A Randomized Phase 2 Study of Obinutuzumab for Prevention of Chronic Graft-vs.-Host Disease After Allogeneic Peripheral Blood Stem Cell Transplantation

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A Randomized Phase 2 Study of Obinutuzumab for Prevention of Chronic Graft-vs.-Host Disease After Allogeneic Peripheral Blood Stem Cell Transplantation

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Study Agent: Obinutuzumab (Gazyva©, Genentech, Inc)

Study Exempt from IND Requirements per 21 CFR 312.2(b)

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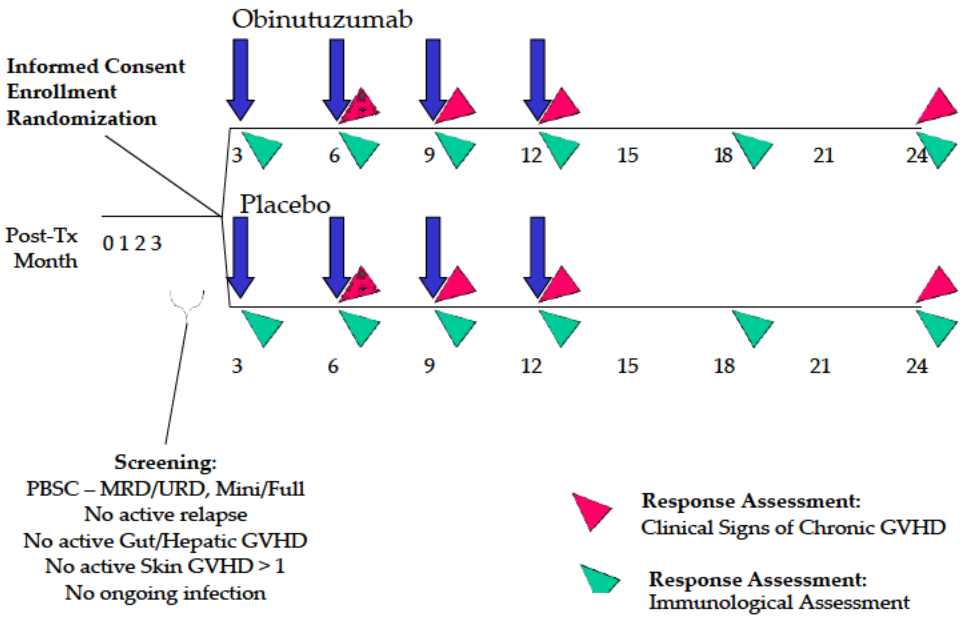
SCHEMA


Obinutuzumab
Informed Consent
Enrollment
Randomization
3
6
9
12
15
18
21
24
Placebo
Post-Tx
Month
0 1 2 3
3
6
9
12
15
18
21
24
Screening:
PBSC – MRD/URD, Mini/Full
No active relapse
No active Gut/Hepatic GVHD
No active Skin GVHD > 1
No ongoing infection
Response Assessment:
Clinical Signs of Chronic GVHD
Response Assessment:
Immunological Assessment

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1. OBJECTIVES

1.1 Study Design

This is a prospective, multicenter, randomized phase II trial of prophylactic obinutuzumab vs. placebo for prevention of chronic Graft vs. Host Disease (cGVHD) after Hematopoietic Cell Transplantation (HCT)**.** A single dose of obinutuzumab or placebo will be administered prophylactically at 3, 6, 9 and 12 months after HCT. Clinical and immunological endpoints are measured sequentially. 200 subjects will be randomized and analyzed in a modified intention-to-treat fashion.

1.2 Primary Objectives

The primary objective is to determine the effect of obinutuzumab prophylaxis on the incidence of corticosteroid-requiring cGVHD after allogeneic HCT. The primary endpoint of this phase II trial is the rate of corticosteroid-requiring cGVHD one year after HCT.

1.3 Secondary Objectives

Secondary objectives are to determine the overall rate of cGVHD after HCT, the rate of NIH moderate-severe cGVHD after HCT, the cumulative incidence of non-relapse mortality and relapse, adverse hematologic events and infections, immunosuppression-free survival (IFS) at 1 and 2 years from transplantation, progression-free and overall survival at 1 and 2 years from transplantation, and immunologic correlates of B cell depletion.

2. BACKGROUND

2.1 Chronic GVHD and B Cells

cGVHD involves inflammatory T- and B-cell responses against allogeneic and autologous antigens and is the most important late complication of allogeneic HCT.[1] With the increasing use of mobilized peripheral blood progenitor cells, and a gradual reduction in early HCT-related mortality,[2] a steady increase in the incidence of cGVHD has occurred. As a result, cGVHD is the leading cause of late morbidity, impaired quality of life, and mortality after allogeneic HCT.[1;3;4]

The mainstay of treatment of cGVHD is systemic corticosteroids, which are associated with incomplete responses and considerable toxicity. Aside from corticosteroids, there are no standards for the treatment of cGVHD, and management of these patients is challenging. There is a desperate need for effective therapeutics in cGVHD, but a preventative approach would be more fruitful. Graft manipulation (through *in vivo* or *ex vivo* T cell depletion or $CD34^+$ selection) can prevent cGVHD,[5;6] but graft manipulation has not been associated with an improvement in overall survival due to excess mortality associated with opportunistic infections and possibly relapse. Allogeneic tolerance induction with post-HCT cyclophosphamide may prevent cGVHD, but long-term outcomes have not been compared with traditional GVHD prevention strategies.[7]

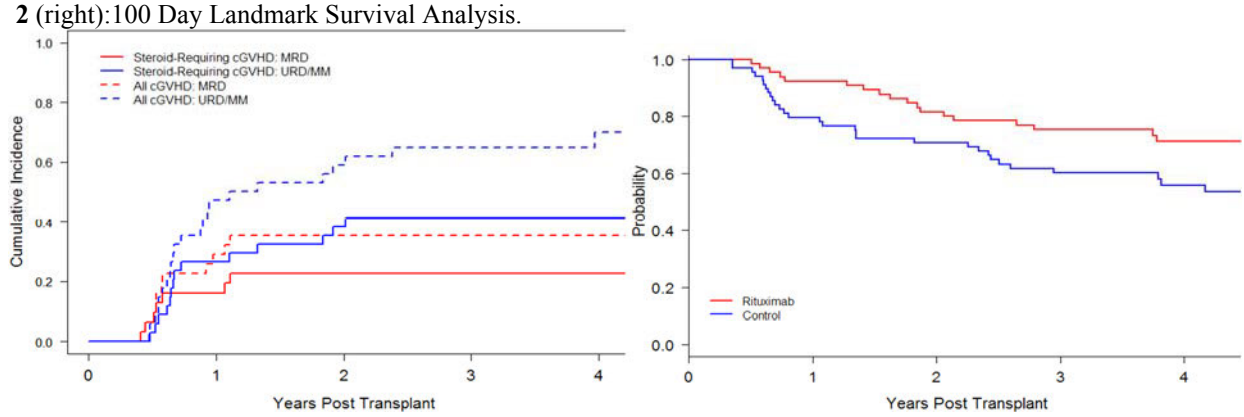
Based on our initial association between the development of anti-H-Y antibodies in sex-mismatched HCT and the occurence of cGVHD,[8] we and other groups have reported on the use of B cell depletion with rituximab as therapy for established cGVHD.[9;10] Common to all reported studies, rituximab administration is safe with a low incidence of adverse events. The response rate to a 4 week course of therapy in steroid-refractory settings (375 mg/m^2/week in most series), has been as high as 83%,[11] although response rates in

the 65% range are more commonly reported.[10] Cutaneous and myofascial disease were the most responsive in most series.

