MSK PROTOCOL COVER SHEET

A Phase I/II Trial of Ipilimumab after CD34-Selected Allogeneic Stem Cell Transplantation for Patients with Relapsed/Refractory Multiple Myeloma

Principal Investigator/Department: Gunjan Shah, MD/Medicine

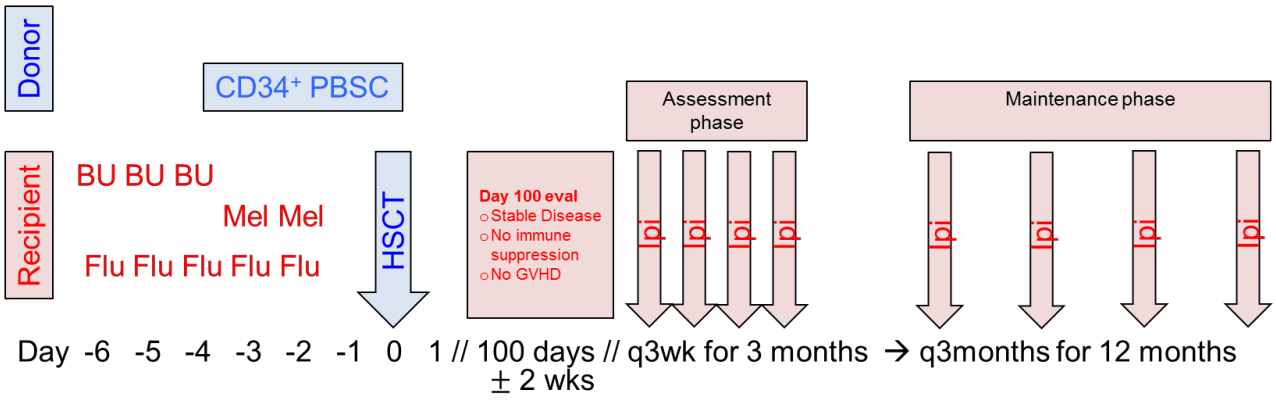
Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase I/II, single arm, open label trial to explore the safety and efficacy of ipilimumab when used as a maintenance strategy after CD34-selected allogeneic hematopoietic stem cell transplant (alloHSCT) for relapsed/refractory multiple myeloma (MM). We hypothesize that ipilimumab used in the context of CD34-selected alloHSCT platform will be safe and will reduce the risk graft-versus-host disease that has been associated with checkpoint inhibition in conventional alloHSCT. We also hypothesize that ipilimumab used after alloHCT and in the absence of active disease has potential to overcome the immune dysregulation that drives MM relapse by directing a newly reconstituting host immune system away from immune senescence and toward effective anti-tumor surveillance.

Patients with multiple myeloma that have undergone more than 2 lines of prior therapy, and those eligible for CD34-selected alloHSCT from 10/10 matched human leucocyte antigen (HLA)-compatible donors are eligible for enrollment. All enrolled patients will be evaluated at day 100 (±2 weeks) after alloHSCT to assess for eligibility to receive ipilimumab. The Phase I cohort will be made up of 6 patients treated with ipilimumab 3 mg/kg every 3 weeks for 4 doses (assessment phase). Each patient in this group during the assessment phase will be evaluated twice weekly for four 3-week cycles. In the absence of dose-limiting toxicity (DLT) in a given patient, the patient will then be treated for 4 further doses every 3 months in a maintenance phase. The DLT window is from the first dose of ipilimumab until three weeks following the the fourth dose in the initial assessment phase. If DLTs are observed in no more than one patient during the assessment phase of Phase I, a single arm Phase II study will be initiated and will accrue an additional 33 patients using the same dose (first every 3 weeks for 4 doses in an assessment phase followed by every 3 months for 4 doses). If more than one patient in the initial Phase I cohort has any observed DLT with the target ipilimumab dose, a second 6-patient Phase I cohort at a reduced ipilimumab dose will be opened to determine the dose for Phase II. Patients in all cohorts will be scheduled to receive ipilimumab for 4 doses in assessment phase and four in maintenance phase (total therapy duration 15 months; until 18 months post alloHSCT) unless limited by intolerance to therapy or disease relapse. We anticipate to complete accrual in two years.

Figure 1:



This potentially effective relapse prevention strategy would address an unmet need in patients with high risk multiple myeloma in whom numerous other strategies have failed and may also provide context to incorporate ipilimumab as a component of combination chemotherapy strategies in this challenging patient population.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Phase I:

The primary objective of the phase I component of this study is to identify a dose of ipilimumab administered to patients with relapsed refractory multiple myeloma (RRMM) following CD34-selected alloHSCT for a subsequent phase II trial.

Phase II:

Primary:

The primary objective of the phase II component of this study is to estimate the 11-month (from time of ipilimumab) progression free survival (PFS) in patients with high-risk RRMM treated with ipilimumab 100 days after HSCT.

Secondary:

1. To describe the toxicities associated with ipilimumab.
2. To estimate the cumulative incidence of grade II-IV acute GVHD.
3. To estimate the cumulative incidence of chronic GVHD
4. To describe the association between donor lymphocyte infusions (DLI) and progression-free survival.

Exploratory objectives:

We aim to analyze immunologic and biochemical correlates in ipilimumab recipients through characterization and quantification of peripheral blood and bone marrow T cell phenotype, and other mononuclear cell populations both before and after alloHSCT, and before and after ipilimumab administration.

3.0 BACKGROUND AND RATIONALE

CD34+ selected alloHSCT for Multiple Myeloma

Despite recent therapeutic advances, most MM patients will experience disease relapse during their lifetime. Although the advent of Immunomodulatory imide drugs and proteasome inhibitor-based therapies have improved MM patient outcomes the last fifteen years, outcomes in patients who develop resistance to these agents is universally dismal.(1)

Allogeneic hematopoietic stem cell transplant remains the only curative treatment for eligible patients with RRMM. Although the success of alloHSCT in MM has been challenged by historical rates of non-relapse mortality (NRM) exceeding 40%, these rates have substantially decreased with improvements in supportive care, better patient selection, and modification in conditioning regimen components and intensity.(2) A recent study from our institution using myeloablative conditioning and CD34+ selected allografts in 44 patients treated from 2007-2013 reported 1 year NRM rates of 18%, and grade II-IV acute graft-versus-host disease (GVHD) and chronic GVHD rates of 2% of 0%, respectively.(3)

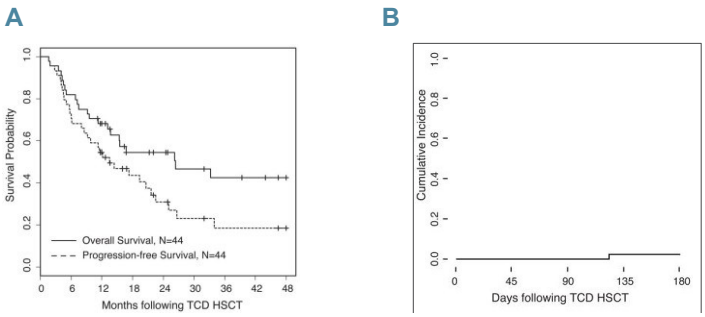


Figure 2: MSKCC outcomes of CD34-selected HSCT in high-risk relapse/refractory multiple myeloma

Relapse rates after alloHSCT have not seen similar improvements and have emerged as a primary challenge in this patient population. In our same institutional population, despite the use of high intensity conditioning to eradicate disease, the reinfusion of a tumor-free allogeneic stem cell source, and potential advent of graft-versus-myeloma effect, progression free survival (PFS) had a median duration 13.5 months and a PFS rate of 31% at 2 years.(3)

Ipilimumab use after alloHSCT in high risk Multiple Myeloma: Rationale for Use

Profound immune dysfunction is observed in myeloma patients and contributes to tumorigenesis, disease resistance and relapse. Targeted immunotherapeutic strategies have generated excitement in the field due to their potential to enhance the effects of established cytotoxic strategies with marginal additional toxicity, and to induce long term remissions through the establishment of a more effective host immune system.(4) Checkpoint inhibition has also generated particular interest in alloHSCT, where this strategy has theoretic potential to enhance the effectiveness of the adoptive allogeneic immune system, and increase its curative potential.(5) Exploration of the CTLA-4 checkpoint inhibitor ipilimumab in a dose escalation and expansion study of 28 patients with hematologic malignancies demonstrated an overall response rate in 7/22 (32%) of patients who received the maximum tolerated ipilimumab dose.(6) An update on this study presented at the ASH 2017 annual meeting reported complete remission, very good partial remission, and partial remission in the 3 MM patients.(7)

Concerns have been raised due to both immune mediated adverse events (IRAEs) and for increased GVHD rates in patients receiving checkpoint inhibitors either alone or in combination before or after alloHSCT (7, 8). IRAEs were also implicated in the suspension of two MM trials exploring pembrolizumab use in combination with pomalidomide or dexamethasone. Davids et al, have addressed these concerns by exploring lower dosing strategies in the context of alloHSCT.(7, 8) At these doses, the toxicities including GVHD were substantially reduced, although at the expense of efficacy. We nonetheless hypothesize that ipilimumab in the context of this proposal will be safe in that we are using it as a single agent, we are using it in the absence of active disease and are using it in a platform depleted of alloreactive donor T Cells, in which we have previously reported exceedingly low rates of GVHD.

