Reduce Intensity Conditioning (RIC) Allogeneic Hematopoietic Stem Cell Transplantation (allo HSCT) for Patients with Relapsed Multiple Myeloma: A pilot study

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PROTOCOL SYNOPSIS

Reduce Intensity Conditioning (RIC) Allogeneic Hematopoietic Stem Cell Transplantation (allo HSCT)
for Patients with Relapsed Multiple Myeloma: A pilot study

Principal Investigator: Srinivas Devarakonda M.D

Study Design: The study is a pilot study to develop a platform for allo HSCT in relapsed multiple myeloma (MM) patients, with the idea of maximizing anti-myeloma effect and minimizing aGVHD (graft versus host disease). First, all patients will undergo conditioning regimen of Flu/Mel (fludarabine, melphalan). For GVHD prophylaxis, the investigator will use post-transplant cyclophosphamide (PTCy), mycophenolate mofetil (MMF) and tacrolimus. Second, the addition of a maintenance with daratumumab (administered for 1 year post allo HSCT), may further reduce the risk of disease relapse long enough in order for the graft versus myeloma to take effect.

Primary Objective:

- To develop a platform for allo HSCT in relapsed multiple myeloma patients to obtain preliminary data on the effect of combined treatment regimen on clinical outcomes

Primary Endpoints

To obtain preliminary data on the effect of the combined treatment regimen on clinical outcomes.

Secondary Endpoints:

- To determine the 2 year progression-free survival (PFS)
- To determine 2 year overall survival (OS)
- To determine the cumulative incidence of grade II-IV acute-graft-versus-host-disease (aGVHD) at day 100 and 180.
- To determine the 100 days, 1 year and 2 year cumulative incidence of treatment-related mortality (TRM)
- To assess one-year GVHD-free Relapse-free Survival (GRFS)
- To determine the cumulative incidence of chronic graft-versus-host-disease (cGVHD)
- To assess overall and best response rates 100 days after allo HCT, 6 months and every 6 months thereafter until end of Daratumumab maintenance.
- To determine rate of relapse after allo HSCT followed by maintenance
  To determine Rate of MRD negativity using Next generation sequencing (FDA approved) in patients achieving a VGPR or better.
- To determine immune reconstitution pattern on days +30, +100, +180 and +365 following allo HSCT.

Patient Eligibility

Patient Inclusion Criteria:

- Patients age 18-75 years old
- High risk relapsed MM patients and who have received at least 2 prior lines of therapy, and have obtained at least a Partial response from their salvage chemo.

  High risk criteria are: patients are one or more of the following: 1: patients who progressed within 24 months from their first autologous stem cell transplant (Criteria from the BMT/CTN 1302(clinical trials.gov identifier:NCT02440464); 2: Patients with at least 2 prior lines of therapy with progression within 12 months from their last line of therapy.; 3: Patients with high risk markers (del13 by conv. karyotyping only; hypodiploidy, 1q amplification or 1p deletion, t(4;14), t(14;16), t(14;20) or deletion of 17p by FISH or conv. karyotyping; R-ISS 3; or Beta-2M ≥ 5.5 mg/L)
- Patients with nonsecretory myeloma are eligible for the study. Assessments of response will be based on PET scans.
- Prior radiation is allowed as this is a very vital management of myeloma bone disease.
- Patients with ≥ PR prior to allo-HSCT
- First allogeneic transplant
- Cardiac function: Ejection fraction ≥45%
- Estimated creatinine clearance greater than 40 mL/minute (using the Cockcroft-Gault formula and actual body weight)
- Pulmonary function: DLCO ≥40% (adjusted for hemoglobin) and FEV1≥50%
- Liver function: total bilirubin < 2x the upper limit of normal and ALT/AST < 2.5x the upper normal limit (Patient who have been diagnosed with Gilbert's Disease are permitted to exceed the defined bilirubin value of 2x the upper limit of normal).
- Female subjects (unless postmenopausal for at least 1 year before the screening visit, or surgically sterilized), agree to practice two (2) effective methods of contraception at the same time, or agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)through 90 days after the last dose of maintenance therapy
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- Able to comply with the study visit schedule and other protocol requirements

Patient Exclusion criteria:

- Karnofsky Performance Score < 70%
- Planned pre-emptive/prophylactic administration of donor lymphocytes
- Active Central Nervous System(CNS) involvement with multiple myeloma defined as csf positivity for plasma cells or a parenchymal CNS plasmacytoma
- Patients with POEMS, Waldenstrom macroglobulinemia
- Cannot have had prior allogeneic transplant
- Uncontrolled bacterial, viral or fungal infection (currently taking medication and with progression or no clinical improvement) at time of enrollment
- Patients with prior malignancies <3 years except resected basal cell/squamous cell carcinoma, treated carcinoma in-situ. Other cancers treated with curative intent < 3 years previously will not be allowed unless approved by the Principal investigator
- Patients seropositive for the human immunodeficiency virus (HIV).
- Patient with active Hepatitis B or C determined by serology and/or NAAT
- Patients with > grade 2 sensory peripheral neuropathy
- Myocardial infarction within 6 months prior to enrollment, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant
- Failure to have fully recovered (i.e. no toxicities > Grade 1) from the reversible effects of prior chemotherapy
- Patient with serious medical of psychiatric illness likely to interfere with participation on this clinical study
- Hypersensitivity to any of the drugs involved in this trial
- Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial
- Enrollment of subjects who require concurrent radiotherapy (which must be localized in its field size) should be deferred until the radiotherapy is completed and 3 weeks have elapsed since the last date of therapy
- Major surgery within 14 days of start of trial
- Patients unable or unwilling to adhere to the study assessment schedule
- Female patients who are pregnant or breastfeeding. A negative pregnancy test will be required for all women of child bearing potential

Patient Eligibility Criteria Prior to Begin Maintenance Therapy:

Between Day +90 and Day +150 after allogeneic HCT, patients will receive daratumumab maintenance. If patients do not meet the eligibility criteria for initiating maintenance, they will continue to be followed per the protocol.

Patient Eligibility Criteria Prior to Initiating Maintenance Therapy:

- Platelet count ≥ 75,000/mm3
- Absolute neutrophil count (ANC) ≥ 1000/mm3

- Total bilirubin < 2x the upper limit of the normal range (ULN), except in patients with Gilbert's syndrome
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- No ≥ grade 2 visceral (gut or liver) acute GVHD. No ≥ Grade 3 any other acute GVHD
- All non-hematologic toxicities should have resolved to ≤ grade 1
- Negative for Hepatitis B virus by PCR
- Patients must be in at least a partial response

Stem Cell Donor and Source

- Matched related
- Matched unrelated
- 1 antigen mismatch related or unrelated
- Haploidentical
- Peripheral stem cell source will be used except in Haploidentical where Bone marrow stem cells will be required

Donor Exclusion Criteria:

- Donors will be excluded if they are an identical twin of the recipient
- Females who are pregnant (positive serum β HCG) or uninterruptible breastfeeding will be excluded
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- Donors receiving experimental therapy or investigational agents will be excluded unless approved by the protocol chair and Officer
- Donors not willing and able to donate PBSC will be excluded
- Related and unrelated donors will be identified according to institutional guidelines

Disease to be Included

- Relapsed Multiple Myeloma patients with a partial response (PR) or better prior to allo-transplantation.

Treatment Plan

Patients meeting the eligibility criteria for transplant/enrollment will be treated with conditioning regimen of fludarabine and melphalan. GVHD prophylaxis consists of cyclophosphamide, tacrolimus and mycophenolate mofetil, and post allo-HSCT maintenance with daratumumab: Patients will receive fludarabine 30 mg/m2 (when creatinine clearance 40 – 70 mL/min, reduce to 24 mg/m2) from Day -5 to Day -2 and melphalan 70 mg/m2 on Day -3 and Day -2 intravenously (50 mg/m2 for patients 71 and older). On Day 0, patients will receive the donor stem cells. GVHD Prophylaxis will be cyclophosphamide/tacrolimus/ mycophenolate mofetil: Cyclophosphamide 50 mg/kg will be given on days +3, and +4. Tacrolimus will start on day +5 at 0.05 mg/kg orally twice daily to achieve a target serum level of 5-10 mg/ml. Tacrolimus may change to i.v as necessary. Serum levels of tacrolimus will be measured per institution guideline. Tapering of tacrolimus will start after day 90 post HSCT with goal of having the patient

receive no immune-suppressive medication by 6 months in absence of GVHD. Mycophenolate Mofetil (MMF) will be given at a dose of 15 mg/kg three times a day (based on actual body weight) with a maximum total daily dose not to exceed 3 grams (1 gram TID, IV or oral), starting Day +5 to day 35 post-transplant. Patients will start maintenance Daratumumab between 90-150 days post allo-HSCT as long as counts are acceptable (absolute neutrophil ≥1000/μL; Platelets ≥ 75,000/μL) and in the absence of disease progression. Patients will receive daratumumab maintenance (given at 16 mg/kg weekly for 8 doses, followed by every 2 weeks for 8 doses, then monthly). Maintenance will continue for 1 year in absence of unacceptable toxicity, disease progression or death.