Several novel strategies have been attempted in cGVHD therapy using rituximab. Miklos *et al* have performed a pilot study of rituximab in combination with corticosteroids as initial therapy of cGVHD. 35 subjects with new-onset cGVHD that required corticosteroid treatment received rituximab (375 mg/m^2/week x 4) in combination with prednisone (1 mg/kg/day). A second course was allowed for incomplete responses. Response, defined as a complete or partial response with a prednisone dose of <0.25 mg/kg/day, was noted in 40% of subjects at 6 and 12 months, suggesting promising but incomplete activity. While there were 6 deaths from cGVHD within 12 months of rituximab therapy, only 2 subjects suffered a relapse of their malignancy.[12]

Given the promising activity of rituximab in the treatment of established cGVHD, and reports of cGVHD prevention with peri-HCT B cell depletion,[13;14] we explored the role of rituximab as prevention of cGVHD.[15] In this phase II trial (DFCI 05-377), rituximab (375 mg/m^2) was administered at 100 days, 6, 9 and 12 months after HCT (n=65). The cumulative incidence of cGVHD and systemic corticosteroid-requiring cGVHD at 2 years from HCT were 48% and 31% respectively, lower than rates in a concurrent control cohort (60%, p=0.1 and 48.5%, p=0.015, respectively). In related donors, the incidence of cGVHD and corticosteroid-requiring cGVHD at 2 years was 35% and 23%, whereas the corresponding figures in unrelated donors was 59% and 38% (Figures 1, 2). Rituximab was safe, with no severe infusional events and a 2 year cumulative incidence of grade 3-5 infections of 15%. There was no difference in relapse incidence (34% vs. 28%, p=0.79), but treatment-related mortality at 4 years from HCT was significantly lower in treated subjects when compared with controls (5.1% vs. 19.0%, p=0.02), and overall survival was superior at 4 years (71% vs. 56%, p=0.05). In a multivariable regression model, only rituximab use (HR 0.56, 95% CI 0.31-1.00, p=0.048) and high/very high disease risk index (HR 1.90, 95% CI 1.02-3.53, p=0.04) were significantly associated with overall survival.

Figure 1 (left): Incidence of cGVHD with rituximab cGVHD prophylaxis, stratified by donor type. **Figure 2** (right):100 Day Landmark Survival Analysis.



In a similar experience, Miklos and colleagues also tested the role of rituximab as prevention of cGVHD, and reported similar outcomes using a TLI/ATG preparative regimen.[16] In this experience involving 35 subjects, Rituximab (375 mg/m^2) was infused weekly (days +56, 63, 70, 77). The cumulative incidence of cGVHD was 20%, which is lower than the published rates of cGVHD using this regimen.[17]

2.2 Study Agent

Obinutuzumab (also known as RO5072759, GA101, Gazyva) is a humanized glycoengineered type II anti-CD20 monoclonal antibody (mAb). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics: high-affinity binding to the CD20 antigen, high antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP); low complement-dependent cytotoxicity (CDC) activity; and high direct cell death induction. These nonclinical features of obinutuzumab may translate into an anti-CD20 monoclonal antibody with superior clinical efficacy compared to other anti-CD20-mAb.

Obinutuzumab is FDA-approved for use in combination with chlorambucil for the treatment of individuals with previously untreated chronic lymphocytic leukemia.

Obinutuzumab will be provided by Roche/Genentech Inc.

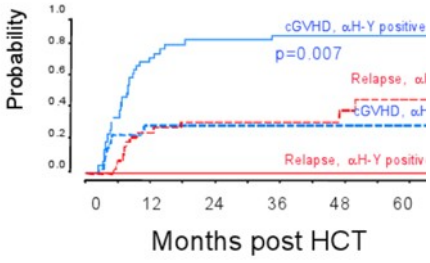
2.3 Rationale

In both the preliminary experiences of prevention of cGVHD with rituximab, prevention of cGVHD was incomplete. While it is understood that B cells are not entirely responsible for the pathogenesis of cGVHD, it is hypothesized that a more potent anti-B cell agent could be a more effective prophylaxis agent, since it is known that rituximab-unresponsive cGVHD patients have B cells with a $CD20^{Lo}$ phenotype and persistent elevations in BAFF,[18] rendering them more resistant to apoptosis via activation of the BCR pathway.[19]

We therefore propose a randomized, placebo-controlled Phase II trial of obinutuzumab. The size and randomized nature of this multicenter study has the potential to change the field of allogeneic HCT, and could result in improved patient outcomes across multiple tumor types, and across all conditioning intensities.

2.4 Correlative Studies Background

Figure 3: Association between anti-H-Y antibodies with cGVHD and protection from relapse



While many mHA are likely involved in cGVHD, the F→M HCT model provides a convenient set of known mHA whose antibody responses can be tracked. The Miklos lab has identified a series of 9 highly immunogenic minor histocompatibility (mHA) proteins on the Y chromosome (H-Y proteins). Subjects who underwent F→M HCT, were found to have significantly higher levels of anti-H-Y IgG antibodies, which correlated with a higher rate of cGVHD after HCT. As shown in Figure 3, H-Y antibodies are associated with a higher probability of cGVHD but lower levels of relapse, displaying both the GVHD and GVL effects of the allo-immune response.[8] While antibody responses in humans are correlated with cGVHD, it is important to note that in the mouse, deposition of IgG is involved in the pathology of cGVHD.

The DBY-2 peptide (KNDPERLDQQLANLDLNSEK) contains the DBY-2 epitope, frequently recognized in allogeneic F→M antibody responses that occur following HCT. Miklos was able to demonstrate the presence of circulating B cells expressing immunoglobulin receptors that specifically bind DBY-2. In a retrospective analysis of 28 subjects undergoing F→M HCT without prior cGVHD, DBY-2–binding B cells were detected in 16 subjects (57%) 6 months after HCT, with appropriate negative controls, including healthy female donors or male donor PBMC incubated with high-titer anti–DBY-2 IgG (Figure 4).[20] Importantly, 15 of these 16 developed cGVHD, including 6 who were diagnosed at the time of the anti-DBY-2 analysis. The absolute and relative number of DBY-2–specific B cells was significantly higher 6

months after HCT in patients who developed NIH moderate or severe cGVHD compared with those with NIH mild cGVHD or no cGVHD at all (P = 0.02; Figure 5). It is important to note that none of the patients with detectable anti-DBY-2 B cells yet had detectable circulating anti-DBY-2 IgG, suggesting that the detection of the B cell is a more relevant marker of impending cGVHD than identification of the circulating antibody. If the anti-DBY-2 antibody is pathogenic then it also argues that intervention prior to the elaboration of the anti-DBY-2 antibody may be fruitful in cGVHD prevention. The phenotype of the DBY-2 specific B cells corresponds to the commonly accepted phenotype for naïve or transitional B cells ($CD19^+IgM^+IgD^+CD27^-CD38^+CD5^-$), which allows more precise identification of the target B cell for further interventional strategies.

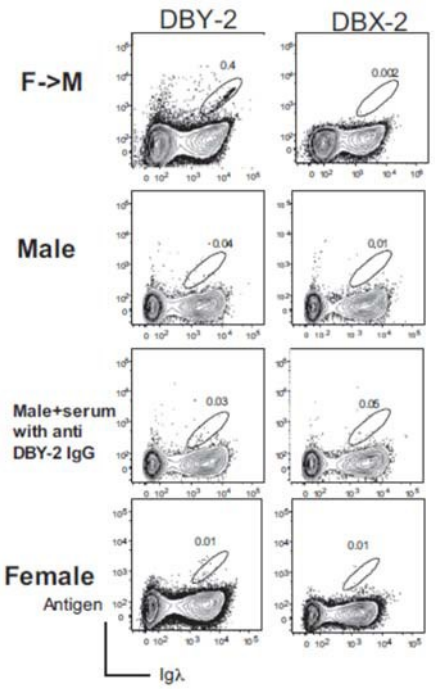
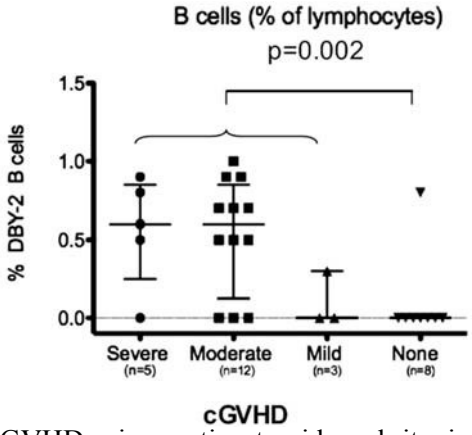


Figure 4 (left): DBY-2–binding B cells are detected in some F→M patients after HCT but not in healthy male and female donors (left column). Data for the X chromosome homologue DBX-2 are shown in right column. Data for 1 representative F→M HCT patient, 6 months after HCT (top) and for healthy controls (2nd through 4th panels). (Adapted from Sahaf *et al*, 2013).