Ipilimumab after alloHSCT: Rationale for Dosing

Ipilimumab is a CTLA-4 inhibitor, currently FDA approved in melanoma and renal cell carcinoma. The dosing for ipilimumab is based on prior Phase I/II trials. Bashey and others reported a Phase I trial with 29 patients with malignancies that were recurrent or progressive after alloHSCT, who received ipilimumab as a single infusion at dose cohorts between 0.1 and 3.0 mg/kg.(NCT00060372).(9) Dose-limiting toxicity was not encountered, and ipilimumab did not induce GVHD or graft rejection. However, organ-specific immune adverse events (IAE) were seen in 4 patients (grade 3 arthritis, grade 2 hyperthyroidism, recurrent grade 4 pneumonitis). This was further studied in a Phase I/Ib multicenter study, where 28 patients with relapsed hematologic cancer after allogeneic HSCT received induction therapy with ipilimumab at a dose of 3 or 10 mg/kg of body weight every 3 weeks for a total of 4 doses, with additional doses every 12 weeks for up to 60 weeks in patients who had a clinical benefit (6). While substantial IAE and GVHD was noted with 10mg/kg, at a dose of 3mg/kg, minimal side effects were seen. Chronic GVHD of the liver developed in one patient; this was the only dose-limiting toxic effect in that cohort. Immune-related adverse events were observed in two patients (grade 2 pneumonitis in one patient and grade 2 diarrhea in one patient). These events were rapidly reversed with glucocorticoids and did not preclude further administration of ipilimumab. Additionally, a Phase II study has been reported with ipilimumab and lenalidomide in 17 patients with relapsed lymphoid malignancies after alloHSCT and in high-risk patients after autologous HSCT. Patients received 10 mg of oral lenalidomide

daily for 21 days followed by intravenous ipilimumab at 3 mg/kg body weight. The regimen was repeated 4 weeks later for a total of 4 treatments. Immune-mediated toxicity was limited to 1 patient with asymptomatic hypothyroidism and 1 with dermatitis in the allogeneic and autologous groups, respectively. One allogeneic transplant recipient had a flare of prior graft-versus-host disease (GVHD) while taking lenalidomide that precluded further treatment. All others finished treatment without GVHD. Four of 10 patients in the allogeneic group had complete responses, and 3 had partial responses. Of note, all these patients had active disease, and were being treated for a relapse and were post conventional (T cell replete) alloHSCT.

Based on the above and ongoing MSKCC adult BMT protocol, we hypothesize that ipilimumab dosed at 3 mg/kg every 3 weeks followed by a maintenance phase of every 3 months dosing for 4 further doses will be safe and well tolerated in our cohort of patients. As ipilimumab has not been explored in MM, as a maintenance strategy after alloHSCT, or after CD34+ selected alloHSCT, we will initiate a dose de-escalation cohort should we find DLT in more than one patient at the currently accepted clinical dose, as outlined in Figure 1 and Table 1.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This phase I/II trial is designed to assess the safety and efficacy of ipilimumab administered to patients with relapsed refractory multiple myeloma (RRMM) following CD34-selected allogeneic hematopoietic stem cell transplantation (alloHSCT). The phase I cohort of 6 patients will be treated with ipilimumab 3 mg/kg every 3 weeks for 4 doses. If DLTs (defined in section 10.2) are observed in no more than 1 patient, a single arm Phase II study will be initiated and will accrue an additional 33 patients using the same dose. If the initial Phase I cohort has an observed toxicity rate of more than 1 out of the six patients with the target ipilimumab dose, a second 6-patient Phase I cohort at a reduced ipilimumab dose will be opened to determine a lower dose for the Phase II. Patients in all cohorts will be scheduled to receive ipilimumab for 4 doses, once every 3 weeks, followed by 4 doses, once every 3 months, unless limited by DLT or disease relapse.

4.3 Intervention

Intervention 1: Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT)

This protocol will enroll patients with multiple myeloma that has relapsed or remained refractory despite administration of more than 2 lines of therapy. The patient will be admitted to a single room on the Adult Transplantation Service and allogeneic CD34-selected PBSC or marrow transplantation performed as per MSKCC adult BMT guidelines. Patients will also be required to meet organ and comorbidity based alloHSCT eligibility criteria and have a 10/10 matched eligible donor. All patients will be conditioned for transplantation with busulfan (3.2mg/kg/day with pharamacokinetic dosing adjustment to achieve an average daily busulfan AUC of 3700 mmol/min as described in Section 10.1), melphalan (70 mg/m2/day x 2 doses) and fludarabine (25mg/m2/day x 5 doses), according to the trial diagram outlined in Figure 1. Patients with a measured or calculated creatinine clearance of 40-70ml/min will have the fludarabine dose reduced to 80% (20mg/m2/day). Donor stem cells will be mobilized by administration of granulocyte-colony stimulating factor (G-CSF) for 5 or 6 days and harvested from peripheral blood. No drug prophylaxis against GVHD will be administered after transplant.

I**ntervention 2: Ipilimumab**

Patients will be evaluated at approximately day 100 (±2 weeks) after allo-HSCT and those meeting the criteria in sections 6.1.2 and 6.2.2.will be eligible to receive the first dose of ipilimumab.

Following administration of ipilimumab patients will be evaluated clinically according to MSKCC BMT standard of care. Subsequent doses will be given every 3 weeks for 4 doses as per the schedule outlined in Table 1 and will be administered only in the absence of DLTs. A DLT will be defined as any grade 3 or greater expected immune adverse effect attributable to ipilimumab described in the BMS brochure v2019 as graded by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, or unexpected grade 3 (CTCAE v. 5.0) or greater adverse event developing within 3 weeks of ipilimumab administration attributable to ipilimumab within the assessment phase as determined by the PI, or new development of grade 2-4 acute GVHD from start of ipilimumab to 3 weeks after 4th dose of ipilimumab administration during the assessment phase that requires treatment with systemic glucocorticosteroids, or loss of chimerism.

Patients not eligible to receive ipilimumab will continue to be followed in the trial as per standard MSK guidelines. Patients who do not receive ipilimumab will be considered non-evaluable for the primary objective and replaced. Patient who receive at least one dose of ipilimumab will be considered evaluable for the primary objective.