Accrual
Relapsed MM patients who are candidates for allo-HSCT will be assessed for accrual. 20 patients will be accrued.

Accrual Period
The estimated accrual period is 2 years.

Follow-up Period
Patients will be followed for 1 year after end of Daratumumab treatment

Stopping Rule:
Monitoring of the key safety endpoint of death will be conducted. Day 100 post-transplant mortality will be monitored. The null hypothesis that the Day 100 mortality rate is less than or equal to 10%. The stopping rule will be triggered if there is significant evidence that the overall death rate exceeds 10%, that is, if the lower bound of the one-sided 95% CI exceeds 10%. The rationale of a lower confidence bound is to be certain that the estimated true rate is not significantly higher than the rates deemed clinically acceptable. If the number of death equals or exceeds the numbers in the table below, then the study will be suspended to accrual pending further consultation with the DSMB. We will first enroll 3 patients and assess toxicity through day 100, before continuing enrollment.

One year non-relapse mortality after allo-HSCT is 16-20%. Given that patients will be on daratumumab maintenance, while not expected, monitoring for excessive mortality is necessary. At one year post allo-HSCT, patients would have transitioned to the monthly daratumumab. The stopping rule will be triggered if the one-year non-relapse mortality exceeds 20%.

The rate of chronic GVHD(cGVHD) occurs in 50-60% of patients undergoing allo-HSCT, with 30-35% being extensive cGVHD. The stopping rule will be triggered if the rate of extensive cGVHD exceeds 35%.

Table: Incidence of death

Number of patients enrolled	Number of death
3	2
4-8	3
9-14	4
15-20	5

Contents

1. BACKGROUND and RATIONALE

1.1. Relapsed Multiple Myeloma and Transplantation

Multiple Myeloma (MM) accounts for approximately 20% of all hematologic malignancies and 2% of all cancer deaths in the United States (1). Due to the improved PFS resulting in prolonged time off treatment without symptoms and improved quality of life, autologous stem cell transplantation (AHSCT) has become an integral part of treatment in patients with newly diagnosed MM. The introduction of the novel agents–thalidomide, lenalidomide and bortezomib-has improved on both PFS and OS (2-10). The addition of maintenance treatment post AHSCT has further improved the PFS (from median 23-27 months to 41-53 months), and in one study, OS (3 yr. 84% versus 80%)(11, 12). Despite this improvement in response, a vast number of patients relapse and treatment of relapse remains a major challenge. AHSCT and salvage therapies at time of relapse, has led to improvement in the survival of patients with MM (10). However, as MM has become a chronic disease with a longer succession of remissions and relapses, finding effective treatment is critical for prolonging PFS/OS. The options include retreatment with previous regimens, and/or moving on to more recently used drugs. However, despite this, patients become resistant to chemotherapy and have progressive MM.

Allo HSCT is a reasonable upfront option in these patients and offers a potential cure and was found to be highest when this modality was used earlier in the disease course and when used as a strategy for consolidation of remission induced by salvage therapy (13, 14). In a prospective EBMT trial, it was shown that patients who had relapsed from a previous AHSCT and received allo-HSCT had an overall response rate of 90%, including a CR rate of 40% (15). Reduced intensity conditioning (RIC) allo HSCT offers the potential advantage of decreased treatment related mortality (TRM) while preserving the GVM effect (16, 17). Prospective studies utilizing upfront RIC allo HSCT incorporated autologous HSCT prior to allo HSCT (18-21). Novel agents were not incorporated or available at the time. Conditioning regimen was not consistent and consisted of low dose total body radiation, fludarabine/busulfan/antithymoglobulin or fludarabine/Melphalan. aGVHD prophylaxis consisted of mycophenolate mofetil/cyclosporine or methotrexate/cyclosporine. The PFS and OS ranged 31-39 months and 35-50 months respectively. TRM was 11-16%, aGVHD 32-40% and cGVHD up to 66%. No maintenance was done. Overall, the results of allogeneic HSCT have continued to improve significantly over the years as was seen in a steady decline in TRM by the Center for International Blood and Marrow Transplant Research (CIBMTR) analysis (22). However, the relapse after allogeneic HSCT remains a challenge (22, 23) and the emerging data suggest that the outcomes of allogeneic

HSCT could be further improved with the use of novel agents (23). BMT CTN 1302 was one such multicenter trial that aimed to address whether the addition of novel agent Ixazomib to maintenance following allo HSCT results in improved PFS and is associated with lower rates of GVHP, in patients with high risk multiple myeloma (BMT CTN1302).

We here, propose a concept that, even if not curative, may improve PFS and OS, for haploidentical, mismatch or matched related or unrelated patients who relapse after autologous AHSCT. In this study, to improve on the PFS and OS, and to reduce aGVHD, we propose to use allo HSCT for all transplant eligible relapsed MM patients. Patients obtaining a partial response or better with any salvage regimen will proceed to allo HSCT with a related or unrelated donor. Conditioning regimen will consist of fludarabine, melphalan and aGVHD prophylaxis will consist of post-transplant cyclophosphamide (PTCy), mycophenolate mofetil (MMF) and tacrolimus. Maintenance with monthly daratumumab will be administered for 1-year post allo-HSCT starting between 90-150 days post allo-HSCT.

1.2. Daratumumab in Multiple Myeloma

The optimal intensity of conditioning regimens for allo-HSCT is still controversial for patients with multiple myeloma. Fully myeloablative regimens have been largely abandoned, whereas nonmyeloablative stem cell transplant regimens (e.g., total body irradiation of 2 Gy) without anti-multiple myeloma activity have been associated with lower transplant related mortality (TRM) risk but increased relapse (17). The pendulum of regimen intensity has now swung back to reduced-intensity conditioning with regimens that incorporate intermediate doses of active anti-multiple myeloma therapy. The most popular approach in the United States is a combination of fludarabine and melphalan at a dose of 140 mg/m2 (CIBMTR data). The addition of monoclonal antibody to maintenance is being explored as an additional strategy to increase the antineoplastic potential without incurring additional toxicity.

Daratumumab has been approved by the Food and Drug Administration (FDA) to treat a type of blood cancer called multiple myeloma. Daratumumab is especially potent & highly effective in the treatment of relapsed & refractory MM, both as monotherapy and in combination. It is a monoclonal antibody (a type of antibody that identifies and attaches to certain proteins within the body to bring about an immune response, help the immune system work, or block signals telling the cancer cells to divide). Daratumumab can target tumor cells for elimination via antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and phagocytosis. Daratumumab may also initiate CD38-mediated signal transduction, leading to cell death. In preliminary studies, daratumumab has demonstrated promising activity in combination with lenalidomide and dexamethasone. The efficacy and safety profiles of daratumumab monotherapy in heavily pretreated patients with RRMM were examined in the open-label, phase 1/2 GEN501 study and the phase 2 SIRIUS study (24, 25). Daratumumab also demonstrated a manageable safety profile marked by a low incidence of grade ≥3

infusion-related reactions (IRRs) and few treatment discontinuations as a result of adverse events (AEs).

1.3. Rational for Post-transplant Cyclophosphamide

High dose cyclophosphamide is a potent immunosuppressor that has been successfully used to prevent GVHD in unrelated, HLA-matched sibling and haploidentical bone marrow/PBSC transplants in single center as well as multi-center studies (26, 27). Cyclophosphamide (Cy) administered early post HSCT preferentially kills allo-reactive T cells while sparing resting, non allo-reactive T cells leading to suppression of GVHD as well as graft rejection (28). Following a regimen of fludarabine, Cy and low dose TBA, GVHD prophylaxis consisted of Cy on days +3 and +4 post-transplant, tacrolimus, and MMF (27). Post transplantation immunosuppression with high-dose Cy, tacrolimus, and thrice-daily MMF was associated with an acceptably low incidence of fatal graft rejection, severe aGVHD, and extensive cGVHD, while allowing prompt engraftment, and low incidence of severe opportunistic infections. Cumulative incidences of grades II-IV and grades III-IV acute GVHD by day 200 were 34% and 6% respectively. Also, the transplantation regimen is truly non-myeloablative, as autologous hematopoiesis recovered in 8 of 9 patients who rejected their grafts. There was lower incidence of extensive chronic GVHD among recipients of two versus one dose of post-Cy (5% versus 25%; p=.05). The cumulative incidences of non-relapse mortality (NRM) and relapse at 1 year were 15% and 51%, respectively. Overall and event-free survival (EFS) at two years after transplantation were 36% and 26%, respectively. In addition, two retrospective studies also reported encouraging results on the use of post-transplant cyclophosphamide following Allo-HSCT. Lower rates for aGVHD and cGVHD were observed using post-transplant Cy (29, 30).