Figure 5 (below): HY-specific B-cells predict cGVHD severity.



In the study cited above of primary therapy of cGVHD using corticosteroids and rituximab, cGVHD clinical response was predicted by a naïve ($CD19^+CD38^-IgD^+CD27^-$) B cell phenotype (p=0.03).[12] 15 cGVHD subjects underwent had F→M HCT, and 6 (38%) were H-Y IgM positive while 9 (56%) were IgG positive at cGVHD diagnosis. Among 15 F→M HCT recipients with cGVHD treated with rituximab, 11 responded, and both H-Y IgM and IgG became undetectable for at least 6 months following rituximab. In contrast, the 4 F→M subjects who did not respond remained H-Y IgG positive. Moreover, 2 subjects that redeveloped H-Y IgG later had recurrent cGVHD. H-Y antigen-specific B cells depleted after rituximab recovered in 6 of the 11 F→M assayed, suggesting that alternative anti-B cell strategies are required.

In the Stanford trial of primary prevention of cGVHD with rituximab, rituximab administration significantly reduced B cell allogeneic immunity. In 10 F→M recipients enrolled in this trial, there was complete prevention of alloreactive H-Y antibody development, and none of these subjects developed cGVHD. In comparison, among 25 F→M HCT patients who used the same TLI-ATG conditioning regimen but without prophylactic rituximab during this time period, 14 of the 25 (56%) developed H-Y antibodies, with 13 of the 25 (52%) developing cGVHD (p=0.01).[16] Similarly, in our trial of primary cGVHD prevention with rituximab (DFCI 05-377), of 13 F→M recipients, none developed anti-DBY antibodies between 6 months and 1 year from HCT, whereas 4 of 10 F→M control recipients developed anti-DBY antibodies in the same time period (p=0.02).

In this clinical trial, samples from all F→M recipients will be collected and analyzed for the presence of pathogenic alloreactive H-Y antibodies as well as pathogenic anti H-Y B cells. Samples will also be analyzed for non H-Y restricted antibodies (preliminary data not shown).

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Subjects deemed potentially eligible by their treating physicians will be screened for enrollment after d+60 from transplantation

3.1.2 Patients who have undergone either ablative or non-myeloablative allogeneic stem cell transplantation are eligible.

3.1.3 Peripheral blood stem cells must have been used as the stem cell source.

3.1.4 Patients must have received transplantation from donors (both related and unrelated) who are identical at 8 HLA loci (A, B, C and DRβ1), or mismatched at no more than 1 locus (7/8). Among related donors, HLA C typing is not required (6/6 HLA matches). Class I typing is to be performed by PCR-SSP techniques and CDC techniques. Class II typing is performed by PCR-RFLP +/- PCR-SSP techniques.

3.1.5 No evidence of relapsed or residual malignancy within 30 days of trial entry. All patients must undergo appropriate staging for their malignancy (i.e. bone marrow aspiration for the leukemias and PET-CT scanning for the lymphomas). Evidence of a persistent cytogenetic abnormality will constitute evidence of residual or relapsed disease in the leukemias, where present. Individuals with CLL are eligible if there is no more than 20% residual leukemia in the bone marrow at the time of study entry.

3.1.6 Patients who have undergone a non-myeloablative stem cell transplant must have > 80% donor hematopoiesis within 30 days of study enrollment. Chimerism within 30 days of study entry must be greater than, equal to, or no more than 5% less than the chimerism measured at approximately day+30 (if performed).

3.1.7 Age ≥ 18.0

3.1.8 ECOG performance status ≤2 (Karnofsky ≥60%) (See Appendix A)

3.1.9 Participants must have normal marrow function as defined by:

- WBC ≥ 2,500/μL
- Absolute Neutrophil Count ≥ 1,000/μL
- Platelets ≥ 50,000/μL

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.1.11 The effects of obinutuzumab on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of obinutuzumab administration.

3.2 Exclusion Criteria

3.2.1 Allogeneic stem cell transplantation using a single or multiple umbilical cord blood units or using bone marrow.

3.2.2 Allogeneic stem cell transplantation using in vivo or ex vivo T cell depletion, either by cell manipulation or with T cell depleting antibodies (Any anti-thymocyte globulin preparation or alemtuzumab given within 30 days of transplantation)

3.2.3 Participation in a clinical trial evaluating another preventative strategy for chronic GVHD, or ongoing participation in a clinical trial for therapy of acute GVHD. Prior completion of experimental therapy for acute GVHD is permissible if the experimental agent was used > 30 days prior to enrollment.

3.2.4 Any evidence of ongoing gastrointestinal or hepatic acute GVHD, or evidence of greater than ongoing Stage I cutaneous acute GVHD. Ongoing, tapering therapy for resolved acute GVHD is permissible.

3.2.5 Any evidence of prior active or resolved chronic GVHD.

3.2.6 Any evidence of cGVHD or late aGVHD between enrollment and first dose of obinutuzumab.

3.2.7 History of severe allergic reaction to obinutuzumab

3.2.8 No Donor Lymphocyte Infusion (DLI) prior to day 100, and no plans for a DLI in the upcoming 30 days.

3.2.9 Evidence of any active uncontrolled infection (bacterial, viral or fungal) or evidence of natural exposure to Hepatitis B, Hepatitis C or HIV. Evidence of Hepatitis B exposure includes the presence of Hepatitis B surface antigenemia, a positive serological test for Hepatitis B core antibody or nucleic acid testing (NAT testing) that is positive for Hepatitis B. Vaccination to Hepatitis B is not an exclusion criteria. Testing done in the pre-transplant setting is sufficient to rule out infection.

3.2.10 Pregnancy or lactation. Negative pregnancy test is required within the screening window for women of child bearing potential.

3.2.11 Active use of any other investigational agents.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

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

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

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

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the DFCI by the Study Coordinator.

Following registration, participants should begin protocol therapy within 14 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

For information regarding the registration process, please refer to section 3.7 of the DSMP located in appendix D.

5. TREATMENT PLAN

5.1 Stem Cell Transplantation

All subjects will undergo allogeneic stem cell transplantation according to locally approved clinical trials or treatment plans. No specific conditioning regimen or GVHD prophylaxis regimen is mandated. The stem cell source must have been peripheral blood stem cells. No *in vitro* or *in vivo* T cell depletion is permitted. Participation in a clinical trial evaluating novel approaches to acute GVHD prophylaxis is not

allowed, but participation in a trial evaluating novel agents for therapy of acute GVHD is allowed, as long as the experimental agent was discontinued > 30 days prior to trial entry.

5.2 Trial Screening and Entry

Subjects deemed potentially eligible by their treating physicians will be screened for enrollment after day +60 from transplantation. Once screened, deemed eligible and registered, the subject will be randomized in a 1:1 to the active treatment (obinutuzumab) or placebo arm. Stratification will be by center, conditioning intensity and donor type, using a permuted block algorithm within strata. Blinding will be maintained at the level of the Research Pharmacy.

5.3 Treatment Regimen

Obinutuzumab or placebo will be administered at a dose of 1000 mg, intravenously, at 3, 6, 9 and 12 months from transplantation. The first dose is administered at day +90 (+/- 10 days), followed by doses at days +180 (+/- 10 days), 270 (+/- 10 days) and +365 (+/- 10 days).