The phase I cohort of 6 patients will be treated with ipilimumab 3 mg/kg every 3 weeks for 4 doses. If no DLTs are observed, a single arm Phase II study will be initiated and will accrue an additional 33 patients using the same dose. If the initial Phase I cohort has an observed toxicity rate of more than 1 out of the 6 patients with the target ipilimumab dose, a second 6-patient Phase I cohort at a reduced ipilimumab dose of 1mg/kg will be opened to determine the appropriate lower dose for Phase II. Patients in all cohorts will be scheduled to receive ipilimumab for 4 doses, once every 3 weeks, followed by 4 doses, once every 3 months unless limited by DLT or disease progression.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

5.1 Busulfan (Busulfex®)

a. Source and pharmacology: Supplier: Otsuka Pharmaceutical; Busulfan is a bifunctional alkylating agent known chemically as 1, 4-butanediol, dimethanesulfonate. BUSULFEX® (busulfan). This is an agent in which two labile methanesulfonate groups are attached to opposite ends of a four carbon alkyl chain. In aqueous media, busulfan hydrolyzes to release the methanesulfonate groups. This produces reactive carbonium ions that can alkylate DNA. DNA damage is thought to be responsible for much of the cytotoxicity of busulfan.

b. Formulation and stability: It is supplied as a clear, colorless, sterile, solution in 10 mL single use ampoules. Each ampoule of BUSULFEX contains 60 mg (6 mg/mL) of busulfan, the active ingredient, a white crystalline powder with a molecular formula of CH3SO2O (CH2)4OSO2CH3 and a molecular weight of 246 g/mole. Busulfan is dissolved in N, N-dimethylacetamide (DMA) 33% wt/wt and polyethylene glycol 400, 67% wt/wt. Busulfan"s solubility in water is 0.1 g/L and the pH of a >0.5% solution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP as recommended for infusion reflects the pH of the diluent used and ranges from 3.4 to 3.9.

c. Solution preparation: Prepare and Mix per MSKCC Guideline.

d. Storage and stability: Unopened ampules of BUSULFEX must be stored under refrigerated conditions between 2° -8° C (36° -46° F).

e. Clinical considerations: Busulfan is emetogenic. Busulfan is administered intravenously over 3 hours. Seizure prophylaxis is co-adminstered according to institutional guidelines. Acetaminophen and metronidazole should not be given 24 hours pre or post busulfan administration.

5.2. *Melphalan (Evomela®)*

a. Source and pharmacology: Supplier: Spectrum Pharmaceuticals. A derivative of nitrogen mustard, an analog of mustard gas. It is a polyfunctional alkylating agent that causes miscoding, cross-linkage of DNA, and single-strand breakage of DNA. It inhibits cellular glycolysis, respiration, and protein synthesis. It is cell cycle-

phase non-specific.

b. Formulation and stability: A lyophilized powder of 50 mg melphalan per vial.

c. Solution preparation: . Prepare and Mix per MSKCC Guideline.

d. Storage and stability: The intact packages should be stored at room temperature (15- 30°C) protected from light.

e. Administration: Intravenous, over 30 minutes.

5.3 *Fludarabine (FLUDARA®)*
a. Source and pharmacology: Supplier: Berlex Laboratories, Inc. FLUDARA FOR INJECTION contains fludarabine phosphate, a fluorinated nucleotide analog of the antiviral agent vidarabine, 9-ß-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase. The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-ß-D-arabinofuranosyl). Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The mechanism of action of this antimetabolite is not completely characterized and may be multi-faceted.

b. Formulation and stability: Each vial of sterile lyophilized solid cake contains 50 mg of the active ingredient fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to adjust pH to 7.7. The pH range for the final product is 7.2-8.2. Reconstitution with 2 mL of Sterile Water for Injection USP results in a solution containing 25 mg/mL of fludarabine phosphate intended for intravenous administration. FLUDARA FOR INJECTION is supplied in a clear glass single dose vial (6 mL capacity) and packaged in a single dose vial carton in a shelf pack of five

c. Solution preparation: Prepare and mix per MSKCC Guideline.

d. Storage and stability: As per MSKCC Guideline.

e. Administration: Intravenous, over thirty minutes.

5.4. *Anti-Thymocyte Globulin (Rabbit) (Thymoglobulin®)*
a. Source and pharmacology: Supplier: Sangstat, The Transplant Company®. Thymoglobulin® [Anti-thymocyte Globulin (Rabbit)] is a purified, pasteurized, gamma immune globulin, obtained by immunization of rabbits with human thymocytes. This immunosuppressive product contains cytotoxic antibodies directed against antigens expressed on human T-lymphocytes.

b. Formulation and stability: Thymoglobulin is a sterile, freeze-dried product for intravenous administration after reconstitution with sterile Water for Injection, USP (WFI). Each package contains two 7 mL vials: Vial 1: Freeze-Dried Thymoglobulin Formulation Active ingredient: Anti-thymocyte Globulin (Rabbit) 25 mg - Inactive ingredients: Glycine (50 mg), mannitol (50 mg), sodium chloride (10 mg); Vial 2: Diluent Sterile Water for Injection, USP 5 mL. The reconstituted preparation contains approximately 5 mg/mL of Thymoglobulin, of which >90% is rabbit gamma immune globulin (IgG). The reconstituted solution has a pH of 7.0± 0.4. Human red blood cells are used in the manufacturing process to deplete cross-reactive antibodies to non-T-cell antigens. The manufacturing process is validated to remove or inactivate potential exogenous viruses. All human red blood cells are from US registered or FDA licensed blood banks. A viral inactivation step (pasteurization, i.e., heat treatment of active ingredient at 60°C/10 hr) is performed for each lot. Each Thymoglobulin lot is released following potency testing (lymphocytotoxicity and E-rosette inhibition assays), and cross-reactive antibody testing (hemagglutination, platelet agglutination, anti-human serum protein antibody, antiglomerular basement membrane antibody, and fibroblast toxicity assays on every 5th lot).

c. Solution preparation: Prepare and mix per MSKCC Guideline.

d. Storage and stability: As per MSKCC Guideline.

e. Administration: Infuse through a 0.22-micron filter. Set the flow rate to deliver the dose over 12 hours. : Patients will receive pre-hydration and anaphylaxis prophylaxis to include diphenhydramine and acetaminophen according to institutional guidelines. Methylprednisolone 1 mg/kg may be administered concurrently with ATG.

5.5 Ipilimumab (Yervoy)

a. Source and pharmacology:

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal immunoglobulin (Ig) G1κ specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4, cluster of differentiation [CD] 152), which is expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody (mAb) that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell (Treg) function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response. Ipilimumab 3 mg/kg has been approved for use in advanced melanoma in over 47countries, including the United States (US, 25-Mar-2011), the European Union (EU, 13-Jul-2011), and Australia (Jul-2011). Yervoy 10 mg/kg is approved as adjuvant treatment of unresectable or metastatic melanoma in the US.

The pharmacokinetics of ipilimumab were studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every three weeks for 4 doses. Peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined. Upon repeated dosing every 3 weeks, the clearance (CL) of ipilimumab was found to be time-invariant, and systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean C_{min} at steady-state was 19.4 mcg/mL following repeated doses of 3 mg/kg. The mean value for terminal half-life was 15.4 days and for CL was 16.8 mL/h

b. Formulation and stability: Ipilimumab currently comes packaged in a concentrated form in either a 50 mg (5 mg/mL) or 200 mg (5 mg/mL) single use vial. This concentrated solution should be diluted with 0.9% Sodium Chloride or 5% Dextrose Injection to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 4 mg/mL.

c. Solution preparation: Ipilimumab injection, 50 mg/10 mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL), can be used for intravenous (IV) administration without dilution after transferring to a polyvinyl chloride (PVC), non-PVC/non-di(2-ethylhexyl)phthalate (DEHP), or glass container and is stable for 24 hours at 2°C to 8°C or room temperature/room light. Ipilimumab injection may be diluted in 0.9% sodium chloride injection or 5% dextrose injection to concentrations between 1 mg/mL and 4 mg/mL and stored in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light.

d. Storage and stability: Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% sodium chloride injection or 5% dextrose injection in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. Vials should be protected from light and should not be frozen.

e. Administration: The diluted solution may be infused over 90 minutes using a volumetric pump at the protocol- specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm) as per manufacturer's guidelines. Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

6.1 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.2 Participant Inclusion Criteria

6.2.1 Inclusion Criteria prior to Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT)

- Willing and able to participate as a research subject and provide informed consent (**Note:** an LAR may sign the consent form on the partipant's behalf)
- Diagnosis of relapsed refractory multiple myeloma defined as more than 2 lines of prior therapywith at least a very good partial remission to most recent salvage therapy.
    - Patients should have R-ISS stage II or III disease at diagnosis or high risk cytogenetics by IMWG criteria (t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, and gain(1q)) at any time since diagnosis

Note:. A line of therapy is treatment between diagnosis and progression or between two progressions

- Eligible for CD34-selected HSCT according to MSKCC adult BMT guidelines.
- Have a 10/10 matched donor
- Age ≥ 21, < 73 years.
- Karnofsky (adult) Performance Status ≥ 70%.
- Patients must have adequate organ function measured by:
    a) *Cardiac*: LVEF at rest must be ≥ 50%
    b) *Hepatic:*
        - < 3x ULN ALT
        - < 1.5 ULN total serum bilirubin, unless there is congenital benign hyperbilirubinemia.
    c) *Renal:* serum creatinine <1.2 mg/dl or if serum creatinine is outside the normal range, then CrCl > 40 ml/min (measured or calculated/estimated) with dose adjustment of Fludarabine for <70ml/min as per section 4.2.
    d) *Pulmonary:* DLCO > 50% of predicted (corrected for hemoglobin).