The Blood and Marrow Transplant Clinical Trials Network conducted multicenter phase 2 trials for individuals with leukemia or lymphoma and no suitable related donor. RIC was used with either unrelated double umbilical cord blood (dUCB) or HLA-haploidentical related donor bone marrow transplantation (26). The 1-year probabilities of overall and progression-free survival were 54% and 46%, respectively, after dUCB transplantation (n=50) and 62% and 48%, respectively, after haploidentical bone marrow transplantation (n=50). The day +56 cumulative incidence of neutrophil recovery was 94% after dUCB and 96% after haploidentical bone marrow transplantation. The 100-day cumulative incidence of grade II-IV acute GVHD was 40% after dUCB and 32% after haploidentical bone marrow transplantation. The 1-year cumulative incidences of NRM and relapse after dUCB transplantation were 24% and 31%, respectively, with corresponding rates of 7% and 45%, respectively, after haploidentical bone marrow transplantation. Post-transplant cyclophosphamide (PTCy) as GVHD prophylaxis was developed initially for haploidentical bone marrow transplantation after non-ablative conditioning but, recently, several small studies have extended the approach to myeloablative conditioning and to PBSC transplantation. To date, haploidentical non-ablative transplantation with PTCy has used bone marrow as the graft source. Use of PBSC instead of marrow may allow wider applicability of this approach but there is

concern about higher risks of acute and chronic GVHD due to the 5-10 fold higher number of T-cells in the allograft. Recently, groups in Houston and Seattle/London reported small studies in which PBSC were substituted for bone marrow with post-Cy in the haploidentical donor setting (31). In both studies, the incidences of severe acute GVHD, chronic GVHD and non-relapse mortality at 1 year with PBSC were comparable to the rates seen with the bone marrow. A phase II multicenter trial, PROGRESS I, was done in an attempt to primarily determine if the three new GVHD prophylaxis approaches using novel agents such as maraviroc, bortezomib, and PTCy, improve the rate of GVHD relapse free survival (GFRS) at one year after allo HSCT (32). An event for this time to event outcome is defined as time from allo HSCT to grade III-IV aGVHD, cGVHD requiring systemic immunosuppression, relapse, or death by any cause. Donors were 6/6 HLA matched related, or 7/8 or 8/8 HLA matched unrelated. Using these novel strategies, MMF/Tacrolimus/PTCy was shown to be associated with a superior 1-year GRFS (p 0.0467), lower rates of severe aGVHD (p 0.0066), cGVHD requiring immunosuppression (p 0.0413) and better GVHD-free survival (p 0.0121). There were no differences in relapse/progression, treatment related mortality, disease free survival, count recoveries, or overall survival compared to control. Kasamon et al (33) recently, demonstrated the feasibility and acceptable safety profile of non-myeloablative T-cell replete mismatch unrelated donor bone marrow transplantation with PTCy based GVHD prophylaxis for hematologic malignancies. Rates of GVHD and toxicity were low. Therefore, the inclusion of PTCy with MMF and tacrolimus as GVHD prophylaxis after non-ablative conditioning regimen seems to be justified.

2. STUDY OVERVIEW AND OBJECTIVE

2.1. Study Overview

Patients who achieve a high quality and prolonged duration of response with initial therapy will ultimately relapse. Thus, management of relapsed disease is a critical aspect of MM management. Given the small number of relapsed myeloma patients treated with an allogeneic transplant, there is considerable unmet need to define the role of allogeneic HCT in relapsed MM population. The introduction of reduced intensity regimen has resulted in reduced TRM in allogeneic HCT for patients with myeloma. However, myeloma relapse still need to be reduced in order to maximize the efficiency of the therapeutic approach in relapsed myeloma population. The purpose of this study is to develop a platform for allo HSCT in relapsed multiple myeloma (MM) patients (34, 35), with the idea of maximizing anti-myeloma effect and minimizing aGVHD (graft versus host disease). First, all patients will undergo conditioning regimen of Flu/Mel (fludarabine, melphalan) for GVHD prophylaxis, the investigator will use post-transplant cyclophosphamide (PTCy) mycophenolate mofetil (MMF) and tacrolimus. Second, the addition of a maintenance with monthly daratumumab (administered for 1 year post allo HSCT), may further reduce the risk of disease relapse long enough in order for the graft versus myeloma to take effect.

2.2. Primary Hypotheses and Study Objectives

2.2.1. Primary hypothesis

Allogeneic Stem cell transplant with post-transplant cyclophosphamide (PTCy) mycophenolate mofetil (MMF) and tacrolimus followed by maintenance with monthly daratumumab (administered for 1 year post allo HSCT), will improve PFS and OS and reduce relapse due to graft versus myeloma effect.

2.2.2. Primary Endpoint

To obtain preliminary data on the effect of the combined treatment regimen on clinical outcomes

To develop a platform for allo HSCT in relapsed multiple myeloma patients to obtain preliminary data on the effect of combined treatment regimen on clinical outcomes

2.2.3. Secondary Endpoints

- To determine the 2 year progression-free survival (PFS)
- To determine 2 year overall survival (OS)
- To determine the cumulative incidence of grade II-IV acute-graft-versus-host-disease (aGVHD) at day 100 and 180.
- To determine the 100 days, 1 year and 2 year cumulative incidence of treatment-related mortality (TRM)
- To assess one-year GVHD-free Relapse-free Survival (GRFS)
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- To assess overall and best response rates 100 days after allo HCT, 3 months, 6 months and every 6 months thereafter until end of Daratumumab maintenance.
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- To determine Rate of MRD negativity using Next generation sequencing (FDA approved) in patients achieving a VGPR or better

To determine immune reconstitution pattern on days +30, +100, +180 and +365 following allo HSCT.

3. PATIENT ELIGIBILITY CRITERIA

3.1. Patient Inclusion Criteria

- Patients age 18-75 years old High risk relapsed MM patients and who have received at least 2 prior lines of therapy, and have obtained at least a Partial response from their salvage chemo.

High risk patients are one or more of the following: 1: patients who progressed within 24 months from their first autologous stem cell transplant (Criteria from the BMT/CTN 1302(clinical trials.gov identifier:NCT02440464); 2: Patients with at least 2 prior lines of therapy with progression within 12 months from their last line of therapy; 3: Patients with with high risk markers (del13 by conv. karyotyping only; hypodiploidy, 1q amplification or 1p deletion, t(4;14), t(14;16), t(14;20) or deletion of 17p by FISH or conv. karyotyping; R-ISS 3; or Beta-2M ≥ 5.5 mg/L)

- Patients with nonsecretory myeloma are eligible for the study. Assessments of response will be based on PET scans.
- Prior radiation is allowed as this is a very vital management of myeloma bone disease.
- Patients with ≥ PR prior to allo-HSCT
- First allogeneic transplant
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- Estimated creatinine clearance greater than 40mL/minute (using the Cockcroft- Gault formula and actual body weight)
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- Understand and voluntarily sign an informed consent
- Able to comply with the study visit schedule and other protocol requirements

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- Karnofsky Performance Score < 70%

- Planned pre-emptive/prophylactic administration of donor lymphocytes
- Active Central Nervous System(CNS) involvement with multiple myeloma defined as csf positivity for plasma cells or a parenchymal CNS plasmacytoma
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- Patient with serious medical of psychiatric illness likely to interfere with participation on this clinical study
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- Enrollment of subjects who require concurrent radiotherapy (which must be localized in its field size) should be deferred until the radiotherapy is completed and 3 weeks have elapsed since the last date of therapy
- Major surgery within 14 days of start of trial
- Patients unable or unwilling to adhere to the study assessment schedule
- Female patients who are pregnant or breastfeeding. A negative pregnancy test will be required for all women of child bearing potential

3.3 Patient Eligibility Criteria Prior to Begin Maintenance Therapy:

Between Day +90 and Day +150 after allogeneic HCT, patients will receive daratumumab maintenance. If patients do not meet the eligibility criteria for initiating maintenance, they will continue to be followed per the protocol. Starting daratumumab between day 120-150 post transplant is in line with BMT/CTN 1302, which started maintenance Ixazomib between day 60-120 post allogeneic stem cell transplant in patients with relapsed multiple Myeloma (clinical trials.gov identifier:NCT02440464). We

chose this time frame as this is the time when patients are being weaned off immune suppression with graft-versus-myeloma effect.