Premedication with histamine blockers and acetaminophen will be provided (see Section 5.5 below), but corticosteroids at the time of obinutuzumab infusion are not permitted. Placebo will be administered with the same premedications and precautions.

No dose modifications are permitted, although doses may be skipped based on unresolved toxicity (see Section 6: Dosing Delays/Dose Modifications). If a dose is missed, the investigator may choose to continue with protocol-specified treatments within the next dosing time period.

5.4 Pre-Treatment Criteria for Doses 1, 2, 3 and 4

There are no criteria for treatment at dose 1. Dose 1 will be administered at the discretion of the provider.

Criteria for treatment at doses 2, 3 and 4 are:

- WBC ≥ 2,500/μL
- Absolute Neutrophil Count ≥ 1,000/μL
- Platelets ≥ 50,000/μL

The occurrence of acute GVHD prior to doses 2, 3, 4 is allowed as long as all GVHD symptoms are resolved to Gr 0 for hepatic and gastrointestinal disease and Gr I for cutaneous disease, per section 3.2.43.2.4

5.5 Agent Administration

Initial Dose
Research subjects should be premedicated with Acetaminophen (650 – 1000 mg oral) and Diphenhydramine (25-50 mg intravenous).

Obinutuzumab or placebo is administered initially at 50 mg/h. In the absence of infusional reactions, the rate can be increased in increments of 50 mg/h every 30 minutes to a maximum of 400 mg/h. With this schedule, a 1000 mg dose of Obinutuzumab will be infused over 4.25 hours. See Table 1.

Second and Subsequent Doses

Doses and schedules are adapted from Phase I and Phase II studies in non-CLL patient populations.[21-24]

Research subjects should be premedicated with Acetaminophen (650 – 1000 mg, oral) and Diphenhydramine (25-50 mg, intravenous).

In the absence of severe infusional reactions with the initial dose, Obinutuzumab can be administered initially at 100 mg/h. In the absence of infusional reactions, the rate can be increased in increments of 100 mg/h every 30 minutes to a maximum of 400 mg/h. With this schedule, a 1000 mg dose of Obinutuzumab will be infused over 3.25 hours. See Table 1.

Placebo will administered at the same rate with the same pre-medications as obinutuzumab.

Table 1. Administration of Obinutuzumab

1st Dose				
Rate	**Duration**	**Dose Delivered**	**Total Time**	**Cumulative Dose**
50 mg/hr	30 minutes	25 mg	0.5 hours	25 mg
100 mg/hr	30 minutes	50 mg	1 hour	75 mg
150 mg/hr	30 minutes	75 mg	1.5 hours	150 mg
200 mg/hr	30 minutes	100 mg	2 hours	250 mg
250 mg/hr	30 minutes	125 mg	2.5 hours	375 mg
300 mg/hr	30 minutes	150 mg	3 hours	525 mg
350 mg/hr	30 minutes	175 mg	3.5 hours	700 mg
400 mg/hr	45 minutes	300 mg	4.25 hours	1000 mg
2nd and Subsequent Doses				
Rate	**Duration**	**Dose Delivered**	**Total Time**	**Cumulative Dose**
100 mg/hr	30 minutes	50 mg	0.5 hour	50 mg
200 mg/hr	30 minutes	100 mg	1 hours	150 mg
300 mg/hr	30 minutes	150 mg	1.5 hours	300 mg
400 mg/hr	1.75 hours	700 mg	3.25 hours	1000 mg

5.6 Management of Infusion Reactions

Infusion reactions are noted in the presence of high tumor burden in the treatment, and as a result are more frequent in the treatment of CLL in comparison with NHL. Stem cell transplant recipients are leukopenic and are anticipated to have an even lower likelihood of infusion reactions than B cell malignancy patients.

Infusion reactions should be managed according to the grade of the reaction. For Grade 4 reactions, the infusion must be stopped and permanently discontinued. For Grade 3 reactions, the infusion should be temporarily interrupted and appropriate medication administered to treat the symptoms. For Grade 1–2 reactions, the infusion should be slowed down and symptoms treated as appropriate. Upon resolution of symptoms, infusion can be restarted, except following Grade 4 IRR, at no more than half the previous rate and, if the patient does not experience the same adverse event with the same severity, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.

For infusion reactions, additional doses of H_1- and H_2-blocking antihistamine agents are administered. Corticosteroids may be administered but only for Grade 3 or 4 reactions when deemed necessary by the treating physician.

5.7 Immunosuppressive Medication Tapering

Immunosuppressive medications should be tapered according to the treating physicians' discretion with careful attention to the clinical trial or treatment plan to which the participating subject is already enrolled. The date of discontinuation of all immunosuppressive medications will be recorded.

5.8 Concomitant Medication Use

5.8.1 Growth Factors: Growth factors to promote WBC or RBC numbers are allowed as dictated by the clinical situation. They should not be used simply to meet eligibility requirements for subsequent obinutuzumab doses.

5.8.2 Immunoglobulin Repletion: ASBMT guidelines for the repletion of IgG levels should be followed. Prolonged hypogammaglobulinemia is anticipated after B cell depleting therapy.

5.9 Criteria for Taking a Participant Off Protocol Therapy

The following are criteria for removing a participant from active study:

- The development of steroid-requiring cGVHD
- Malignant disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the treatment regimen
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Patients with steroid-requiring cGVHD, unacceptable AEs or intercurrent illness preventing further drug administration who come off treatment should continue to have laboratory studies and clinical assessments performed at the appropriate timepoints. Patients with malignant disease progression do not require laboratory or clinical follow-up. Alternative care options will be discussed with the participant.

An ODQ/CTRIO Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ/CTRIO website or obtained from the ODQ/CTRIO registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Corey Cutler at 617 632-3000 pager #41115.

5.10 Duration of Follow Up

Research subjects will be followed until 2 years from the time of transplantation, or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse events will be followed closely until resolution or stabilization of the adverse event, and then until 2 years from the time of transplantation, or until death, whichever occurs first. Participants who withdraw consent will be followed until that time.

5.11 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form.

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

No dose modifications are permitted.

Dose delays are permitted only within the window of administration for that specific dose (+/- 10 days). Investigators are discouraged from using exogenous colony stimulating factors purely to attain hematologic thresholds acceptable for dosing of obinutuzumab. Criteria for the administration of doses 2, 3 and 4 are found in Section 5.4.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting. Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to obinutuzumab per protocol, all events of death, and any study specific issue of concern.

7.1 Expected Toxicities of Obinutuzumab

7.1.1 Infusion-Related Reactions

Infusion-related reactions (IRRs) were observed consistently in all obinutuzumab trials; the highest incidence of IRR was at the first infusion with the incidence decreasing rapidly with subsequent infusions. The incidence of IRR observed with combination therapy (FC and CHOP) appears similar to that observed with monotherapy. Furthermore, the incidence of IRR appears to be higher in CLL compared to NHL patients and higher in obinutuzumab- compared to rituximab-exposed patients based on evidence from studies BO21003 and BO21999. There is no clear relationship between obinutuzumab dose and the incidence of IRR based on data from study GAO4768g. In Stage 2 of the pivotal Phase III study, BO21004/ CLL 11, investigating GClb vs RClb in patients with CLL, the incidence of IRR, Grade 3/4 IRR and IRR leading to discontinuation was higher in GClb arm compared to RClb. This study investigated several measures to minimize the risk of IRRs including: use of corticosteroids, withdrawal of antihypertensive treatments, slow infusion, and split dosing and the evidence suggests that these risk minimization measures decreased the risk of IRRs (all grades); however, the impact on the incidence of Grade 3-4 events and treatment discontinuations due to IRR was limited.

7.1.2 Thrombocytopenia

The main risk associated with thrombocytopenia is hemorrhage. In trial BO21004/CLL11, the overall incidence of hemorrhagic AEs was comparable between the treatment arms (8% GClb; 7% RClb) with the majority of events being of Grade 1 or 2 severity. However, and importantly, all fatal hemorrhagic events in the GClb arm occurred in Cycle 1 in contrast to such events in the RClb arm which occurred later (beyond 1 year after first administration of study drug).