6.2.2 Inclusion Criteria prior to Ipilimumab

- Non progressive myeloma (partial response or better) as defined by International Myeloma Working Group (IMWG) criteria
- Engraftment of all cell lines without transfusion dependence, defined as
    - absolute neutrophil count > 1.0K/mcL x 3 consecutive days
    - platelets > 50K/mcLx 7 consecutive days without platelet transfusion
    - no platelet or RBC transfusions within the preceding 7 days
- ≥ 80% donor chimerism in the bone marrow

6.3 Participant Exclusion Criteria

6.3.1 Exclusion Criteria prior to Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT)

- Patients ineligible for therapy with ipilimumab, for example:.
  a) Active autoimmune disease or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone equivalents) or other immunosuppressive medications at enrollement. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
  b) History of motor neuropathy considered to be of autoimmune origin (e.g., Guillain-Barre Syndrome, Myasthenia Gravis).
- Female patients who are pregnant or breast-feeding.
- Patients with plasma cell leukemia at the time of diagnosis.
- Patients who have undergone prior allogeneic hematopoietic stem cell transplantation.
- Patients who have had a previous malignancy that is not in remission.

6.3.2 Exclusion Criteria prior to Ipilimumab

- Active infection or treatment for infection (patients on Cytomegalovirus (CMV) therapy will be considered eligible; patients with CMV viremia by PCR or disease with end-organ involvement will not be eligible)
- Active GVHD of any grade or prior grade 3-4 GVHD
- Active immune suppression, defined as
  - active use of calcineurin inhibitors, mycophenolate mofetil, or other immunomodulators
  - steroid dosing exceeding 10 mg/d prednisone or equivalent
- Receiving immunomodulatory agents (ex. thalidomide, lenalidomide, pomalidomide)

7.1 RECRUITMENT PLAN

This study will be conducted at MSKCC. Information regarding this study will be made available on the MSKCC web site, and the trial will be listed on www.clinicaltrials.gov.

Potential research subjects will be identified by members of the patient's treatment team or research team during clinical visits and weekly multidisciplinary meetings. The investigator will use information provided by the patient and/or medical record to confirm that the patient is eligible and contact the patient regarding study enrollment. Physicians will discuss with the patient his/her diagnosis, prognosis, risks and benefits of study participation, as well as treatment alternatives which will include standard treatment options and may include other investigational options. All patients will be required to sign an IRB approved informed consent prior to enrollment on study. All eligible patients, regardless of sex and race, will be approached for participation. The investigators are aware of the NIH policy concerning inclusion of women and minorities in clinical research populations. All patients will be seen by MSKCC BMT physicians and associated MSKCC co-investigators, enrolled, and registered at MSKCC. All co-investigators agree to follow the treatment in the protocol and to conduct the proposed investigation according to recognized principles of good clinical practice. Participation is voluntary. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

This protocol will be the priority study for patients with multiple myeloma who are undergoing allo HSCT.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

7.2 Randomization

Not applicable.

8.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.1 PRE-TREATMENT/INTERVENTION

The patient will receive an extensive medical evaluation within approximately 45 days prior to starting preparatory cytoreduction as per MSKCC adult BMT guidelines. This evaluation includes:

- Complete physical exam and medical history
- Dental evaluation (not required within 45-day window)
- CBC with differential

- Coagulation profile (PT, PTT, INR)
- Blood Type and screen (any time prior to enrollment)
- Myeloma specific analyses include – Serum protein electrophoresis (SPEP), Serum Immunofixation (IF), quantitative immunoglobulins, Serum Free Light Chain assay, β -2 microglobulin, LDH; 24 hr urine collection for total protein, creatinine clearance, urine protein electrophoresis (not required if total protein is < 10.0 mg/dl), urine immunofixation.
- Serum chemistries including BUN, creatinine, electrolytes, glucose, total protein, albumin, liver function tests (AST, ALT, bilirubin, and alkaline phosphatase).
- Infectious disease markers will be performed as per each department's guidelines or at the discretion of the treating attending.
- HTLV-1 and 2 as well as HIV-1 and 2 serology
- Pregnancy test for women of childbearing age (and repeated as necessary per institutional guidelines prior to starting conditioning)
- Urinalysis
- Electrocardiogram, echocardiogram or a gated pool scan if needed
- Pulmonary function test
- FDG-PET/CT (for patients with positive bone lesions at baseline; may be substituted by PET/MRI at the discretion of the investigator)
- Chest X-ray (Chest CT scan and FDG-PET scan if indicated)
- Samples of bone marrow and/or blood cells will be obtained to assess disease status and to define donor/host differences.
- An additional blood will be drawn in 2 CPT tubes and 1 SST tube once prior to conditioning for laboratory correlative studies and banked in HOTB.
- Bone marrow assessment will be performed as follows:
    1. Biopsy will be stained with CD138, CD20 and kappa/lambda.
    2. Aspirate will be sent for the following tests:
        a. Routine staining and cell counts
        b. One heparinized syringe with 5ml of marrow for flow cytometry for routine myeloma markers
        c. Two syringes with EDTA and 2-4ml of marrow in each syringe for karyotype for chromosomal abnormalities and FISH.
        d. An additional 3-6ml marrow in EDTA will be drawn for correlative studies

10.0 TREATMENT/INTERVENTION PLAN

10.1. Preparative cytoreduction

The patient will be admitted to a single room on the Adult Transplantation Service and allogeneic CD34-selected PBSC or marrow transplantation performed as per MSKCC adult BMT guidelines. Patients can co-enroll on MSK protocols with busulfan, melphalan, and fludarabine conditioning in which the protocol intervention ends prior to day 100. For co-enrolled patients, busulfan, melphalan, fludarabine, and rabbit antithymocyte globulin (rATG) dosing will follow the co-enrolled protocol. For patients not co-enrolled on another protocol, patients will receive:

On day -6, patients will receive the Busulfan 3.2mg/kg/day with PK levels drawn per standard of practice. Busulfan PK modeling will be done using these levels using an in-house liquid chromatography tandem mass spectrometry assay, per current standard of care. If necessary, dose adjustments will be made based on the first dose kinetics to ensure that patients achieve a target average daily busulfan AUC goal of 3400 – 4400 mmol/min. Busulfan will be administered on days -6, -5, and -4.

Melphalan (70mg/m^2/day IV) will be administered on days -3 and -2.

Fludarabine (25mg/m^2/day IV) will be administered on days -6, -5, -4, -3, and -2.

Patient will also receive rATG (thymoglobin 2.5mg/kg/day IV) on day -3 and -2 with a total ATG dose cap of 450mg.

Adjusted body weight will be used for busulfan, melphalan, and rATG if the patient's actual weight is >125% of adjusted body weight. Patients with a measured or calculated creatinine clearance of 40-70ml/min will have the fludarabine dose reduced to 80% (20mg/m2/day).