Patient Eligibility Criteria Prior to Initiating Maintenance Therapy:

- Platelet count ≥ 75,000/mm3
- Absolute neutrophil count (ANC) ≥ 1000/mm3
- Total bilirubin < 2x the upper limit of the normal range (ULN), except in patients with Gilbert's syndrome
- ALT/AST < 2.5x the upper normal limit
- No ≥ grade 2 visceral (gut or liver) acute GVHD. No ≥ Grade 3 any other acute GVHD
- All non-hematologic toxicities should have resolved to ≤ grade 1
- Negative for Hepatitis B virus by PCR
- Patients must be in at least a partial response

3.4 Stem Cell Donor and Source

- Matched related
- Matched unrelated
- 1 antigen mismatch related or unrelated
- Haploidentical
- Peripheral stem cell source will be used except in Haploidentical where Bone marrow stem cells will be required

3.5 Donor Exclusion Criteria

- Donors will be excluded if they are an identical twin of the recipient
- Females who are pregnant (positive serum β HCG) or uninterruptible breastfeeding will be excluded
- HIV seropositive donors will be excluded
- Donors receiving experimental therapy or investigational agents will be excluded unless approved by the protocol chair and officer
- Donors not willing and able to donate PBSC will be excluded
- Related and unrelated donors will be identified according to institutional guidelines

3.6. Diseases to be Included

- Relapsed Multiple Myeloma patients with a partial response (PR) or better prior to allo-transplantation

3.7. Inclusion of Women and Minorities

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

4. TREATMENT PLAN

	Day -5	Day -4	Day -3	Day-2	Day-1	Day 0	Day +3	Day +4
Fludarabine 30 mg/m^2, i.v	X	X	X	X				
Melphalan 70 mg/m^2 i.v			X	X				
Peripheral blood stem cell infusion						X		
Cyclophosphamide 50 mg/kg							X	X

4.1. Administration Schedule to Patients

- Patients meeting the eligibility criteria for transplant/enrollment will be treated with conditioning regimen of fludarabine and melphalan.
- Patients will receive fludarabine 30 mg/m2 (when creatinine clearance 40 –60 mL/min, reduce to 24 mg/m2) from Day -5 to Day -2 and melphalan 70 mg/m2 on Day -3 and Day -2 intravenously(Melphalan 50 mg/m2 for patients 71 years and older)
- On Day 0, patients will receive the donor stem cells.
- GVHD Prophylaxis will consist of: Cyclophosphamide 50 mg/kg will be given on days +3, and +4.
- Tacrolimus will start on day +5 at 0.05 mg/kg orally twice daily to achieve a target serum level of 5-10 mg/ml. Tacrolimus may be changed to i.v as necessary. Serum levels of tacrolimus will be measured per institution guideline. Tapering of tacrolimus will start after day 90 post HSCT with goal of having the patient receive no immune-suppressive medication by 6 months in absence of GVHD. Mycophenolate Mofetil (MMF) will be given at a dose of 15 mg/kg three times a day (based on actual body weight) with a maximum total daily dose not to exceed 3 grams (1 gram TID, IV or oral), starting Day +5 to day 35 post-transplant.
- Patients will start maintenance Daratumumab between 90-150 days post allo-HSCT as long as counts are acceptable (absolute neutrophil ≥1000/μL; Platelets ≥ 75,000/μL) and in the absence of disease progression.
- Patients will receive daratumumab maintenance (given at 16 mg/kg weekly for 8 doses, followed by every 2 weeks for 8 doses, then monthly) Maintenance will continue for 1 year in absence of unacceptable toxicity, disease progression or death

Table 1: Fludarabine/Melphalan Conditioning

4.2. Stem Cell Administration

Stem cells will be administered on Day 0 to all patients according to institutional guidelines after appropriate processing and quantification has been performed by the institutional laboratory. Stem cells are administered through an indwelling central venous catheter.

4.3. Supportive Care

All supportive care will be given in keeping with BMT CTN Manual of Procedures (http://www.cibmtr.org/DataManagement/TrainingReference/Manuals/Pages/index.aspx , https://web.emmes.com/study/bmt2/public/MOP/BMT%20CTN%20Technical%20MOP%20ver%202.0.pdf), and institutional practice.

4.3.1. Growth Factors

Growth factors will only be used on a case-by-case basis as determined by the treating physician (example, if absolute neutrophil cell count (ANC) recovery to 0.5 x 10^9/L (500/μL) has not occurred by Day +14, severe infection).

4.3.2. Prophylaxis Against Infection

- Antibiotic, antifungal and antiviral prophylaxis will be given according to institutional guidelines.
- Pneumocystis carinii prophylaxis will start on Day 30 post-transplant and continued according to institutional guidelines.
- CMV and EBV: Monitoring and treatment strategy will be done according to institutional guidelines.

4.4. Participant Risks

4.4.1. Fludarabine

Fludarabine (Flu) can lower the white blood cell count, in particular the CD4+ T-cells. The immunosuppression observed with the use of Flu increases the risk of infection, which can be life threatening. Hematopoietic suppression and immunosuppression are expected to occur as a direct effect of the antimetabolite. The most serious toxicity of Flu is neurological, and may consist of both peripheral neuropathy and encephalopathy. Toxicity can be manifested by fatigue, weakness, paresthesias, visual disturbances, somnolence and coma, that usually develop between 30 and 60 days from therapy. The incidence of serious neurological toxicity has been 36% in patients treated with > 96 mg/m2 per day for 5-7 days,131 a dose > 3 times higher than used in this protocol.

Other adverse effects include fever, nausea, vomiting, diarrhea, stomatitis, skin rash, cough and idiopathic pneumonitis.

4.4.2. Melphalan

High dose melphalan is well tolerated by patients when they are supported with blood component transfusions, PBSC/marrow transplantation and broad-spectrum antibiotics. The duration of profound bone marrow suppression decreases with the use of PBSC infusion and colony stimulating factors. Gastrointestinal toxicity, which includes severe stomatitis, esophagitis and diarrhea, can be severe or life-threatening. Most patients receiving high dose melphalan will require parental narcotics for mucositis-related pain, IV hydration; may require IV alimentation and broad spectrum IV antibiotics. Despite moderate to severe symptoms in many patients, recovery is the norm, coincident with recovery of granulocytes. Other toxicities reported include pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, hemolytic anemia, and allergic reactions.

4.4.3. Mycophenolate mofetil (MMF)

MMF side effects include: Neurologic: headache, tremor, insomnia, dizziness, excessive fatigue, weakness, Cardiovascular: tachycardia. Pulmonary: dyspnea. Gastrointestinal: nausea, vomiting, dyspepsia, abdominal pain, diarrhea, hematemesis and hematochezia. Hematologic: Neutropenia, thrombocytopenia, unusual bruising, and anemia. Endocrine and metabolic: hyperlipidemia. Miscellaneous: rash, edema, change in vision, infection, second cancers, teratogenicity, miscarriage, limited effectiveness of birth control, and progressive multifocal leukoencephalopathy (PML)

4.4.4. Cyclophosphamide

Cyclophosphamide side effects include: Gastrointestinal: nausea, vomiting, anorexia, mucositis, stomatitis, abdominal pain, diarrhea. Cardiovascular: cardiomyopathy, fluid weight gain/edema. Hematologic: myelosuppression, hemolytic anemia. Miscellaneous: skin rash, alopecia, hemorrhagic cystitis, pulmonary toxicity, temporary lethargy, secondary cancers, gonadal function impairment, sterility, and damage to fetus if taking drug while pregnant.

4.4.5. Tacrolimus

Tacrolimus side effects include: Cardiovascular: hypertension. Neurologic: confusion, dizziness, insomnia, seizures, tremors, changes in how clearly one can think. Gastrointestinal: nausea, vomiting. Hematologic: microangiopathic hemolytic anemia, thrombocytopenia. Endocrine and metabolic: hypomagnesemia, hypokalemia, hypocalcemia, erlipidemia. Miscellaneous: unwanted hair growth, changes in vision,

liver problems, reversible renal insufficiency, infections and post-transplant lymphoproliferative disorders

4.4.6. Daratumumab Administration

Daratumumab will be dosed at 16mg/kg following guidelines provided in package insert. Dose is calculated based on actual body weight.

Very common side effects with daratumumab (affects more than 1 in 10 patients).

- Infusion related reaction (see separate section)
- Infection of the upper respiratory tract infection such as nose, sinuses throat or airway
- Infection of the lung
- Low neutrophils
- Low platelets
- Low red blood cells
- Low lymphocytes
- Numbness/tingling of the hands, feet or limbs
- Headache
- Cough
- Shortness of breath
- Diarrhea
- Nausea
- Vomiting
- Muscle spasms
- Fatigue
- Fever
- Swelling of hands, feet or limbs

Common side effects with daratumumab (affects 1 to 10 in 100 patients).