7.1.3 Other AEs

Other AEs of particular interest include neutropenia, infections including progressive multifocal leukoencephalopathy (PML), and hepatitis B virus (HBV) reactivation.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** 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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - 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.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.3.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.3.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

The appearance of signs or symptoms known to be associated with acute or chronic GVHD are specifically exempt from AE or SAE reporting, regardless of their severity.

Similarly, infectious complications following stem cell transplantation are common, and will not be reported as AEs unless the clinical investigator deems the infection to be very atypical for the post-transplant setting, or the infection results in death.

Relapse of the original malignancy will not be reported as an AE, but will be monitored, as detailed in section 12.7

7.4 Serious Adverse Events for Genentech Reporting

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to obinutuzumab.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.4.1 Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

7.4.2 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

7.4.3 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

7.4.4 Pregnancy

If a female patient becomes pregnant while receiving obinutuzumab or within one year after the last dose of obinutuzumab, or the partner of a male patient becomes pregnant while receiving therapy or within three months of completing therapy, a report should be completed and expeditiously submitted to the Roche/Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to obinutuzumab should be reported as an SAE.

7.4.5 GVHD

Neither acute or chronic GVHD require reporting to Genentech.

7.4.6 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior obinutuzumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

7.5 Adverse Events of Special Interest (AESIs) for Genentech

AEs of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of Obinutuzumab. Adverse events of special interest (AESI) in clinical trials are sent to Genentech within 24 hours, even when they are considered non-serious by the investigator.

The following AESIs must be reported to the Sponsor expeditiously irrespective of regulatory seriousness criteria:

- Tumor Lysis Syndrome (serious and non- serious events)

The following events can be reported as AESI only when considered SERIOUS by the investigator:

- Serious neutropenia
- Serious infection
- Serious Infusion Related Reaction (IRR)

Other selected events can be considered for reporting as AESIs:

- infections (including PML)

- neutropenia (including late onset neutropenia - defined as neutrophil count < 1000 cells/mm3, occurring 28 days or more after obinutuzumab treatment has been completed or stopped; prolonged neutropenia - defined as neutrophil count < 1000 cells/mm3, which does not resolve after 28 days (without obinutuzumab treatment),
- thrombocytopenia (including acute thrombocytopenia - events occurring during and within 24 hours post obinutuzumab infusion)
- Hepatitis B reactivation
- cardiac events
- second malignancies
- GI perforation.

7.6 Serious Adverse Event Reporting to Roche/Genentech

Investigators must report all AESIs and SAEs to Roche/Genentech within the timelines described below. The completed MedWatch/case report (Appendix B) should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints with an AE should be sent to:

Fax: (650) 238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

A cover sheet for faxes to Roche/Genentech is found in Appendix C
A copy of the submitted institutional AESIs,SAEs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) should be forwarded to the Overall PI.

Relevant follow-up information should be submitted to Roche/Genentech Drug Safety as soon as it becomes available.

Serious AE reports that are related to obinutuzumab will be transmitted to Roche/Genentech within 15 calendar days of the Awareness Date.

The Principal Investigator will periodically forward listings of non-serious AEs originating from the Study to Roche/Genentech.

In addition to SAEs and pregnancy reports, the following Special Situations Reports should be collected and transmitted to Roche/Genentech even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol

Product Complaints:
All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges

deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Investigators should also report events to their IRB as required.

7.6.1 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (item 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)

- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the to each investigational product and suspect medication

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Roche/Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Roche/Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Roche/Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A form is available at
http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

7.7 Expedited Reporting to Hospital Risk Management

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

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Obinutuzumab

8.1.1 Description

Obinutuzumab is a humanized and glycoengineered type II anti-CD20 monoclonal antibody of the IgG1 subclass. It recognizes a specific epitope of the CD20 molecule found on B-cells. The molecular mass of the antibody is approximately 150 kDa.

An antibody-producing cell line was established from the CHO K1 cell line.

INN:	Obinutuzumab
Code Number:	Drug substance: RO5072759 Drug product: Ro 5072759/F06-01 (1000 mg/vial)
Chemical Name:	Humanized glycoengineered type II anti-CD20 monoclonal antibody

Other Names:	GAZYVA®, GAZYVARO™, huMAb<CD20>, GA101
Chemical Structure:	H2L2 polypeptide structure consisting of two light chains and two heavy chains held together by disulfide bonds.
Molecular Weight:	Approximately 150 kDa
Description:	The drug substance is a clear, colorless to slightly brownish liquid. The drug product is a colorless to slightly brownish liquid concentrate.

8.1.2 Form

Obinutuzumab is provided as a single 1000 mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50 mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188 and HPW. HPW meets the specified limits for highly purified water according to Ph.Eur. and for WFI according to USP.

8.1.3 Storage and Stability

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light.

For microbiological stability, the diluted obinutuzumab infusion solution should be used immediately.

8.1.4 Compatibility

Do not mix obinutuzumab with other drugs.

No incompatibilities between obinutuzumab and polyvinylchloride (PVC) or non-PVC polyolefin bags and administration sets have been observed.

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability

Obinutuzumab will be distributed to the Study Sites directly from Genentech, Inc.

8.1.7 Preparation

Prepare the solution for infusion, using aseptic technique, as follows:
Inspect visually for any particulate matter and discoloration prior to administration.
Dilute into a 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag. Do not use other diluents such as dextrose (5%).
Remove 20 ml overfill from 0.9% sodium chloride 250 ml bag. Remove an additional 40 ml from the 0.9% sodium chloride 250 ml bag.
Withdraw 40 mL (1000 mg) of obinutuzumab and inject into the 0.9% sodium chloride bag.

Mix diluted solution by gentle inversion. Do not shake.
Total volume for administration is 250 ml.
Final concentration is 4 mg/ml.
The prepared infusion solution should be used immediately or may be stored at 2 to 8 degrees C (36 to 46 degrees F) for up to 24 hours.

8.1.8 Administration

Initial Dose
Research subjects should be premedicated with Acetaminophen (650 – 1000 mg oral) and Diphenhydramine (25-50 mg intravenous).

Obinutuzumab is administered initially at 50 mg/h. In the absence of infusional reactions, the rate can be increased in increments of 50 mg/h every 30 minutes to a maximum of 400 mg/h. With this schedule, a 1000 mg dose of Obinutuzumab will be infused over 4.25 hours.

Second and Subsequent Doses
Research subjects should be premedicated with Acetaminophen (650 – 1000 mg oral) and Diphenhydramine (25-50 mg intravenous).

In the absence of severe infusional reactions with the initial dose, Obinutuzumab can be administered initially at 100 mg/h. In the absence of infusional reactions, the rate can be increased in increments of 100 mg/h every 30 minutes to a maximum of 400 mg/h. With this schedule, a 1000 mg dose of Obinutuzumab will be infused over 3.25 hours.

Doses and schedules are adapted from Phase I and Phase II studies in non-CLL patient populations.[21-24]

Placebo will administered at the same rate with the same pre-medications as obinutuzumab.

8.1.9 Ordering

Obinutuzumab will be ordered directly from Genentech, Inc by each study site.

8.1.10 Accountability

Each research Pharmacy will maintain a careful record of the inventory and disposition of the agent using locally approved drug accountability forms.

8.1.11 Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Roche/Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly (no less frequently than monthly) line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Roche/Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

8.1.12 Destruction and Return

All unused obinutuzumab will be destroyed and disposed by the Research Pharmacy at the conclusion of the trial according to local pharmacy practices.