10.2 Therapy with ipilimumab

		Ipilimumab Safety Assessment Phase				Ipilimumab Maintenance Phase			
	Pts	Dose	Freq	Doses	Duration	Dose	Freq	Doses	Duration
Phase I	6	3 mg/kg	q3 wks	4	12 wks	3 mg/kg	q3 mo	4	12 mo
Phase Is*	6	1 mg/kg	q3 wks	4	12 wks	1 mg/kg	q3 mo	4	12 mo
Phase II	33	from Phase I/Is	q3 wks	4	12 wks	from Phase I/Is	q3 mo	4	12 mo

Table 1: Ipilimumab Dosing Schedule in Expansion and *Safety Cohorts. (Freq = frequency; Mo = Month;; Pts = number of patients; wk(s) = week(s).) * Phase I safety cohort, if needed

Following administration of ipilimumab patients will be evaluated clinically according to MSKCC BMT standard of care. Subsequent doses will be given every 3 weeks for 4 doses as per the schedule outlined in Table 1 and will be administered only in the absence of dose-limiting toxicities (DLT). DLT will be defined as: any grade 3 or greater expected immune adverse effect attributable to ipilimumab described in the BMS brochure v2019 as graded by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, or unexpected grade 3 (CTCAE v. 5.0) or greater adverse event developing within 3 weeks of ipilimumab administration during the assessment phase attributable to ipilimumab as determined by the safety monitoring board, or new development of grade 2-4 acute GVHD within 3 weeks of ipilimumab administration during the assessment phase that requires treatment with systemic glucocorticosteroids, or loss of chimerism.

For dose 2 and onwards, within 48 hours prior to ipilumimab dose, patients should have Platelet count >50K/mcL, Hemoglobin >= 7g/dL, Total Bilirubin <= 1.5 x ULN, and AST/ALT <= 1.5 x ULN. Tyroid function tests should be drawn prior to each dose.

Patients who do not receive ipilimumab will be considered non-evaluable for the primary objective and replaced. Patients who discontinue treatment due to DLT will continue to be followed in the trial as per standard MSK guidelines and their blood and their archived for research. Patient who receive at least one dose of ipilimumab will be considered evaluable for the primary objective.

To receive maintenance doses of ipilimumab, patients should:

1. Phase I – not have had DLT in DLT window
   Phase II – not have had any grade 3 or greater expected immune adverse effect attributable to ipilimumab or unexpected grade 3 or greater adverse event developing within 3 weeks of ipilimumab administration
2. Not have new development of acute GVHD within 3 weeks of ipilimumab administration during the assessment phase that requires treatment with systemic glucocorticosteroids
3. ≥ 80% donor chimerism in the bone marrow

4. Clinical benefit with at least a partial remission by IMWG criteria

Prophylactic DLI should not be given prior to Day 180 after alloHSCT and should be separated from maintenance ipilimumab doses by 2-4 weeks. Patients who have not achieved a complete remission by Day 180 are eligible for prophylactic DLI. DLI for disease progression should only be given once patient is removed from the treatment portion of the study, but the patient will be monitored for toxicity and efficacy.

10.3. Supportive Care

a. *Prophylaxis against infections* Standard of care guidelines will be followed for prophylaxis against post-transplant infections by opportunistic organisms, including Pneumocystis jiroveci, fungal organisms, DNA herpesviruses and more specifically CMV.
b. *Prophylaxis against menorrhagia* All post-pubertal females will receive prophylaxis against menorrhagia according to our standard of care guidelines.
c. *Transfusions* All blood product transfusions will be performed as per standard of care and BMT guidelines.
d. *Nutritional support* Nutritional status will be carefully monitored by the physician, and high-calorie parenteral alimentation will be introduced as clinically indicated. Vitamin supplements will be as clinically indicated.

10.4 Clinical Lab Work

CBC with differential and CMP will be checked at day 28, at day 100, prior to each dose of Ipi, and at the 6, 9, 12, 18, and 24 month visits.

Chimerism at baseline (pretreatment) can be either blood or bone marrow (through the diagnostic molecular pathology order). Additionally, baseline chimerism may be done at any time pre-transplant. For the day+28 time point, only bone marrow chimerism is required. Chimerism will be studied in peripheral blood prior to ipilimumab administration during days 100-180 and complete donor loss (i.e. loss of chimerism) is considered a DLT. Chimerism will be checked monthly from 6-12 months and ongoing as clinically indicted until normal values are reached.

T cell donor chimerism, reconstitution and function will be assessed starting day 100 prior to each ipilimumab dose then monthly from 6 months to 12 months if the absolute lymphocyte count is equal to or greater than 0.5 K/mcL or if clinically indicated. T-cell chimerism analysis is not required when a patient's absolute lymphocyte count is less than 0.5 K/mcL. Additional subset chimerism is at the discretion of the clinical team.

10.5 Concomitant Medications

Immunomodulatory medications such as thalidomide, lenalidomide, or pomalidomide may not be given during the ipilimumab treatment period.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

11.1 Clinical Tests:

All patients will be closely monitored and evaluated as per MSKCC BMT standard of care guidelines. Study specific assessment schedule listed below.

Table 2: Schedule of Assessments

Procedures	Pre-treat	Days post-transplant											Months post-transplant					
		7	14	21	28	35	42	56	70	84	100	100-180	6	9	12	18	24	36
Window	45	± 2d	± 2d	± 2d	± 2d	± 2d	± 2d	± 7d	± 7d	± 7d	± 14d	Prior to each cycle of Ipi	± 14d	± 14d	± 30d	± 30d	± 30d	± 30d
Eligibility	X											X[10]						
Informed consent	X																	
H&P	X											**X**[12]						
Dental eval	X																	
CBC w/ differential	X				X						X	X	X	X	X	X	X	
CMP	X				X						X	X	X	X	X	X	X	
Coagulation profile	X																	
Blood type & Screen	X																	
Serology[1]	X																	
Pregnancy test[2]	X																	
HTLV-1/2, HIV-1/2	X																	
Urinalysis	X																	
EKG, Echo or gated pool scan	X																	
PFT	X														X			
Chest X ray	X																	
BM biopsy and aspirate[3]	X				X						X		X	X	X	X	X	
BM Chimerism[4]	X				X						X		X	X	X	X	X	
Peripheral Blood Chimerism[4]	X										X	X	X	X	X	X	X	
Myeloma analysis[5]	X				X						X	X	X	X	X	X	X	
Immune function[6]					X						X		X	X	X	X	X	
Research Bloods[7]	X				X						X	X	X	X	X	X	X	
FDG-PET/CT[8]	X										X		X		X		X	

GVHD eval[9]		X	X	X	X	X	X	X	X	X	X	X	X		X			
Toxicity assessment											X	X	X	X	X	X	X	
Phone call																		X[9]

1. Infectious disease markers will be performed as per BMT service guidelines or at the discretion of the treating attending.
2. For women of child-bearing potential, only. Serum pregnancy test is required within 14 days prior to treatment.
3. Bone marrow biopsy will be stained with CD138, CD20 and kappa/lambda. Aspirate will be sent for the following tests:
    a. Routine staining and cell counts
    b. One heparinized syringe with 5ml of marrow for flow cytometry for routine myeloma markers
    c. Two syringes with EDTA and 2ml of marrow in each syringe for FISH for chromosomal abnormalities
    d. An additional 3-6ml marrow in EDTA will be drawn for correlative studies
4. Chimerism at baseline (pretreatment) can be either blood or bone marrow. Additionally, baseline chimerism may be done at any time pre-transplant. For the day+28 time point, only bone marrow chimerism is required. Chimerism will be studied in peripheral blood prior to ipilimumab administration during days 100-180 and complete donor loss (i.e. loss of chimerism) is considered a DLT. Chimerism will be checked monthly from 6-12 months and ongoing as clinically indicted until normal values are reached.
5. Myeloma analyses includes: serum protein electrophoresis (SPEP), serum immunofixation (IF), quantitative immunoglobulins, serum free light chain assay, β -2 microglobulin, LDH; 24-hour urine collection for total protein, creatinine clearance, urine protein electrophoresis (not required if total protein is < 10.0 mg/dl), urine immunofixation. β -2 microglobulin will only be performed pre-treatment.
6. IgG, IgA, IgM, Lymphocyte subsets, B naïve memory translational, T naïve memory effectory, T regulatory (RNB), mitogen proliferation
7. Blood will be drawn in 2 CPT tubes and 1 SST tube for laboratory correlative studies and stored in HOTB for batch testing as defined in section 11.2.2.
8. Patients with positive bone lesions at baseline will have repeat imaging with FDG-PET/CT (can be substituted by PET/MRI at investigator discretion) at day 100, 6 months, and 12 months post-transplant
9. GvHD evaluations will be performed as per the ABMT service guidelines. GvHD evaluations may be conducted by phone for remote patients. This will be appropriately documented in EMR.
10. Refer to section 4.2 for eligibility criteria to be assessed prior to starting the first cycle of ipilimumab.
11. Patients will be called at 36 months post-enrollment to assess for second primary malignancies.
12. For the Phase 1 portion, patients will be seen prior to each dose of ipilmumab and will receive twice weekly phone calls to assess for DLTs.