- The flu
- Sepsis
- Irregular heartbeat

Uncommon side effects with daratumumab (affects 1 to 10 in 1,000 patients).

- Shingles (Herpes zoster)
- High blood pressure
- Low oxygen
- Swelling of the throat
- Inflammation of lung tissue (pneumonitis)
- Difficulty with blood testing prior to blood transfusion (Indirect Antiglobulin Testing positive)

Infusion-Related Reactions

Infusion–related reactions were reported in approximately half of all patients treated with daratumumab and most were grade 1 or 2. It usually occurs with the first infusion and during or within the first few hours of the start of the infusion.

Signs and symptoms of infusion-related reactions may include respiratory symptoms, such as stuffy nose, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms are having trouble breathing (wheezing), runny nose, fever, chest discomfort, itching of the skin, and low blood pressure or high blood pressure. Most of the observed infusion-related reactions so far were mild or moderate, and ended by temporarily stopping the infusion and giving medicines to treat the side effect.

Severe reactions include narrowing and obstruction of the respiratory airway (bronchospasm), low oxygen, shortness of breath, high blood pressure, swelling in the throat and fluid accumulation in the lungs (pulmonary edema).

Pre-Infusion Medications:

First infusion: Acetaminophen 325 mg orally, diphenhydramine 25 mg orally or IV, dexamethasone 20 mg orally or IV, montelukast 10 mg orally, and famotidine 20 mg orally or IV.

Subsequent infusions: Acetaminophen 325 mg orally, diphenhydramine 25 mg orally or IV, and dexamethasone 20 mg orally or IV.

Post-Infusion medication: dexamethasone 20 mg orally on day after Daratumumab infusion

Management of infusion reactions: we will interrupt infusion for any reaction and manage as appropriate per USPI information and institutional guideline. We will reduce the infusion rate for grade 1, 2, or 3 reaction. We will permanently discontinue therapy for an anaphylactic reaction or life-threatening grade 4 infusion reaction and treat with appropriate emergency care per instirutional guideline (eg, glucocorticoids, epinephrine, bronchodilators, and/or oxygen as appropriate).

Please refer to the respective USPI for each drug for management of study-drug related toxicities.

5. Management of Toxicities

Toxicities will be scored as per the NCI's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Toxicities of the blood/bone marrow, gut, liver, and skin will be excluded from the common toxicity criteria and evaluated separately since they are likely to be affected by GVHD.

5.1. GVHD

Acute GVHD is graded according to the Bone Marrow Transplant Clinical Trials Network Methods of Procedure (BMT CTN MOP) (see Appendix D). The first day of acute GVHD onset at a certain grade will be used to calculate cumulative incidence curves for that GVHD grade (e.g. if the onset of grade I acute GVHD is on day 20 post-transplant and the onset of Grade II is on Day 60 post-transplant, then time to grade II is day 60). The endpoint of acute GVHD will be evaluated through day 180 post-transplant.

Whenever possible, the diagnosis of GVHD should be confirmed with a biopsy of the involved organ and histological examination of a biopsy specimen by a pathologist experienced in the diagnosis of GVHD. Diagnosis of isolated hepatic GVHD must be made by liver biopsy.

Specific therapy of GVHD will not be mandated by protocol, although it is recommended that only Grade II-IV GVHD be treated with systemic therapy. A recommendation for initial therapy of GVHD is methylprednisolone, 2 mg/kg/d IV (or an equivalent corticosteroid). If the patient responds to steroids, the steroid will be tapered as per institutional standards.

5.2. Veno Occlusive Disease (VOD)

Treatment of veno-occlusive disease of the liver will be treated per institutional standards.

5.3. Idiopathic Pneumonia Syndrome/Diffuse Alveolar Hemorrhage

Treatment of idiopathic pneumonia syndrome/diffuse alveolar hemorrhage will be treated per institutional standards.

5.4. Thrombotic Microangiopathy

Thrombotic microangiopathy will be defined according to BMT CTN guidelines. The diagnostic criteria include complement biomarker analysis and the concurrent occurrence of: Red cell fragmentation on a manual differential (2 + schistocytes) with a negative Coombs test, and LDH > normal and either renal dysfunction (doubling of serum creatinine or a decrease > 50% in the measured creatinine clearance) or

Neurological dysfunction unexplained by another etiology. Thrombotic microangiopathy should be managed as per institutional guidelines

5.5. Engraftment Failure

Engraftment will be considered to be three consecutive measurements ANC > 0.5 x 109/L (500/µL) over three or more days. If the ANC ≤ 0.1 x 109/L on Day 28, evaluation for graft failure will be initiated, including bone marrow aspiration/biopsy, cytogenetics and/or fluorescence in situ hybridization (FISH) if appropriate. Plans for a second stem cell infusion will be made depending on the results of the work-up.

5.6. Patient Withdrawal

A patient should be removed from the treatment whenever it is necessary to safeguard his/her welfare. Occurrence of a significant adverse event or laboratory abnormalities unexpected for these patients may also necessitate discontinuation from the treatment. Additional reasons for removing a patient from the study are:

- Patients who participate in another investigational drug trial
- Patients' non-compliance with the protocol
- Patients who express a desire to withdraw from the study (the patient has the right to withdraw for any reason without prejudice)
- Evidence of progressive disease would require withdrawal of the patient from the treatment.
- Any other reasons deemed by the principal investigator and treating physician.

The reason for any patient withdrawal from treatment should be recorded on the CRF and the occurrence should be reported to the principal investigator by email. When a patient is removed from treatment, he/she will receive treatment according to the standard of care (SOC) in the medical center and will be followed-up according to the study schedule whenever possible.

A patient who is removed from treatment by the investigator due to an AE or SAE will be followed until resolution of the toxicity to Grade 1 or baseline. All the tests that are required to assess the patient condition will be made as frequent as necessary until the AE or SAE has been resolved. Samples that have already been obtained will be processed.

A patient who withdraws consent before starting the study will not be followed up.

A patient who is removed from treatment by the investigator since he/she did not keep the appointments will be hard to follow given the circumstances. The extreme situation of this occurrence is a patient who is defined as "lost to follow-up". Attempts to follow up on the subject will be made as long as the consent has not been withdrawn by the subject. Samples that have already been obtained will be processed.

6. Study Drug Supply

Tacrolimus, Cyclophosphamide, Mycophenolate Mofetil and Daratumumab are commercially available agents and will be administered as described in section 4.

7. Statistical Consideration

This study is a pilot study focusing on developing a platform for allo-HSCT in relapsed multiple myeloma patients. Total of 20 patients will be expected to be enrolled across 2 years and these patients will be followed up for 2 years. Clinical outcomes such as GVHD, relapse and survival data will be collected and analyzed as detailed below. These outcome data analysis will be purely viewed as preliminary and hypothesis generating and will be used to guide the design of future larger studies.

The safety and tolerability of this combined treatment regimen in allo-HSCT, adverse events by grade will be summarized. The occurrence of grade 3+ adverse events according to CTCAE will be summarized as well. Adverse events will initially be reviewed regardless of attribution, but also according to whether adverse events are possibly, probably, or definitely related to treatment.

Secondary endpoint analysis plan:

The 2-year progression-free survival (PFS), will be measured from the date of transplant until the date of relapse or date of death from any cause. Patients who do not relapse or die will be censored at the date of last clinical assessment. Kaplan-Meier curves will be generated to estimate the PFS rates at 2 years post-transplant. To evaluate the potential association between patient characteristics and PFS, the log-rank test will be used to compare the PFS curves and Cox proportional hazard regression model will be used to estimate the hazard ratio. The overall survival (OS) will be defined as the time from the date of transplant to death or last contact date if no death. GVHD-free Relapse-free Survival (GRFS), measured from the date of transplant until the date of grade II-IV acute GVHD, chronic GVHD, disease relapse or progression, or death from any cause, whichever occurs first. Patients who do not experience an event will be censored at the date of last clinical assessment. A similar analysis approach described above for PFS will be applied for the GRFS analysis.

To examine the cumulative incidence of grade II-IV acute GvHD (aGVHD), the event will be onset of grade II-IV aGvHD and time to aGvHD will be defined as the period of time from transplantation to the event of aGvHD. Death and early relapse without aGvHD will be competing risks. Cumulative incidence rate of aGVHD with 95% confidence intervals will be estimated from the cumulative incidence curves. To evaluate the association between patient characteristics and aGVHD, the Gray's test accounting for competing risks will be used to compare the cumulative incidence curves and a proportional hazards model for the sub distribution of competing risks will be used to estimate the

hazard ratio. The cumulative incidence of chronic GVHD (cGVHD) will be similarly analyzed. To determine the rate of relapse, the event time will be from the date of transplant to relapse treating death from any cause as a competing risk. Patients without relapse or death will be censored at last clinical assessment date. The similar analysis approach used for outcome of aGVHD will be applied.