8.2 Placebo

Placebo compound will be prepared by each research pharmacy to physically resemble the active treatment agent. Placebo will be 0.9% sodium chloride 250 ml bag. Remove 20 ml overfill from the bag for a total volume 250 ml

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Approximately 40-50 subjects enrolled in this clinical trial will be F→M subjects, 50% of who will receive obinutuzumab prophylaxis. Comparing obinutuzumab and placebo recipients, we will examine whether effective prevention of alloreactive B cells development, H-Y antibody development or a reduction in H-Y antibody titers correlate with prevention of clinical cGVHD or subsequent severity of cGVHD. We will determine if H-Y antibodies that predate the initial administration of obinutuzumab are predictive of eventual cGVHD development. This latter observation will inform future studies, which may examine earlier administration of obinutuzumab after HCT. All subjects will undergo routine immunophenotyping to monitor the kinetics of BAFF and B cell recovery after obinutuzumab/placebo administration.

Samples will be collected in conjunction with study visits, and no additional study visits are required to fulfill the correlative study objectives.

Peripheral Blood Samples:
Peripheral blood samples will be collected at 3 months, 3.5 months, 6 months, 9 months, 12 months, 18 months, and 24 months from the time of transplantation.
The volume and frequency will not exceed the recommended blood amounts. (It will not exceed 200 mL/day and a maximum of 275 mL in a four week period).
Processing and Shipping Samples:
This is optional for non-DFHCC centers.

Samples will be processed as follows.

1. Blood from the first tube will be used for immune cell subset analysis by flow cytometry.
2. The remainder of the tube will be used for DNA extraction.
3. If the non-DFHCC centers prefer to process the samples on-site, the 1st tube of would be frozen as whole blood, and the DNA would later be extracted at Dana-Farber.
4. The 2nd tube will be centrifuged, and 4 mls of plasma will be frozen in vials of 1 ml each.
5. The remaining blood from the 2nd tube and the 3rd tube will be used for Ficoll-Paque density gradient sedimentation, and the isolated mononuclear cells frozen in aliquots of approximately 20 million cells per 1ml-vial in 10% DMSO.
6. All samples should be stored in 1.8cc Nunc vials.
7. Frozen plasma should be stored at -70° C to -20° C. Cryopreserved mononuclear cells should be stored in vapor phase liquid nitrogen.
8. Samples older than 48 hours are too old to bank, except for DNA.

Domestic samples will be shipped on dry ice priority overnight to Dana-Farber for banking. It is recommended that World Courier be used for shipping if possible. Samples will be labeled with a de-

identified number, date blood drawn, sample type, cell count and DF/HCC protocol number. The key for identification should be sent to the study chair (Corey Cutler).

The shipping address for the samples is:

Attn Doreen Hearsey
Cell Manipulation Core Facility
Pasquarello Tissue Lab, Jimmy Fund building, J604
Dana-Farber Cancer Institute
44 Binney St
Boston, MA 02115
Lab telephone: 617-632-3087

The samples should only be shipped on Sunday-Thursday, for Monday through Friday delivery. The laboratory cannot receive samples after 4pm on Friday or on the week-end.

Samples (whole blood, serum, and cells) will be banked to be used at a future date for correlative studies

Sample storage:
Samples (cells and plasma) will be eventually stored at the Pasquarello Tissue Bank (under the supervision of Jerome Ritz, MD) for up to 5 years following the end of the study. Corey Cutler, MD, will be the administrator. All samples will be de-identified prior to being sent out for testing. The key will be stored securely by and accessible only to the administrator. Requests for samples from non-study investigators will be granted only if they fall within the scope of this study. If they do not, the samples will not be released without IRB approval.

Staff from the Pasquarello Tissue Bank will coordinate sample collection, processing and storage.

10. STUDY CALENDAR

	Month											
	Pre-transplant	Screening[2]	3[3]	3.5	6[3]	6.5	9[3]	9.5	12[3]	12.5	18[10]	24[10]
Obinutuzumab			⊗		⊗		⊗		⊗			
Placebo			⊗		⊗		⊗		⊗			
Medical History		●	●	●	●		●		●		●	●
Physical Examination		●	●	●	●		●		●		●	●
CBC with differential		●	●	●[4]	●	●[4]	●	●[4]	●	●[4]	●	●
Pulmonary Function Test		●							●			●
Pregnancy Test		●										
Informed Consent		●										
Chimerism analysis[5]		●			●		●		●		●	●
Tumor Staging		●										
Immunology[6]			●	●	●		●		●		●	●
Chronic GVHD Assessment[9]					●		●		●		●	●
Toxicity Assessment			●	●	●		●		●		●	●
Infectious Disease Testing[7]	●											
Patient Survey[8]					●		●		●		●	●

[1]As measured from the time of transplantation.

[2]Screening can begin 60 days from transplantation

[3]The administration of Obinutuzumab at month 3, 6, 9 and 12 can be +/- 10 days. Similarly, the required follow-up after the first administration of Obinutuzumab occurs +/-4 days 14 days after the administration of Obinutuzumab.

[4]CBC after obinutuzumab should be 14 +/-4 days from the administration of obinutuzumab. CBCs can be performed at local providers, except after the first infusion.

[5]Chimerism studies are required at screening for only subjects who have undergone non-myeolablative transplantation. Chimerism analysis will be performed by single locus microsatellite DNA probes. Total and T cell chimerism measurements should be performed at all evaluation timepoints for all patients regardless of

conditioning regimen.

[6]Quantitative immunoglobulin measurement; Lymphocyte subset analysis for B cells, T cells; ELISA for minor histocompatibility antigens DBY, DBX under the appropriate clinical conditions (sex-mismatch); Plasma banking, and storage of additional mononuclear cells. See Section 9 for additional details.

[7]Testing done in the pre-transplant setting is sufficient to rule out active Hepatitis A, Hepatitis B, Hepatitis C, and HIV infection.

[8]Patient GVHD will be administered to patients during the Month 6, 9, 12, 18, and 24 appointments. Continue to administer at follow-up visits even if patient has been taken off treatment. Survey is located in Appendix E.

[9]Provider cGVHD survey administered at the month 6, 9, 12, 18, and 24 appointments.

[10]There is a +/- 21 day window for month 18 and month 24 appointments.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.

11.1 Data Reporting

11.1.1 Method

The ODQ/CTRIO will collect, manage, and perform quality checks on the data for this study.

11.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ/CTRIO according to the schedule set by the ODQ/CTRIO.

11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. 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 by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

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.

11.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix D.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or

Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12. STATISTICAL CONSIDERATIONS

This is a prospective, multicenter, randomized phase II trial of prophylactic obinutuzumab vs. placebo for prevention of cGVHD after HCT**.** The primary objective is to determine the effect of obinutuzumab prophylaxis on the incidence of corticosteroid-requiring cGVHD after allogeneic HCT. A single dose of obinutuzumab or placebo will be administered prophylactically at 3, 6, 9, and 12 months after HCT.

12.1 Study Design/Endpoints

This is a randomized, Phase II trial. The primary objective is to determine the rate of corticosteroid-requiring cGVHD when obinutuzumab is used as cGVHD prophylaxis.

The primary endpoint of this phase II trial is the rate of corticosteroid-requiring cGVHD at one year from HCT.

Secondary objectives are to determine the overall cGVHD rate after HCT, NIH moderate-severe cGVHD rate after HCT, cumulative incidence of non-relapse mortality and relapse, adverse hematologic events and infections, immunosuppression-free survival (IFS) at 1 and 2 years from transplantation, progression-free and overall survival at 1 and 2 years from transplantation, and immunologic correlates of B cell depletion. IFS is defined as time from randomization to relapse, institution of systemic immune suppression, or death, whichever occurs first.

12.2 Sample Size, Accrual Rate and Study Duration

The sample size is 200 eligible patients, based on event rates from DFCI 05-377. In this study, 65 patients who received rituximab as cGVHD prophylaxis were compared to a contemporaneous control group and the 1-year corticosteroid-requiring cGVHD rate was 21% in the rituximab group and 38% in the control group. Based on this information, we assume that the 1-year corticosteroid-requiring cGVHD rate will be 38% in the control group and hypothesize that there will be at least a 45% reduction in the obinutuzumab group to a 1-year corticosteroid-requiring cGVHD rate of 21%. With 200 eligible patients, the study will have 80% power to detect a 45% reduction in the obinutuzumab arm using a two-sided test at a significance level of 0.1. This power calculation is based on Fisher's exact test.