11.2. Research Tests:

11.2.1. Peripheral Blood Evaluations: During treatment, peripheral blood samples (2 CPT and 1 SST) will be obtained immediately prior to conditioning therapy (pre-treatment baseline), immediately prior to ipilimumab infusions,and at 6, 9, 12,18 and 24 months after alloHSCT (windows above). Collected blood samples may be analyzed for research purposes, including but not limited to:

- T cell phenotype: Immunophenotype will be assessed by multi-parameter FACS and/or CyTOF including but not limited to markers to determine CD4/CD8 ratio, Th1/Th2/Th17/Treg/Tfh subtype, activation/exhaustion markers, and memory/effector status. mRNA expression analysis of sorted T cells will also be performed.
- Cytokine analysis: Concentrations of cytokines including but not limited to proinflammatory (IFNγ, TNFα, GM-CSF, IL-2, IL-4, IL-5, IL-8) and immune suppressive cytokines (TGFβ, IL-10) will be assessed (10).

11.2.2 Bone Marrow Evaluations: Collected bone marrow aspirate/biopsy samples may be analyzed for research purposes, including but not limited to:

- Phenotype of T cells by FACS and gene expression analysis (see Section 10.2.1)
- Anti-tumor response by clinical pathologic assessment of bone marrow aspirate and biopsy including MRD assessment by MSKCC clinical 10-marker flow and/or PCR based monitoring of malignant IgH rearrangement.
- Characterize the MM microenvironment and PC immuno-phenotype including but not limited to by multiparameter-flow, CyTOF, quantitative immunofluorescence, MM cell DNA mutation analysis, and/or GEP.
- Assess for plasma and B cell and PC aplasia by FACS and/or IHC

11.2.3 Plasmacytoma Analysis: In patients with an extramedullary plasmacytoma, a biopsy of the responding and/or refractory plasmacytoma(s) may be requested if easily accessible and the patient is agreeable. Obtained tissue will be banked for future analysis that may include but not limited to analysis by FACS, RT-PCR and/or immunohistochemistry to assess the presence of modified T cells and for tumor microenvironment assessment.

12.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for patient/subject eligibility (e.g. a change in diagnosis), the patient will be removed from the study. Also, patients may be removed from the study if requested by the patient. Management will depend on where they are in their treatment course. Such patients will receive appropriate supportive care. The PI may also remove patients from the study form noncompliance. Additionally, patients who experience recurrence of disease prior to ipilimumab will be removed from study and replaced.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

DEFINITIONS OF DISEASE STATUS Patients at each data collection period are classified into one of the following states as defined by the revised International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma(11).

Standard IMWG response criteria	
Stringent complete response	Complete response as defined below plus normal FLC ratio ** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells) ††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, 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 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 these criteria, if present at baseline, a ≥50% reduction in the size (SPD) §§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD) §§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for

	complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD [§§] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD [§§] of the measurable lesion; Hypercalcemia (>11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see above)
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

13.2 Criteria for Study Endpoint Evaluability

13.2.1 Regimen-related and transplant-related mortality

Regimen related toxicity (RRT) refers to those toxicities that can be attributed directly to the preparative regimen (including chemotherapeutic agents, ATG, and ipilimumab).

Transplant-related mortality (TRM) includes the RRT and other fatal complications resulting from the allogenic transplant such as graft failure, GvHD, hemorrhages, and infections.

The grading for monitoring the morbidity and mortality will be based on the NCI/CTEP common toxicity criteria version 5.0. This will include assessment of severity and duration of oral mucositis and sequelae specifically parenteral opioid analgesic use, TPN use, febrile neutropenia, hospital days and intubation.

13.2.2 Immunologic Reconstitution

T cell chimerism and activity will be closely monitored following ipilimumab administration. Immunophenotyping of T-cells, B-cells, and NK cells will be performed at approximately 100 days, and then every month post-transplant until normal values are reached. T-cell proliferations in response to PHA will be performed at approximately 3 months post-transplant and every 3-6 months thereafter until normal values are reached. These tests are not required when a patient's absolute lymphocyte count is less than 0.5 K/mcL.
Immunoglobulin levels will be tested at 3, 6, 9, 12, and 18 months post-transplant and thereafter as clinically indicated. The patient will be revaccinated as per MSKCC adult BMT guidelines

13.2.3 Engraftment and chimerism

Engraftment will be documented by analysis of peripheral blood and bone marrow cells for chimerism by standard diagnostic molecular pathology studies at 1 month, 100 days, and thereafter in the blood prior to ipilimumab administration, and then every 3 months in blood and bone marrow until 18 months post-transplant, and then as needed thereafter. T-cell chimerism analysis is not required when a patient's absolute lymphocyte count is less than 0.5 K/mcL.

13.2.4 Graft failure or rejection

Primary non-engraftment is diagnosed when the patient fails to achieve an ANC 500/mm^3 at any time in the first 28 days post-transplant. If the patient's myeloma recurs during this interval, the patient is scored as having refractory myeloma. In such a situation, the absence of donor hematopoiesis is not evaluable for graft failure or rejection. If host T-cells capable of specifically inhibiting donor hematopoietic progenitor growth in vitro are concurrently detected during graft failure, a presumptive diagnosis of immune mediated rejection is made. If (1) after achievement of an ANC >500/mm^2 the ANC declines to <500/mm^3 for more than 3 consecutive days in the absence of relapse, or, (2) there is absence of donor cells in the marrow and/or blood as demonstrated by chimerism assay in the absence of relapse, a diagnosis of secondary graft failure is made. If, however, recurrence of host myeloma is detected concurrently, the patient is not evaluable for graft failure or rejection.

Patients with evidence of graft failure without evidence of recurrence of host myeloma will have additional studies drawn under 06-107. A separate biospecimen research protocol will be submitted to ascertain cause and define relevant histoincompatibilities. These analyses may include (1) Evaluation of bone marrow aspirates and biopsies for residual or recurrent myeloma, when indicated, (2) Culture and/or molecular analyses of marrow and blood for viral pathogens potentially causing graft failure including CMV, HHV6 and parvovirus B 19, (3) Immunophenotypic and genetic analysis of circulating T-cells and NK cells to ascertain their origin and potential function, (4) Analysis of the functional

activity of residual circulating lymphocytes to determine whether and to what degree they exhibit cytotoxic or cyto-inhibitory activity against donor host or third party PHA-stimulated blasts or clonogenic hematopoietic progenitor cells. If donor-specific reactivity is identified, attempts will be made to identify targeted specificities (HLA or minor alloantigens) whenever possible.

Patients who suffer graft failure will be considered for a secondary transplant. The need for additional immunosuppression or treatment for viral infection prior to the secondary transplant will be determined by the results obtained from chimeric and viral studies and will be done off study.

13.2.5. Graft-versus-host disease

Standard BMT-CTN and IBMTR systems clinical criteria as defined by Rowlings, et al will be used to establish and grade acute GvHD (13). To determine the severity of acute GvHD, data will be collected approximately weekly to characterize the severity of symptoms and signs caused by GvHD and to evaluate possible confounding factors. Real time data collection will include descriptive characteristics of rash and estimated body surface area involved, extent of dermal/epidermal separation, identification of concomitant causes of increased bilirubin other than GvHD, presence or absence of nausea, vomiting or anorexia persistent after engraftment, peak diarrhea volume with annotations concerning the presence after engraftment, peak diarrhea volume with annotations concerning the presence or absence of urinary mixing and estimates of true diarrhea volume, presence or absence of abdominal cramps, presence or absence of frank stool blood or melena, concomitant causes of GI symptoms other than GvHD, biopsy results, identification of any agents used for treatment and autopsy results. Patients will be observed for acute and/or chronic GvHD. Graft-versus-host disease occurring after ipilimumab infusions will be analyzed separately.

