | 3 | 4 |
| e. Itchy skin | 0 | 1 | 2 | 3 | 4 |
| **EYES AND MOUTH:** | | | | | |
| f. Dry eyes | 0 | 1 | 2 | 3 | 4 |
| g. Need to use eyedrops frequently | 0 | 1 | 2 | 3 | 4 |
| h. Difficulty seeing clearly | 0 | 1 | 2 | 3 | 4 |
| i. Need to avoid certain foods due to mouth pain | 0 | 1 | 2 | 3 | 4 |
| j. Ulcers in mouth | 0 | 1 | 2 | 3 | 4 |
| k. Receiving nutrition from an intravenous line or feeding tube | 0 | 1 | 2 | 3 | 4 |
| **BREATHING:** | | | | | |
| l. Frequent cough | 0 | 1 | 2 | 3 | 4 |
| m. Colored sputum | 0 | 1 | 2 | 3 | 4 |
| n. Shortness of breath with exercise | 0 | 1 | 2 | 3 | 4 |
| o. Shortness of breath at rest | 0 | 1 | 2 | 3 | 4 |
| p. Need to use oxygen | 0 | 1 | 2 | 3 | 4 |
| **EATING AND DIGESTION:** | | | | | |
| q. Difficulty swallowing solid foods | 0 | 1 | 2 | 3 | 4 |
| r. Difficulty swallowing liquids | 0 | 1 | 2 | 3 | 4 |
| s. Vomiting | 0 | 1 | 2 | 3 | 4 |
| t. Weight loss | 0 | 1 | 2 | 3 | 4 |
| **MUSCLES AND JOINTS:** | | | | | |
| u. Joint and muscle aches | 0 | 1 | 2 | 3 | 4 |
| v. Limited joint movement | 0 | 1 | 2 | 3 | 4 |
| w. Muscle cramps | 0 | 1 | 2 | 3 | 4 |
| x. Weak muscles | 0 | 1 | 2 | 3 | 4 |
| **ENERGY:** | | | | | |
| y. Loss of energy | 0 | 1 | 2 | 3 | 4 |
| z. Need to sleep more/take naps | 0 | 1 | 2 | 3 | 4 |
| aa. Fevers | 0 | 1 | 2 | 3 | 4 |
| **MENTAL AND EMOTIONAL:** | | | | | |
| bb. Depression | 0 | 1 | 2 | 3 | 4 |
| cc. Anxiety | 0 | 1 | 2 | 3 | 4 |
| dd. Difficulty sleeping | 0 | 1 | 2 | 3 | 4 |

Lee S, Cook EF, Soiffer R, Antin JH.

Development and validation of a scale to measure symptoms of chronic graft-versus-host disease.

Biol Blood Marrow Transplant. 2002;8(8):444-52.

## 22. Appendix F

Listed in Table 5.4.1 are ADRs that occurred with greater frequency (difference > 0.2%) in abatacept-treated subjects than in placebo-treated subjects. The list is presented by system organ class and frequency, using the following categories: very common (≥ 10%); common (≥ 1% < 10%); uncommon (≥ 0.1% < 1%); and rare (≥ 0.01% < 0.1%). Within each frequency grouping, undesirable effects are presented in order of decreasing frequency.

**Table 5.4.1: Adverse Drug Reactions in Placebo-controlled Studies**

| System Organ Class | Frequency | Adverse Drug Reaction |
|---|---|---|
| Infections and infestations | Common | Lower respiratory tract infection (including bronchitis), urinary tract infection, herpes simplex, upper respiratory tract infection (including tracheitis, nasopharyngitis), rhinitis |
| | Uncommon | Tooth infection, infected skin ulcer, onychomycosis |
| Neoplasms benign and malignant (including cysts and polyps) | Uncommon | Basal cell carcinoma |
| Blood and the lymphatic system disorders | Uncommon | Thrombocytopenia, leukopenia |
| Psychiatric disorders | Uncommon | Depression, anxiety |
| Nervous system disorders | Very Common | Headache |
| | Common | Dizziness |
| | Uncommon | Paraesthesia |
| Eye disorders | Uncommon | Conjunctivitis, visual acuity reduced |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Cardiac disorders | Uncommon | Tachycardia, bradycardia, palpitations |
| Vascular disorders | Common | Hypertension, flushing |
| | Uncommon | Hypotension, hot flush |
| Respiratory, thoracic and mediastinal disorders | Common | Cough |
| Gastrointestinal disorders | Common | Abdominal pain, diarrhea, nausea, dyspepsia |
| | Uncommon | Gastritis, mouth ulceration, aphthous stomatitis |
| Skin and subcutaneous tissue disorders | Common | Rash (including dermatitis) |
| | Uncommon | Increased tendency to bruise, alopecia, dry skin |
| Musculoskeletal, connective tissue and bone disorders | Uncommon | Arthralgia, pain in extremity |

**Table 5.4.1: Adverse Drug Reactions in Placebo-controlled Studies**

| System Organ Class | Frequency | Adverse Drug Reaction |
|---|---|---|
| Reproductive system and breast disorders | Uncommon | Amenorrhea |
| General disorders and administration site conditions | Common | Fatigue, asthenia |
| | Uncommon | Influenza-like illness |
| Investigations | Common | Blood pressure increased, liver function test abnormal (including transaminases increased) |
| | Uncommon | Blood pressure decreased, weight increased |

Source: Company Core Data Sheet, dated 19-Aug-2010.