Accrual from 3 participating clinical sites (DFCI, MGH, Stanford) is projected to be approximately 100 patients/year, given competing trials and relapse or death prior to 3 months from HCT. Based on this projection, we anticipate that the study will complete its accrual in 2 years.

Patients who initially join the study but are later deemed ineligible due to exclusion criteria 3.2.6 will not be counted toward the overall accrual goal.

All surviving patients will be followed at least for 1 year after HCT for the evaluation of the primary endpoint

Special attention will be paid to the recruitment of women and minorites per NIH guidelines.

12.3 Randomization and Stratification Factors

Randomization will be 1:1, stratified by center, conditioning intensity (myeloablative vs. reduced intensity) and donor type (matched related vs. matched unrelated) using permuted block algorithm within strata.

QACT will notify the research pharmacy of the randomization status of the patient by fax and via email (DFCIPharmacyIDS@partners.org) . The remainder of the study team will be blinded to which arm the patient will receive.

12.4 Blinding

Blinding will be performed at the level of the Research Pharmacy. Obinutuzumab or placebo will be issued from the Research Pharmacy without identifying labels to prevent unblinding at the bedside.

The research pharmacy will not be blinded. Unblinding will occur when knowledge of the treatment is essential for the emergency management of adverse events. Unblinding may also occur at the request of the Principal Investigator when all patients have come off study treatment. In case of an emergency, the treating physician or study investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. In these events the primary and backup unblinded study members will be the Clinical Research Manager Daniel Surette, and Regulatory Coordinator Jennifer Sherwill, and these members will not otherwise be accessing patient data.

12.5 Interim Monitoring Plan

The study will be monitored using standard procedures and processes by an independent Data and Safety Monitoring Board (DSMB) of the Dana-Farber Harvard Cancer Center (DF/HCC).

Monitoring of key safety endpoints (relapse, grade 3 or higher treatment related toxicity, grade III-IV acute GVHD after study enrollment) will be conducted in accordance with the DF/HCC DSMB meeting. Since a concern for excess relapse exists, even though our preliminary studies do not support this, we will compare the relapse rate along with other key safety endpoints between two arms at each interim analysis. If, at any interim analysis, this difference is significant at the two-sided level of 0.05, this would trigger a consultation with the DF/HCC DSMB for additional review of early stopping. However, this will not be a formal stopping rule that would mandate automatic closure of study enrollment.

Interim analyses for efficacy will be performed every six months in conjunction with semi-annual DF/HCC DSMB meeting, beginning at the 25% information time, which is anticipated to occur approximately 1.5 years after the start of the trial. The interim results will be reported to the DF/HCC DSMB. However, these interim analyses will not have an effect in terms of stopping accrual to the study and terminate the study early in favor of alternative (superiority) or null hypothesis (futility). This is because i) due to a small sample size at the first interim analysis, stopping early for futility would result in substantially wide confidence intervals, larger Type II error, and thus leading to greater uncertainty about the magnitude of the steroid requiring cGVHD difference, ii) by the time of the second interim analysis, the study is anticipated to complete accrual, iii) even if the steroid requiring cGVHD difference is not as large as targeted, investigators are interested in learning the magnitude of the difference for further investigation,
iv) stopping early for superiority would provide less safety data than planned and potential difficulty with the efficacy analysis and its interpretation.

12.6 Analysis of Primary Endpoints

The primary endpoint of this phase II trial is one year corticosteroid-requiring cGVHD rate.

The primary analysis will be a modified intent-to-treat analysis (mITT) fo with all randomized patients who receive any amount of the study drug, either obinutuzumab or placebo. Patients who are randomized but do not receive the study drug and off the study will not be included in mITT and be replaced (Section 5.11). The primary analysis will be performed using i) a Chi-square test for comparison of crude proportions, ii) comparison of cumulative incidence rates of corticosteroid-requiring cGVHD in the context of competing risks framework. In this analysis, death or relapse without developing a corticosteroid-requiring cGVHD will be considered as a competing event and cumulative incidence of death or relapse without developing cGVHD will also be reported, iii) multivariable competing risks regression analysis using the Fine and Gray model[25].

12.7 Analysis of Secondary Endpoints

Secondary objectives include to determine the overall cGVHD rate after HCT, NIH moderate-severe cGVHD rate after HCT, cumulative incidence of non-relapse mortality and relapse, adverse hematologic events and infections, immunosuppression-free survival (IFS) at 1 and 2 years from transplantation, progression-free and overall survival at 1 and 2 years from transplantation, and immunologic correlates of B cell depletion.

For the comparison of GVHD, NRM and relapse, competing risks data analysis will be performed using Gray test[26] and Fine and Gray competing risks regression analysis[25]. For PFS, OS, and IFS, standard survival analysis will be performed. Adverse hematologic events will be compared by cumulative incidence measures. All analysis will be repeated by disease group (myeloid vs. lymphoid).

12.8 Analysis of Correlative Studies

The primary analysis for the correlative studies is concerns male recipients with female donors (F→M) and H-Y minor histocompatibility antigens (mHA). The analysis will be exploratory without adjustment for multiple testing. Based on the recent report from the Miklos lab27, we hypothesize that patients with multiple anti-H-Y antibodies (defined as >=2 antibodies out of 6) at study entry are more likely to develop corticosteroid-requiring cGVHD at one year after HCT. Assuming 50 patients (from both arms) will undergo F→M HCT, if the one-year corticosteroid-requiring cGVHD rate is 55% and 15% for patients with and without multiple anti-H-Y antibodies, respectively, there will be 84% power to detect this difference. This power calculation is based on Fisher's exact test at the two-sided significance level of 0.1 assuming 18 patients in F→M 27 will have multiple anti-H-Y antibodies at the study entry.
Using the H-Y protein arrays developed in the Miklos lab, we measured IgG antibodies specific for DBY (one of HY mHA proteins) in 13 F→M who received rituximab prophylaxis (DFCI#05-377) and 10 F→M who did not receive rituximab. After 6 months post HCT, no one in the rituximab group developed anti-DBY reactivity whereas 4 out of 10 in the control group developed the anti-DBY reactivity (p=0.02). Extrapolating this result to this randomized phase II trial, if the anti-DBY response rates are 5% and 40% in the obinutuzumab and placebo group, respectively, in F→M, there will be 88% power to detect this difference (Table). This power calculation is based on Fisher's exact test at the two-sided significance level of 0.1 assuming 25 patients will undergo F→M HCT in each treatment group.

Table. Power for various levels of responses between obinutuzumab and placebo arm

anti-DBY reactivity	(10%, 35%)	(5%, 35%)	(5%, 40%)
Power	57%	79%	88%

When data are available, we will repeat a similar analysis for multiple antibodies and investigate whether a combination of antibody responses is more discriminatory. We will also investigate whether H-Y antibodies measured prior to the initial administration of treatment are predictive of eventual cGVHD using ROC (receiver operating characteristic) curve analysis and multivariable regression analysis after adjusting for treatment arm. In addition, an appropriate statistical analysis will be applied for routine immunophenotype data analysis including BAFF and B cell recovery as well as for new or existing autosomal mHA that may be associated with development of cGVHD across all recipient and donor sex combinations.

12.9 Reporting and Exclusions

12.9.1 Evaluation of Toxicity

All participants will be evaluable for toxicity as long as a single infusion of obinutuzumab or placebo is initiated.

12.9.2 Evaluation of the Primary Efficacy Endpoint

The primary analysis will be an intent-to-treat analysis with all randomized patients included for evaluation of the primary endpoint.

13. PUBLICATION PLAN

The results of this study will be submitted to a peer-reviewed journal for consideration of publication within 24 months of the end of follow-up. Submission of an abstract to a scientific meeting may occur prior to completion of the study follow-up period.