To determine the 100-day, 1-year and 2-year cumulative incidence of treatment-related mortality (TRM), the event will be death due to reasons other than disease and the time will be measured from the date of transplant to date of death. The competing risk for NRM will be death due to disease. The cumulative incidence curve accounting competing risks will be generated to estimate the cumulative incidence rate at various time points.

The assess the overall and best response rate at various time points, the proportion of each type of response with a 95% CI will be reported for all evaluable patients, assuming a binomial distribution. MRD status will be performed on patients with VGPR or better pre-transplant, day +100 and day+365 post-transplant. The rate of minimal residual disease-negativity is defined as the proportion of patients who achieved minimal residual disease-negative status at the respective time point, in accordance with the International Myeloma Working Group criteria.(36) Minimal residual disease was evaluated by next-generation sequencing using ClonoSEQ Assay 2.0.(37)

8. Stopping Rule:

Monitoring of the key safety endpoint of death will be conducted. The rate of overall mortality will be monitored up to Day 100 post-transplant. The null hypothesis that the Day 100 mortality rate is less than or equal to 10%. The stopping rule will be triggered if there is significant evidence that the overall death rate exceeds 10%, that is, if the lower bound of the one-sided 95% CI exceeds 10%. The rationale of a lower confidence bound is to be certain that the estimated true rate is not significantly higher than the rates deemed clinically acceptable. If the number of death equals or exceeds the numbers in the table below, then the study will be suspended to accrual pending further consultation with the DSMB. We will first enroll 3 patients and assess toxicity through day 100, before continuing enrollment.

One year non-relapse mortality after allo-HSCT is 16-20%. Given that patients will be on daratumumab maintenance, while not expected, monitoring for excessive mortality is necessary. At one year post allo-HSCT, patients would have transitioned to the monthly daratumumab. The stopping rule will be triggered if the one-year non-relapse mortality exceeds 20%.

The rate of chronic GVHD(cGVHD) occurs in 50-60% of patients undergoing allo-HSCT, with 30-35% being extensive cGVHD. The stopping rule will be triggered if the rate of extensive cGVHD exceeds 35%.

Table 3: Incidence of death

Number of patients enrolled	Number of death
3	2
4-8	3
9-14	4
15-20	5

9. Accrual and Accrual Period

Relapsed MM patients who are candidates for allo-HSCT will be assessed for accrual. A total of 20 patients will be accrued. The estimated accrual period is 2 years.

10. Follow-Up Period

Patients will be followed for 1 year after end of Daratumumab treatment
Follow-Up and Schedule of Events

10.1. Follow-up Schedule for Patients (Recipients)

Study Visit	Target Day Post-Transplant
1 week	7 ± 3 days
2 week	14 ± 3 days
3 week	21 ± 7 days
4 week	28 ± 7 days
5 week	35 ± 7 days
6 week	42 ± 7 days
7 week	49 ± 7 days
8 week	56 ± 7 days
9 week	63 ± 7 days
10 week	70 ± 7 days
11 week	77 ± 7 days
12 week	84 ± 7 days
100 day	100 ± 9 days
6 month	180 ± 28 days
12 month	365 ± 28 days
18 month	547 ± 28 days
24 month	730 ± 28 days

10.2. Evaluation During Treatment

Clinical examination, ECOG/WHO PS, vital signs, toxicity assessment and documentation of concomitant medications will be performed at each outpatient visit. Toxicity will be assessed according to the NCI CTCAE.

10.3. Post-Treatment Follow-up

After the end of study treatment (whatever the reason for discontinuation), the patient will be followed for up to one year to evaluate the incidence of acute and chronic GVHD, relapse, PFS and OS.

All patients who discontinue the trial secondary to an adverse event thought to be related to protocol therapy (probably, possible, or definite) should be followed until resolution, stabilization, return to a baseline condition, or death.

Overall and progression free survival will be determined through clinic visits or phone interviews with clinical research staff.

10.4. Sample Collection for Immunologic Correlative Studies

All patients enrolled on this trial will have samples procured for all proposed laboratory correlative studies as summarized in Section 13. Samples will be collected and sent to the appropriate research lab(s) for processing. Upon receipt, each sample will be recorded and coded with a unique sample number to keep patient identification confidential. PBMCs and plasma (and/or serum) will be aliquoted and cryopreserved. The vials of viably frozen cells for all time points for each patient will be thawed at the same time whenever possible to avoid inter-experimental variability.

10.5. Patient Study Calendar

Schedule of Study Assessments	Baseline [1]	Day +0	Day +7	Day +14	Day +21	Day +28	Day +35	Day +42	Day +49	Day +56	Day +63	Day +70	Day +100	Day +180	Day +365	Day +547	Day +730
Informed Consent	x																
Medical History- anti-cancer therapies	x																
Physical exam	x												x	x	x		
Vital Signs[2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Karnofsky performance status	x	x	x			x			x				x	x	x	x	x
HCT-Specific Comorbidity Index score	x																
Complete blood count[3]	x	x	x	x	x	x					x		x	x	x	x	x
Serum chemistry, and liver function test[4]	x	x	x	x	x	x					x		x	x	x	x	x
Pregnancy test	x																
HIV evaluation	x																
Infectious disease panel[5]	x																
EKG and LVEF[6]	x																
Quantitative Immunoglobulins[7]													x	x	x	x	x
CD34/CD3 cell dose infused		x															
Immune reconstitution panel & Other Correlative studies[8]	x	x				**X**							**X**	**X**	**X**		
ANC and Platelet recovery[9]			x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse event (CTCAE) assessment[10]			x	x	x	x	x	x	x	x	x	x	x	x	x		
Acute GVHD assessment			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Bone marrow biopsy & aspirate	x												x		x		x

(response assessment)`[11]																	

[1]Baseline refers to the period prior to conditioning. Assessments should be made within 4 weeks prior to start of transplantation.
[2] Vital signs: blood pressure, pulse rate, respiratory rate and temperature, weight
[3] Daily during the post-infusion period while hospitalized (recommended) and once weekly after discharge until Day 28.
[4] Serum chemistries panel: electrolytes, BUN, ALT, AST, creatinine, bilirubin, alkaline phosphatase, LDH, albumin. Electrolytes to include sodium, potassium, chloride, carbon dioxide, and calcium.
[5] Infectious disease panel: Cytomegalovirus (CMV) antibody, Hepatitis B sAg, Hepatitis C Ab, HIV /HCV NAT, HIV Ab, HTLV Ab, Epstein-Barr Virus (EBV) IgG and IgM, herpes simplex virus (HSV) IgG and IgM
[6] LVEF: left ventricular ejection fraction to be determined by MUGA or echocardiogram
[7] IgG, IgM and IgA.
[8] Peripheral blood for immune reconstitution panel drawn in one-10ml EDTA or ACD-solution-A tube and sent to Dr. Lozanski in the OSU-Medical Center Clinical flow Cytometry Laboratory. Day 0 will be apheresis product
[9] Record time to neutrophil engraftment defined as first of three consecutive days with ANC ≥ 0.5 x 10^9/L, and platelet engraftment defined as first day of platelet count ≥ 20,000 x 10^9/L, without transfusion for 7 consecutive days.
[10] Adverse event assessment will include a review of all toxicities experienced during the entire assessment period and the highest grade for each toxicity during the assessment period will be recorded on the Toxicity form in AdvantageEDC.
[11]Bone marrow aspirate and biopsy required at baseline. On Days +100, +365, and +730. Other bone marrow biopsy will be performed if clinically indicated. Other tests and/or imaging studies for response assessment will be performed as clinically indicated.

11. Analysis Definitions and Endpoints

11.1. Safety Endpoints

We will describe the safety profile of treatment by the recording of adverse events experienced by patients in the trial and by the monitoring of clinical laboratory values. Adverse events and toxicities in both donors and patients will be described using the NCI CTCAE V 5.0 criteria. Frequency and severity of adverse events according to body system and severity criteria will be described. In addition, frequency of grade 3 or 4 adverse events will be described separately. Causality will also be noted.

Laboratory assessments will also be described according to the NCI CTCAE V5.0 criteria, with separate descriptions for grade 3 or 4 laboratory abnormalities. Clinically significant laboratory abnormalities will be described as well.

11.2. Efficacy Analysis Endpoints

Neutrophil and platelet engraftment: Neutrophil engraftment will be defined as first of three consecutive days with ANC $\geq 0.5 \times 10^9$/L post-conditioning regimen induced nadir. Similarly platelet engraftment is defined as first day of platelet count $\geq 20{,}000 \times 10^9$/L, without transfusion for 7 consecutive days.