Patients with moderate to severe acute GvHD (grade I2-4) will be treated in standard fashion with high-dose IV methylprednisolone (1-2mg/kg/day) or in combination with other immunosuppressants as per ongoing trials on GvHD. Patients failing to respond to steroids will be considered for treatment with experimental treatments available at the time of diagnosis of GvHD.

Chronic GvHD will be diagnosed and graded according to the criteria of Sullivan(14) treated with standard or experimental immunosuppressive therapy. Treatment will consist of corticosteroids, cyclosporin A or azathioprine, or combinations of these agents. Other novel treatments could be used if available at the investigator's discretion, i.e. thalidomide and psoralen/ultraviolet A phototherapy (PUVA).

14.0 BIOSTATISTICS

This is a phase I/II study designed to examine the efficacy and safety of ipilimumab for patients with relapsed or high-risk multiple myeloma. The primary objective of Phase I is to determine the dose of ipilimumab for the Phase II and that of Phase II is to assess the efficacy of ipilimumab.

Phase I: A maximum of 12 patients will be accrued and DLTs will be assessed in these patients. DLTs are defined in Section 4.2 and the DLT evaluation window is three weeks from the final q3 week dose of the initial intense phase. If any DLT is observed in more than one of the six patient cohort, a lower dose of ipilimumab will be evaluated in a new six patient cohort. The phase II study will commence if no more than one patient in the cohort has a DLT. The proportion of patients who have a DLT among the six will be reported along with an exact 95% confidence interval.

DLT are defined in Section 10.2. The table below shows the probabilities of de-escalation for different true underlying rates of toxicity.

	True Toxicity Rates						
	0.1	0.15	0.2	0.25	0.3	0.35	0.4
Probability of De-escalation	0.11	0.22	0.34	0.47	0.58	0.68	0.77

If the dose is reduced and more than one patient in the six patient reduced-dose cohort has a DLT, the trial will stop.

Phase II The primary endpoint of the phase II study is progression-free survival (PFS). PFS is defined as time from of initiation of ipilimumab to progressive disease or death from any cause. Response and progression are based on the criteria of the International Myeloma Working Group (Section 13). Based on historical MSKCC data on patients who would have been eligible to receive ipilimumab based on this protocol (based on critiera under Intervention 2, in Section 4.2), the estimate of median PFS is 11 months. The intervention will be considered promising if the 11-month PFS improves to 70% or higher. A total of 39 patients will accrue onto the phase II study. This includes the six patients treated at the same dose level in the phase I study. Using the nonparametric Kaplan-Meier survival estimate, the study will be considered promising if the PFS-estimate at 11 months surpasses the critical value of 62%. Allogeneic patients are closely followed in this setting per standard of care evaluations. However, the study design conservatively allows for 15% dropout (patients censored prior to the 11-month time period). The one-sided type I error for this design is 0.10 and the the power is 0.86. In addition to the 11-month PFS estimate, the median PFS along with the corresponding confidence interval will be reported. Patient who receive at least one dose of ipilimumab will be considered evaluable for the primary objective.

Sequential Stopping Rules for Phase II Assessment Phase:

These stopping rules will be applied to the 33 phase II patients who were not included in the initial phase I study during the assessment phase.

Immune related adverse events (irAE):

The stopping rule is as follows: if 2 in the first 8 patients, 3 in the first 17 patients, 4 in the first 29 patients, or 5 anytime develop AE the study will stop. If the true toxicity rate is 5%, the probability the study will be declared unsafe is 0.107; the probability increases to 0.97 if the true toxicity rate is 25%.

Grade 4 Non-Hematologic Adverse Events:

The stopping rule is as follows: if 2 in the first 8 patients, 3 in the first 17 patients, 4 in the first 29 patients, or 5 anytime develop AE the study will stop. If the true toxicity rate is 5%, the probability the study will be declared unsafe is 0.107; the probability increases to 0.97 if the true toxicity rate is 25%.

Grade II-IV GVHD:

The stopping rule is as follows: if 2 in the first 8 patients, 3 in the first 17 patients, 4 in the first 29 patients, or 5 anytime develop AE the study will stop. If the true toxicity rate is 5%, the probability the study will be declared unsafe is 0.107; the probability increases to 0.97 if the true toxicity rate is 25%.

Treatment-related Mortality:

The stopping rule is as follows: if 3 in the first 8 patients, if 4 in the first 14 patients, if 5 in the first 20 patients, if 6 in the first 27 patients, or if 7 anytime have TRM the study will stop. If the true TRM rate is 10%, the probability the study will be declared unsafe is 0.10; the probability increases to 0.82 if the true toxicity rate is 25%.

Sequential Stopping Rules for Safety During Maintenance Phase:

These stopping rule will be applied to the 39 phase I-II patients and will include any events during the phase II assessment phase.. If the dose is de-escalated in the phase I study, the protocol will be amended, and the stopping rules will be extended to include all 12 phase I patients.

Immune related adverse events (irAE):

The stopping rule is as follows: if 3 in the first 12 patients, 4 in the first 22 patients, 5 in the first 32 patients, or 6 anytime develop irAE the study will stop. If the true toxicity rate is 5%, the probability the study will be declared unsafe is 0.04; the probability increases to 0.87 if the true toxicity rate is 20%.

Grade 4 Non-Hematologic Adverse Events:

The stopping rule is as follows: if 3 in the first 12 patients, 4 in the first 22 patients, 5 in the first 32 patients, or 6 anytime develop irAE the study will stop. If the true toxicity rate is 5%, the probability the study will be declared unsafe is 0.04; the probability increases to 0.87 if the true toxicity rate is 20%.

Grade II-IV GVHD:

The stopping rule is as follows: if 3 in the first 12 patients, 4 in the first 22 patients, 5 in the first 32 patients, or 6 anytime develop grade II-IV GVHD the study will stop. If the true toxicity rate is 5%, the probability the study will be declared unsafe is 0.04; the probability increases to 0.87 if the true toxicity rate is 20%.

Treatment-related Mortality:

The stopping rule is as follows: if 3 in the first 8 patients, if 4 in the first 13 patients, if 5 in the first 20 patients, if 6 in the first 26 patients, if 7 in the first 33, or 8 anytime have TRM the study will stop. If the TRM rate is 10%, the probability the study will be declared unsafe is 0.1; the probability increases to 0.86 if the true toxicity rate is 25%.If one of these stopping rules is crossed, accrual to the study will be suspended and patients will not receive additional doses. The decision to either reopen or terminate the study will made after all safety data is reviewed by the study team in collaboration with the IRB and the FDA.

Secondary:

1. The toxicities associated with ipilimumab will be summarized. Descriptive statistics will be used to summarize toxicities by grade and phase of treatment.
2. The cumulative incidence of grade II-IV acute GVHD will be estimated using cumulative incidence functions. This will be estimated from the time of ipilimumab administration. Competing risks include relapse and death.
3. The cumulative incidence of chronic GVHD will be estimated using cumulative incidence functions. This will be estimated from the time of ipilimumab administration. Competing risks include relapse and death.
4. The association between donor lymphocyte infusions (DLI) and progression-free survival will be estimated. PFS is measured from the time of ipilimumab administration, similar to the primary objective. This will be explored using a time-dependent covariate within Cox proportional hazards regression.

Exploratory:

Descriptive analysis of T cell phenotype and other mononuclear cell populations both before and after alloHSCT, and before and after ipilimumab administration will be done. Changes in T cell subpopulations before and after alloHSCT and ipilimumab administration will be analyzed descriptively; a Wilcoxon rank sum test may be used to further evaluate an association.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

Prior to consideration for transplant, all patients will undergo a series of consultations discussing the risks and potential benefits of an allogeneic stem cell transplantation as a standard of care and the added risks associated with enrollment in this study. The risks and potential benefits of the transplant procedure, as well as the participation in any given research, experimental, or therapeutic protocol will be discussed.