Results will be made publicly available on www.clinicaltrials.gov in accordance to the requirements posted on that website.

Any literature articles that are a result of the study will be sent to Roche/Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Email: ga101-gsur@gene.com
Fax: 866-706-3927

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	**15.** Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B MEDWATCH 3500 REPORTING FORM

HTTP://WWW.FDA.GOV/ABOUTFDA/REPORTSMANUALSFORMS/FORMS/DEFAULT.HTM

APPENDIX C SAFETY REPORTING FAX COVER SHEET

Genentech
A Member of the Roche Group

ROCHE/GENENTECH SUPPORTED RESEARCH

AE/SAE FAX No: (650) 238-6067

Page 1 of ____

Roche/Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	**____/___/___ dd / mmm / yyyy**
Follow-up Report Date	
Patient Initials (Please enter a dash if the patient has no middle name)	____ -_____-_____

SAE or Safety Reporting questions, contact Roche/Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

APPENDIX D **DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLAN**

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (ie FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Office of Data Quality: A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ/CTRIO also coordinates quality assurance efforts related to multi-center clinical research.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, **Corey Cutler, MD** will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC *ODQ/CTRIO*.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.

- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC *ODQ/CTRIO* case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed to the Coordinating Center at 617-582-9103.

- Copy of Eligibility Checklist
- Signed participant consent form
- HIPAA authorization form
- Source documentation confirming eligibility criteria

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC *ODQ/CTRIO*

- Upon receiving confirmation of registration by the *ODQ/CTRIO*, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and if applicable the dose level.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during ODQ/CTRIO's normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Time.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ/CTRIO before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC ODQ/CTRIO will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ/CTRIO requires each institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, ODQ/CTRIO requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7 of the main protocol document.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

The DF/HCC ODQ/CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC ODQ/CTRIO provides a web based training for eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ/CTRIO Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ/CTRIO and distributed on a monthly basis.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.

Participating Institutions should order their own agent.

Each site must ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC internal monitor will provide quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in Coordinating Center initiated teleconferences. A schedule of these calls is forthcoming.

Remote Monitoring
Participating Institutions will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification. Random study subjects will be chosen for intermittent remote monitoring.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.
The accrual expectation for Stanford University School of Medicine is approximately 15 participants per year.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and

whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the ODQ/CTRIO, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ/CTRIO per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor, DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX E – Patient GVHD Survey

Identification (Name):_____ Date:_____

chronic GVHD Symptom Scale

By circling one (1) number per line, please indicate how much you have been bothered by the following problems in the past month:

SKIN:	Not at all	Slightly	Moderately	Quite a bit	Extremely
1. Abnormal skin color……..	0	1	2	3	4
2. Rashes……	0	1	2	3	4
3. Thickened skin…… ……...	0	1	2	3	4
4. Sores on skin……	0	1	2	3	4
5. Itchy skin…… …….	0	1	2	3	4

EYES AND MOUTH:	Not at all	Slightly	Moderately	Quite a bit	Extremely
6. Dry eyes……	0	1	2	3	4
7. Need to use eye drops frequently..	0	1	2	3	4
8. Difficulty seeing clearly……	0	1	2	3	4
9. Need to avoid certain foods due to mouth pain……	0	1	2	3	4
10. Ulcers in mouth……	0	1	2	3	4
11. Receiving nutrition from an intravenous line or feeding tube....	0	1	2	3	4

BREATHING:	Not at all	Slightly	Moderately	Quite a bit	Extremely
12. Frequent cough……	0	1	2	3	4
13. Colored sputum……	0	1	2	3	4
14. Shortness of breath with exercise..	0	1	2	3	4
15. Shortness of breath at rest……..	0	1	2	3	4
16. Need to use oxygen……..	0	1	2	3	4

EATING AND DIGESTION:	Not at all	Slightly	Moderately	Quite a bit	Extremely
17. Difficulty swallowing solid foods….	0	1	2	3	4
18. Difficulty swallowing liquids…….	0	1	2	3	4
19. Vomiting…….	0	1	2	3	4
20. Weight loss……	0	1	2	3	4

MUSCLES AND JOINTS:	Not at all	Slightly	Moderately	Quite a bit	Extremely
21. Joint and muscle aches……...	0	1	2	3	4
22. Limited joint movement……	0	1	2	3	4
23. Muscle cramps……..	0	1	2	3	4
24. Weak muscles……...	0	1	2	3	4

ENERGY:	Not at all	Slightly	Moderately	Quite a bit	Extremely
25. Loss of energy…….	0	1	2	3	4
26. Need to sleep more/take naps…..	0	1	2	3	4
27. Fevers……	0	1	2	3	4

MENTAL AND EMOTIONAL:	Not at all	Slightly	Moderately	Quite a bit	Extremely
28. Depression……	0	1	2	3	4
29. Anxiety……...	0	1	2	3	4
30. Difficulty sleeping…….	0	1	2	3	4

APPENDIX F – Provider GVHD Survey

Provider Assessment

Patient: _____
MRN: _____
Provider Name: _____
Date of Visit: _____
Study Timepoint: _____

At this study timepoint, the patient has:

Documented aGVHD
(Proceed to assessment)

Documented cGVHD
(Proceed to assessment)

No Documented aGVHD or cGVHD
(Do not complete assessment)

	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, capabl of self-care, >50% of waking hours ou 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† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** Maculopapular rash/erythema; Lichen planus-like features; Sclerotic features; Papulosquamous lesions or ichthyosis; Keratosis pilaris-like GVHD	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
SKIN FEATURES SCORE:	No sclerotic features		**S**uperficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** Deep sclerotic features; "Hidebound" (unable to pinch); Impaired mobility; Ulceration

Other skin GVHD features (NOT scored by BSA)
Check all that apply:
Hyperpigmentation
Hypopigmentation
Poikiloderma
Severe or generalized pruritus
Hair involvement
Nail involvement
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

MOUTH *Lichen planus-like features present:* **Yes** **No**	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

*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* **Yes** **No** **Not examined**	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GI Tract ***Check all that apply:*** Esophageal web/ proximal stricture or ring Dysphagia Anorexia Nausea Vomiting Diarrhea Weight loss ≥5%* Failure to thrive	No symptoms	Symptoms without significant weight loss* (<5%)	Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LIVER	Normal total bilirubin and ALT or AP < 3 x ULN	Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	Elevated total bilirubin > 3 mg/dL
Abnormality present but explained entirely by non-GVHD documented cause (specify):				
LUNGS**				
Symptom score:	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)
Lung score: **%** FEV1 ☐	FEV1≥80%	FEV1 60-79%	FEV1 40-59%	FEV1 ≤39%
Pulmonary function tests Not performed				
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

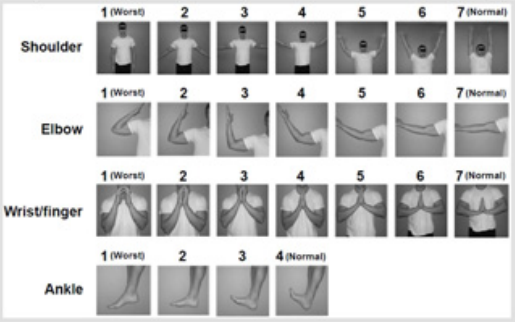
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR** 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.)
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) Not examined *Currently sexually active* Yes No	No signs	Mild signs‡ and females with or without discomfort on exam	Moderate signs‡ and may have symptoms with discomfort on exam	Severe signs‡ with or without symptoms
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

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

Ascites (serositis)___	Myasthenia Gravis___	
Pericardial Effusion___	Peripheral Neuropathy___	Eosinophilia > 500/µl___
Pleural Effusion(s)___	Polymyositis___	Platelets <100,000/µl ___
Nephrotic syndrome___	Weight loss>5%* without GI symptoms ___	Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

Photographic Range of Motion (P-ROM)



† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Abbreviations: 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); ULN (normal upper limit).

‡ To be completed by specialist or trained medical providers (see Supplemental Figure).