Graft versus host disease (GVHD): GVHD occurring anytime after day 100 post transplant will be termed chronic GVHD, otherwise it will be termed acute GVHD. Standard criteria will be used for the diagnosis and grading of acute and chronic GVHD (38, 39) (Appendix D). The first day of acute GVHD onset at a certain grade will be used to calculate cumulative incidence curves for that GVHD grade (e.g. if the onset of grade I acute GVHD is on day 20 post-transplant and the onset of Grade II is on Day 60 post transplant, then time to grade II is day 60). The endpoint of acute GVHD will be evaluated through day 100 post transplant.

Whenever possible, the diagnosis of GVHD should be confirmed with a biopsy of the involved organ and histological examination of a biopsy specimen by a pathologist experienced in the diagnosis of GVHD. Diagnosis of isolated hepatic GVHD must be made by liver biopsy.

Patients will be monitored for development of acute GVHD weekly until day +100. For diagnosis of GVHD, biopsy is recommended, but not required.

Non relapse mortality (NRM): NRM will be defined as death from any cause other than relapse.

Progression free survival (PFS): PFS will be measured from the day of allogeneic stem cell infusion to the day of documented relapse or progression.

Overall survival (OS): OS will be measured from the day of allogeneic stem cell infusion (day 0) to death from any cause, with censoring performed at date of last contact.

11.3. Relapse of Malignancy

11.3.1. Myeloma

For Myeloma, relapse will be diagnosed when:

- Development of new soft tissue plasmacytomas or bone lesions, or
- Definite increase in the size of existing plasmacytomas pr bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measured lesion, or
- Hypercalcemia (>11.5 mg/dl [2.65 mmol/l]), or
- Decrease in hemoglobin of .2g/dl (1.25 mmol/l) without any other known causes, or
- Rise in serum creatinine by 2mg/dl or more (177µmol/l or more) without any other known causes, or
- Reappearance of serum or urine M-protein by immunofixation or electropheresis or development of ≥ 5% plasma cells in the bone marrow in a patient with previous complete response.

(See Appendix C)

11.3.2. Registration Guidelines

Eligible patients and their donors will be entered on study at the Ohio State University. The Study Coordinator should be called between the hours of 8:00 AM and 4:30 PM to verify eligibility.

11.3.3. Assignment of Study Numbers

Each patient and their donor enrolled in the study will be registered in the OSU's Clinical Trials Management Application at study entry. Each patient enrolled will be assigned a sequential study identifier by the Clinical Trials Management Application.

11.3.4. Study Records

Study data will be collected in standardized case report forms (CRF). The investigator or designate will record all patient information, including patient identification, disease stage, previous treatment, as well as information concerning drug administration, results of laboratory tests, toxicity and efficacy data.

A specific form will be used for recording and reporting serious adverse events as defined in section 9

11.3.5. Selection Procedures

All eligible patients and their donors must be registered. This must be done before the start of treatment. On receipt of all the necessary baseline information, a clinical research coordinator will assess whether the patient is eligible or not.

12. Correlative Studies

12.1. Correlative Studies

Immune Reconstitution. Peripheral blood from patients, to assess recovery of quantitative immunoglobulin levels and immune reconstitution following transplantation will be collected in one 10 ml EDTA or ACD-solution-A tube on day of admission, days 0 (apheresis product),+30, +100, +180 and +365 post-transplant.
The peripheral blood samples will be collected and received within 12h following collection. A research account number (R) will be established with the research billing and compliance office. Each sample will have proper permanent label with study identifier by the Clinical Trials Management and printed proper requisition that will have study R#, both on tube and requisition, patient or donor study identification, date and time of specimen collection, sample type blood (peripheral blood, bone marrow, pheresis product) and specific time point the sample represents. Assessment will be done in Dr. Lozanski'a lab in the clinical flow cytometry laboratory. Prior to staining all samples will be analyzed for viability using 7AAD method. Only samples with viability of at least 97% will be accepted for further analysis. All samples will be stained using PrepPlus2 automated staining system (Beckman Coulter) using five color whole blood staining technique with panels of directly conjugated monoclonal antibodies (see table below) used in predetermined quantities. Multiparametric analysis will be performed with gating strategy based on OCD45 staining and light side scatter characteristics that allow good separation of lymphocyte, monocyte and myeloid cell populations. Detailed immunophenotypic characterization of the lymphocyte gate will be performed using Prism plot algorithm (Beckman Coulter). The results will be reported as % of lymphocyte gate and as % of total leukocytes analyzed. The results will also be reported as an absolute number of specific cell types per microliter of blood. Absolute cell number will be calculated based on

dual platform method using % of lymphocytes expressing specific immunophenotypic profile (derived from prism plot) and absolute number of lymphocytes derived from analysis of each whole blood sample using ActDIFF hematology analyzer (Beckman Coulter).

13. Definitions of Adverse Events and Causality

13.1. Monitoring of Adverse Events

Significant adverse events should be identified and recorded, then seriousness, expectedness, and causality will be assessed using the definitions that follow. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting.

13.2. Definitions of Adverse Events and Causality

An **Adverse Event (AE)** is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. For marketed products in the U.S., a **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- Results in death (if the patient's death is suspected as being a direct outcome of the adverse event)
- Is life-threatening (the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect (i.e., exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in a child)
- Requires intervention to prevent permanent impairment or damage
- Overdosage (regardless of adverse outcome) of any study medication. An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important.
- Pregnancy
- Is an important medical event, defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for

allergic bronchospasm, or blood dyscrasias or convulsions that do not result in hospitalization.

The SAE reporting period begins once study drug treatment is initiated to within 30 days following cessation of treatment. AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

Additionally, any serious adverse event considered by an investigator to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the IRB

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Note: The term "life-threatening" in the definition of "Serious Adverse Event" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

An **Unexpected Adverse Event** is not listed in the current US Package Insert may be mentioned in the package insert, but differs from the event because of greater severity or specificity.

Causality is a determination of whether there is a reasonable possibility that the drug may have caused or contributed to an adverse event. It includes assessing temporal relationships dechallenge/rechallenge information, association (or lack of association) with underlying diseases, and the presence (or absence) or a lack of one or more likely causes.

The Investigator must attempt to determine if an adverse event is in some way related to the use of the study drug. This relationship should be described as follows:

Unlikely: The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug.

Unrelated: The adverse event is clearly not related to the study drug.

Possible: The event follows a reasonable temporal sequence from administration of the study drug or the event follows a known response pattern to the study drug *BUT* the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication

Probable: The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition *or* the event cannot be the effect of a concomitant medication

Definite: The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug

Unknown: Based on the evidence available, causality cannot be ascribed

Common Terminology Criteria Adverse Events (CTCAE) – a descriptive terminology developed by the National Cancer Institute (NCI) for use in reporting adverse events. The CTCAE includes a grading (severity) scale for each adverse event term.

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Grade 0	No adverse event or within normal limits
1	Mild adverse event
2	Moderate adverse event
3	Severe adverse event
4	Life-threatening or disabling adverse event
5	Fatal adverse event

13.3. Serious Adverse Events

When the principal investigator has determined that a Serious Adverse Event has occurred, the principal investigator is responsible for providing all Serious Adverse Events to the IRB and within two working days of this determination. This applies to initial and follow-up information.

Follow-up Reports:

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any Serious Adverse Event and complete follow-up forms as necessary. The patient must be followed up until recovery, stabilization or return to baseline. This may mean that follow-up will continue after the patient has completed the trial and that additional investigations may be necessary.
- Any reportable Serious Adverse Events brought to the attention of the Investigator at any time after cessation of the trial and considered by him/her to be reasonably associated with medication administered during the period should also be submitted to the IRB. As with the initial submission to the IRB, the principal investigator is also responsible for providing all follow-ups of Serious Adverse Events to the IRB.

13.4. Reporting of Adverse Event Information Following Study Completion

Collection of safety information following the end of investigational product administration is important in assisting in the identification of possible delayed toxicities or withdrawal effects. All SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time.

13.5. Patient Withdrawal

A patient should be withdrawn from the trial treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible.

Patients should be withdrawn from therapy if any of the following occurs:

- The occurrence of unacceptable toxicity indicating the need for cessation of treatment. Patients may continue with correlative studies.
- Patient has progressive disease while receiving treatment
- The physician feels it is in the best interest of the patient to stop treatment and the physician may determine whether to continue with correlative studies.
- Patient refusal to continue with therapy.
- Non-compliance by the patient with protocol requirements.
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome, if possible.
- Patient becomes pregnant.

- Termination of the study.