**DANA-FARBER CANCER INSTITUTE**
**Nursing Protocol Education Sheet**

| | |
|---|---|
| **Protocol Number:** | **13-358** |
| **Protocol Name:** | **A Phase 1 Study of Abatacept in the Treatment of Patients with Steroid Refractory Chronic Graft Versus Host Disease (cGVHD)** |
| **DFCI Site PI:** | Rob Soiffer, MD |
| **DFCI Research Nurse:** | Mildred Pasek, RN; Susan Stephenson, RN |

***Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.***
***Please also refer to ONC 15: Oncology Nursing Protocol Education Policy***
***** Remember to check the ALERT PAGE*****

**SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL**

| | |
|---|---|
| **Study Design** | Activated T cells have been identified as key players in the cGVHD. **Abatacept** is a recombinant fusion protein that uses a segment of a molecule that is part of the normal immune homeostatic mechanism to suppress T cell activity involved in the immunopathogenesis of autoimmune diseases. **Study Design** – Section 1.1; **Study Rationale** – Section 2.3. **Abatacept** will be administered on Days 1, 15, 29, 57, 85 and 113 – Section 1.1. |
| **Dose Calc.** | • **Abatacept** doses are calculated in mg/kg – Section 5.1<br>• COE will use our institutional standard of practice for dose calculations. |
| **Study Drug Administration** | **Abatacept** *Administration* Guidelines are found in Sections 5.1 and 7.7<br>• IV, administered over 30 minutes on Days 1, 15, 29, 57, 85 and 113 – Section 5.1<br>• Vital signs must be obtained within 10 minutes of prior to the start of the infusion, 15 (+/- 5) minutes after the start of the infusion, within 10 minutes of the end of the infusion and 30 minutes after completion of the infusion (+/- 10 minutes) – Section 5.1<br>• Must use a sterile, nonpyrogenic, low-protein binding filter (pore size of 0.2 µm to 1.2µm) – Section 7.7<br>• Do not infuse concomitantly in the same IV line with other agents – Section 7.7<br>• Do not administer if particulate matter or discoloration is visualized – Section 7.7<br>• Please see Section 6.3 for management of acute **hypersensitivity reactions.** |
| **Dose Modifications & Toxicity** | *Dose Modifications/Dosing Delay for Toxicity* are outlined in Sections 6.1, 6.3 through 6.5 and Appendix F<br>• This protocol uses NCI CTCAE criteria, version 4.0 – Section 6.1<br>• The definition of a DLT is found in Section 5.4. |
| **Concomitant Meds** | *Concomitant Therapy* Guidelines are in Section 6.2<br>• Please review the cited sections for permitted, prohibited, and "use with caution" medications/therapies/foods |
| **Required Data** | *Study Calendar and Assessment Required data* are outlined in Section 9 |
| **Charting Tips** | **All study drugs require documentation of exact administration time.**<br>Please be sure to DOCUMENT study medication **actual** UP/DOWN times in medical record (e.g. LMR, eMAR, nursing notes). **Edit eMAR as needed to match the exact time given**.<br>• If there is a discrepancy in the infusion time, delay in administration, or infusion takes longer than is permitted by the guidelines of the protocol, please **document the reason for the discrepancy in the medical record.**<br>Please be sure to also DOCUMENT the required infusion vital signs, routes of administration. |

13-358: A Phase I study of abatacept in the treatment of patients with steroid refractory chronic Graft Versus Host Disease (cGVHD)

Name: _____
Study Number: _____
MRN: _____
Visit: _____

*Please let us know whether you have been bothered by any of the following problems in the past month.*