The reason and date of discontinuation are to be documented in the patient's medical record and in the CRF.

The investigator should complete all end of treatment procedures when a patient withdraws from treatment. All patients who discontinue the trial secondary to an adverse event should be followed until resolution, stabilization or return to a baseline condition.

All patients who receive one dose of study treatment should be included in any safety analysis.

The investigator may discontinue the trial at any time. Reasons for early trial discontinuation may include, but are not limited to, unacceptable toxicity of study treatment, a request to discontinue the trial from a regulatory authority or an IRB, or poor enrollment.

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15. Appendices

Appendix A: HCT-SPECIFIC COMORBIDITY INDEX SCORE

Comorbidities	Definition	Score
Migraine/headache		**0**
Osteoporosis		**0**
Osteoarthritis		**0**
Hypertension		**0**
Gastrointestinal	Including inflammatory bowel disease	**0**
Mild pulmonary	DLCo and/or FEV_1 >80% or Dyspnea on moderate activity	**0**
Mild renal	Serum creatinine 1.2-2 mg/dl	**0**
Endocrine		**0**
Bleeding		**0**
Coagulopathy	Deep venous thrombosis or pulmonary embolism	**0**
Asthma		**0**
Arrhythmia		**1**
Myocardial	Coronary artery disease, congestive HF, history of medically documented MI, EF 50%	**1**
Mild hepatic	Chronic hepatitis, Bilirubin >ULN- 1.5 X ULN, or AST/ALT >ULN-2.5XULN	**1**
Cerebro-vascular accident	History of transient ischemic attack or cerebro-vascular accident	**1**
Morbid obesity		**1**
Diabetes	Requiring treatment	**1**
Depression/anxiety		**1**
Infection	Requiring continuation of treatment after Day 0	**1**
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	**2**
Moderate pulmonary	DLCo and/or FEV_1 66-80% or Dyspnea on slight activity	**2**
Peptic ulcer	Patients who have required treatment	**2**
Moderate-severe renal	Serum creatinine >2 mg/dl, on dialysis, or prior renal transplantation	**2**
Valvular heart disease	Except mitral valve prolapse	**3**
Prior solid tumor	Requiring treatment with chemotherapy	**3**
Moderate-severe hepatic	Liver cirrhosis, Bilirubin >1.5 X ULN, or AST/ALT >2.5XULN	**3**
Severe pulmonary	DLCo and/or FEV_1 65% or Dyspnea at rest or requiring oxygen	**3**

Total score is the sum of all comorbidities present at time of transplantation.

Appendix B: KARNOFSKY PERFORMANCE STATUS SCALE

Index	Specific Criteria	General
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity; no special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease.	
80	Normal activity with effort, some signs or symptoms of disease.	
70	Care for self, unable to carry on normal activity or to do work.	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.
60	Requires occasional assistance from others but able to care for most needs.	
50	Requires considerable assistance from others and frequent medical care	
40	Disabled, requires special care and assistance.	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, but death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund	
0	Dead	

Appendix C: International Myeloma Working Group Response Criteria

Response Category	Response Criteria[a]
SCR	CR as defined below plus • Normal FLC ration and • Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours
PR	≥ 50% reduction of serum M-Protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are unmeasurable[d] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and the serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above, if present at baseline a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD[e]	Not meeting criteria for CR, VGPR, PR, or progressive disease
Relapse Category[f]	**Relapse Criteria**
Progressive disease	**Requires only one of the following**: Increase of ≥ 25% from baseline in: • Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)[g] • Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 hours) • In patients without measurable serum and urine M-protein levels the difference between involved and

	uninvolved FLC levels, the absolute increase must be > 10 mg/dl. • Bone marrow plasma cell percentage, the absolute % must be ≥ 10%[h]. • Definite development of new bone lesions or soft tissue plasmacytomas increase in the size of existing bone lesions or soft tissue plasmacytomas. • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder.
Clinical relapse (Not used for TTP or PFS)	**Clinical relapse requires one or more of**: • Development of new soft tissue plasmacytoma or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dl [2.65 mmol/l]) • Decrease in hemoglobin of ≥ 2 g/dl (1.25 mmol/l) • Rise in serum creatinine by 2 mg/dl or more (177 μmol/l or more)
Relapse from CR [i]	**Any one or more of the following:** • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥ 5% plasma cells in the bone marrow[j] • Appearance of any other sign or progression

a. All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response criteria.
b. Confirmation with repeat biopsy not necessary.
c. Presence/absence of clonal cells is based upon the κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ration reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.
d. Applicable only to patients who have 'measurable' disease defined by at least one of the following three measurements: Serum M-protein ≥ 1 g/dl, Urine M-protein ≥ 200 mg/24hour, Serum FLC assay involved FLC level ≥ 10 mg/dl provided serum FLC ration is abnormal.
e. Not recommended for use as an indicator of response; stability of disease is best described by providing the time too progression estimates).
f. All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.

Appendix D: Acute GVHD Grading

Stage	Skin	GI	Liver
1	<25% rash	Diarrhea > 500 mL/d or persistent nausea	Bilirubin 2-3 mg/dL
2	25-50% rash	> 1000 mL/day	Bilirubin 3-6 mg/dL
3	> 50% rash	> 1500 mL/day	Bilirubin 6-15 mg/dL
4	Generalized erythroderma with bullae	Large volume diarrhea and severe abdominal pain ± ileus	Bilirubin > 15 mg/dL

Consensus GVHD Grading (Przepiorka, et al., 1995)

Grade	Skin	GI	Liver
I	Stage 1-2	0	0
II	Stage 3 or	Stage 1 or	Stage 1
III	---	Stage 2-4	Stage 2-3
IV	Stage 4	---	Stage 4

Appendix E. Ethical and regulatory

Ethical Principles

The study should be conducted according to the principles outlined by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments; the International Conference on Harmonization Guidelines for Good Clinical Practice; and FDA regulations regarding the conduct of clinical trials and the protection of human subjects.

Protocol Compliance and Protocol Revisions

The study must be conducted as described in this approved protocol. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients. Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to CureTech. If the revision is an administrative letter, the investigator(s) must inform the IRB.

Informed consent

It is the responsibility of the investigator to obtain written informed consent from a patient or a patient's legal representative before any study related procedures are performed. The Investigator will provide an informed consent in compliance with ICH GCP and U.S. FDA guidelines (21 CFR 50). The informed consent document must clearly describe the potential risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the Investigator or site staff and to decide whether or not to participate. The informed consent must be approved by the IRB prior to being presented to a potential patient.

One copy of the patient's signed, dated and witnessed written consent will be kept in the patient's medical record and one copy will be given to the patient or the patient's legal representative.

Institutional Review Board (IRB) Approval

The Investigator must obtain the approval of the protocol, the informed consent document and any other material used to inform the patient about the nature of the trial from the local IRB in the form of a written letter. On the approval letter, which must be signed by the chairperson of the IRB or the chairperson's designee, the following items should be clearly stated: trial title, protocol number and version, study-related documents (protocol, informed consent material, advertisement when applicable), IRB review date, and IRB decision. The trial should not start until a copy of this written approval has been received by the Investigator. If the investigator is a member of the IRB, the Investigator may participate in any discussion of the study, but may not participate in the final vote deciding whether to approve the study.

Annually, or more often if stipulated by the IRB, and at the completion or termination of the study, the Investigator will report the progress of the trial to the IRB and CureTech, Inc. (see contact information in section “Serious Adverse Events”)

Additional Responsibilities of the Investigator
The investigator(s) agrees to perform the study in accordance with ICH Good Clinical Practice and FDA regulations. The Investigator is required to ensure compliance with respect to the investigational drug schedule, visit schedule and procedures required by the protocol.

The investigator should be able to recruit the required number of suitable patients and should have sufficient time to properly conduct and complete the trial. The Investigator should have available an adequate number of qualified staff and adequate facilities for the duration of the trial, and should ensure that all persons assisting with the trial are adequately informed about the protocol, the protocol-defined procedures, protocol therapy and trial related duties and functions..

The Investigator should be responsible for all trial-related medical decisions. During and following a patient’s participation in a trial, the investigator should ensure that adequate medical care is provided to a patient for any adverse events related to the trial.

Use and Completion of Case Report Forms (CRFs)
It is the responsibility of the Investigator to monitor the preparation and accurate use of CRFs to record all observations and other data pertinent to the clinical investigation. All CRFs should be completed in their entirety to ensure accurate interpretation of data. Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed next to the previous value, initialed and dated by the authorized person.

Confidentiality
It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms must never contain the name of a trial patient. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial. Personal medical information may be reviewed by a representative of Merck & Co, Inc., of the IRB, or of regulatory authorities in the course of auditing the trial. Every reasonable effort will be made to maintain such information as confidential.