| | Not at all | Slightly | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|
| **SKIN:** | | | | | |
| a. Abnormal skin color | 0 | 1 | 2 | 3 | 4 |
| b. Rashes | 0 | 1 | 2 | 3 | 4 |
| c. Thickened skin | 0 | 1 | 2 | 3 | 4 |
| d. Sores on skin | 0 | 1 | 2 | 3 | 4 |
| e. Itchy skin | 0 | 1 | 2 | 3 | 4 |
| **EYES AND MOUTH:** | | | | | |
| f. Dry eyes | 0 | 1 | 2 | 3 | 4 |
| g. Need to use eyedrops frequently | 0 | 1 | 2 | 3 | 4 |
| h. Difficulty seeing clearly | 0 | 1 | 2 | 3 | 4 |
| i. Need to avoid certain foods due to mouth pain | 0 | 1 | 2 | 3 | 4 |
| j. Ulcers in mouth | 0 | 1 | 2 | 3 | 4 |
| k. Receiving nutrition from an intravenous line or feeding tube | 0 | 1 | 2 | 3 | 4 |
| **BREATHING:** | | | | | |
| l. Frequent cough | 0 | 1 | 2 | 3 | 4 |
| m. Colored sputum | 0 | 1 | 2 | 3 | 4 |
| n. Shortness of breath with exercise | 0 | 1 | 2 | 3 | 4 |
| o. Shortness of breath at rest | 0 | 1 | 2 | 3 | 4 |
| p. Need to use oxygen | 0 | 1 | 2 | 3 | 4 |
| **EATING AND DIGESTION:** | | | | | |
| q. Difficulty swallowing solid foods | 0 | 1 | 2 | 3 | 4 |
| r. Difficulty swallowing liquids | 0 | 1 | 2 | 3 | 4 |
| s. Vomiting | 0 | 1 | 2 | 3 | 4 |
| t. Weight loss | 0 | 1 | 2 | 3 | 4 |
| **MUSCLES AND JOINTS:** | | | | | |
| u. Joint and muscle aches | 0 | 1 | 2 | 3 | 4 |
| v. Limited joint movement | 0 | 1 | 2 | 3 | 4 |
| w. Muscle cramps | 0 | 1 | 2 | 3 | 4 |
| x. Weak muscles | 0 | 1 | 2 | 3 | 4 |
| **ENERGY:** | | | | | |
| y. Loss of energy | 0 | 1 | 2 | 3 | 4 |
| z. Need to sleep more/take naps | 0 | 1 | 2 | 3 | 4 |
| aa. Fevers | 0 | 1 | 2 | 3 | 4 |
| **MENTAL AND EMOTIONAL:** | | | | | |
| bb. Depression | 0 | 1 | 2 | 3 | 4 |
| cc. Anxiety | 0 | 1 | 2 | 3 | 4 |
| dd. Difficulty sleeping | 0 | 1 | 2 | 3 | 4 |

Patient Signature: _____ Date: _____

RRN/Provider Signature: _____ Date: _____

13-358: A Phase I Study of Abatacept in the Treatment of Patients with Steroid Refractory Chronic Graft Versus Host Disease (cGVHD)

Name: _____ MRN: _____

Study Number: _____ Visit: _____

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **Performance Score:** ☐ **KPS ECOG LPS** | ☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%) | ☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%) | ☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%) | ☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%) |
| **Skin** *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐ | ☐ No Symptoms | ☐ <18% BSA with disease signs but **NO** sclerotic features | ☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch) | ☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus |
| **Mouth** | ☐ No symptoms | ☐ Mild symptoms with disease signs but not limiting oral intake significantly | ☐ Moderate symptoms with disease signs **with** partial limitation of oral intake | ☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake |
| **Eyes** Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done | ☐ No symptoms | ☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca | ☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment | ☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca |
| **GI Tract** | ☐ No symptoms | ☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%) | ☐ Symptoms associated with mild to moderate weight loss (5-15%) | ☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation |
| **Liver** | ☐ Normal LFT | ☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN | ☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN | ☐ Bilirubin or enzymes > 5 x ULN |

**Figure 1.** Organ scoring of chronic GVHD. *AP may be elevated in growing children, and not reflective of liver dysfunction. †Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS)

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **LUNGS**[†] **FEV1** ☐ **DLCO** ☐ | ☐ No symptoms<br>☐ FEV1 > 80% **OR** LFS=2 | ☐ Mild symptoms (shortness of breath after climbing one flight of steps)<br>☐ FEV1 60-79% **OR** LFS 3-5 | ☐ Moderate symptoms (shortness of breath after walking on flat ground)<br>☐ FEV1 40-59% **OR** LFS 6-9 | ☐ Severe symptoms (shortness of breath at rest; requiring $0_2$)<br>☐ FEV1 ≤39% **OR** LFS 10-12 |
| **JOINTS AND FASCIA** | ☐ No symptoms | ☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL | ☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL | ☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.) |
| **GENITAL TRACT** | ☐ No symptoms | ☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam | ☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam | ☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum |

**Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)**

| | | |
|---|---|---|
| Esophageal stricture or web___ | Pericardial Effusion___ | Pleural Effusion(s)___ |
| Ascites (serositis)___ | Nephrotic syndrome___ | Peripheral Neuropathy___ |
| M yasthenia Gravis___ | Cardiomyopathy___ | Eosinophilia > 500µl___ |
| Polymyositis___ | Cardiac conduction defects___ | Coronary artery involvement___ |
| Platelets <100,000/µl ___ | Progressive onset___ | |

**OTHERS:** Specify:_____

**Figure 1 (continued).** is preferred, but if DLCO is not available, grading using FEV1 should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established [29]. The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: >80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; <40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12. GVHD indicates graft versus host disease; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Based on observations checked in the above table, select the severity of chronic GVHD for this assessment.

- None
- Mild chronic GVHD involves only 1 or 2 organs or sites (except the lung: see Note), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites).
- Moderate chronic GVHD involves (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate chronic GVHD.
- Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD. Note: A lung score of 1 will also be considered moderate chronic GVHD. Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.

RRN/Provider Signature: _____ Date: _____