15.1 General Description of Risks to Recipients

Infections and hemorrhage constitute major and continuing risks throughout the period of marrow aplasia. These are, however, also the major risks associated with the primary disease. Certain opportunistic infections remain a risk in transplant patients beyond recovery of circulating leukocytes, for at least 9-12 months post-transplant, e.g. Pneumocystis carinii, cytomegalovirus and Epstein Barr virus.

Common:

Busulfan: Myelosuppression (causing anemia, neutropenia, and thrombocytopenia), fatigue, difficulty sleeping, anorexia, nausea, vomiting, diarrhea, abdominal pain, mucositis, weight gain and swelling (edema), alopecia, fever, infection, headache, worry, and sterility may be seen.

Melphalan: Myelosuppression (causing fatigue, dizziness, headache, bruising, bleeding and infection) nausea, vomiting, diarrhea, mucositis, alopecia, fever, transient liver dysfunction, and sterility may be seen.

Fludarabine: Myelosuppression (causing anemia, neutropenia, and thrombocytopenia), cough, tiredness, anorexia, nausea, vomiting, diarrhea, mucositis, fever, infection, bruising, bleeding, and pain may be seen.

Reproductive risks: Sterility. Male patients may be offered sperm banking before admission for the transplant. Possibilities of preserving the ability to have children for female patients can be discussed with the doctor. Patients should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study. A pregnancy test is required of all females of childbearing age before starting the transplant.

ATG: is a rabbit protein that may induce an immune response in humans. Fever, chills, changes in blood pressure, skin rash and itching, neutropenia, headache, and thrombocytopenia may be seen. Pre-medications (Benadryl, Tylenol and steroids before ATG) have been shown to be effective therapy. Side effects are usually only severe after the first dose.

Ipilimumab: Diarrhea, fatigue, skin itchiness, skin rash, nausea, decreased appetite, fever, vomiting, and infusion site reaction (skin rash or hives) may be seen.

Occasional:

Busulfan: Seizures that are generally preventable by phenytoin therapy started 24 hours prior to administration and continued for 24 hours post busulfan. Abnormal liver function, pulmonary fibrosis, internal bleeding, menopause, cataracts, and hypothyroidism may be seen.

Melphalan: Pneumonitis, pulmonary fibrosis, infection, bruising, bleeding, anemia, hepatitis, renal or bladder dysfunction (increased BUN, creatinine, necrosis), allergic reaction (edema, rash, shortness of breath, low blood pressure), cancer of the bone marrow and secondary cancer (specifically, when treated for a previous cancer) may be seen.

Fludarabine: Damage to brain, lungs, and other organs, which may cause tiredness, changes in thinking, or shortness of breath, confusion, anemia, chills, numbness, increased ALT/AST, buildup of fluid causing swelling, skin rash

ATG: Prior exposure to rabbit proteins may predispose subjects to allergic reactions or serum sickness. Such reactions will be treated with epinephrine and anti-histamines. Serum sickness is an immune disease usually appearing 3-10 days after injection of a foreign serum or serum protein, with reactions such as hives, fever, swollen lymph nodes, edema, arthritis, protein in the urine, or severe inflammation of the kidney. In the event of a severe systemic allergic reaction, a trial of an alternative horse ATG will be administered. If a similar reaction occurs with the equine ATG, no further ATG will be administered. Tachycardia may also be seen.

Ipilimumab: Hypopituitarism, hypophyitis, dehydration, confusion, nerve damage, intestinal/abdominal bleeding, colitis, constipation, heartburn, abdominal pain, abnormal liver function, inflammation of mucous membranes, inflammation of the skin (causing vitiligo, hives, hair loss or thinning, excessive sweating, dry skin), arthralgia, muscle spasms, shivering, fatigue, edema, pain, flu-like illness, weight loss, and shortness of breath may be seen

Rare, and serious:

Busulfan: high doses of Busulfan can cause Veno-Occlusive Disease (VOD), also called sinusoidal obstruction syndrome. Symptoms include jaundice,tiredness, weight gain, swelling, fluid retention in the abdomen, enlarged liver, and pain . This complication is managed by aggressive supportive care with monitoring of fluids and administration of diuretics and infusions of plasma and albumin. Veno-Occlusive Disease in its severe form can be life threatening. There is also a medication, Defibrotide, which has shown to be helpful in treating VOD. Additional rare side effects include buildup of excess fluid around the heart, inflammation of the liver, and cancer of the bone marrow.

Melphalan: Serious hypersensitivity reactions, causing anaphylaxis (which may lead to drop in blood pressure, difficulty breathing, or even death), cardiac arrest, seizures, kidney failure, and VOD may be seen.

Fludarabine: Kidney damage, which may require dialysis, neurotoxicity, including peripheral neuropathy, severe liver injury and/or liver failure, autoimmune hemolytic anemia, phlebitis, and deep vein thrombosis may be seen.

ATG: Severe allergic reaction (anaphylaxis), which may lead to drop in blood pressure, difficulty breathing, or even death may be seen.

Ipilimumab: Sepsis, septic shock, encephalitis, myelitis, urinary tract infection, respiratory infection, paraneoplastic syndrome, mild or severe allergic reactions, adrenal insufficiency, hyperthyroidism, tumor lysis syndrome, changes in mental health status, Guillain-Barré syndrome, fainting, conjunctivitis, abnormal heartbeat, inflammation of the blood vessels, inflammation of the lungs, bowel perforation, inflammation of the gut, ulcers and/or stomatitis, intestinal blockage, pancreatitis, inflammation of the liver and/or liver failure, toxic epidermal necrolysis, inflammation of the thyroid, kidney or CNS, inflammation of skeletal muscles, muscle weakness, kidney failure, absence of menstrual period, change in hair color, Giant cell arteritis, proctitis, psoriasis, erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS), and serous retinal detachment may be seen.

Transplant related risks:

Blood transfusions: Transfusions may induce allergic reactions. Small, subclinical pulmonary emboli may occur, but these rarely if ever require any intervention. Standard pre-medications for blood products may be used before administration of the marrow graft. Fluid overload can be managed with diuretics. Allergic reactions of variable severity can be prevented or mitigated by premedication with antipyretics, antihistamines, and narcotics. These products may also serve as vectors of serious infection (e.g., CMV, hepatitis, AIDS). To circumvent this, prospective blood and marrow donors will be screened per AABB and FAHCT guidelines. CMV antibody (-) blood products will be used in CMV (-) individuals, whenever possible, regardless of the antibody status of the marrow donor. All blood products are irradiated (3000r, 137Cs) to circumvent the risk

of GvHD caused by contaminating lymphocytes in the transfused fractions.

Receiving peripheral blood stem cells: The volume of the T-cell depleted peripheral blood stem cells infused is approximately 30-50 cc. Possible side effects include: changes in blood pressure, fever, headache, shortness of breath, chills, sweats, nausea/vomiting, bad taste in the mouth. Pre-medications are given to reduce these side effects.

Graft-versus-host-disease (known as GvHD): This condition happens when the transplanted donor cells recognizes the patient's body as foreign and attacks it. At least 1-2 out of 10 patients receiving a T cell-depleted transplant will get mild to moderate GvHD. GvHD can be treated with medications (either IV or tablets). A biopsy may be necessary to make the diagnosis of GvHD.

Acute GvHD usually occurs in the first 3 months and may cause: skin rashes, nausea, vomiting, diarrhea, hepatitis, increased risk of infection, ulceration of the surfaces of the oral cavity, esophagus, and intestines, and suppressed or delayed recovery of the hematopoietic and immune system It may be fatal in at least 20-50% of cases and may also predispose to lethal infections which contribute to an additional mortality of 10-25%.. In patients transplanted and engrafted with cliniMACS sorted $CD34^+$ stem cells, this complication has been observed in fewer than 20% of patients and has rarely been severe.

Chronic GvHD can occur any time after the first 3 months. Approximately 50% of patients with acute GvHD may also develop chronic GvHD, manifested to varying degrees by scleroderma-like changes of the skin, cirrhosis of the liver, sclerosis of lacrimal and salivary ducts, chronic inflammation and scarring of the gastrointestinal tract with consequent malabsorption and diarrhea, chronic bronchitis, and suppression of the immune system. This can be treated with standard or protocol-based experimental immunosuppression but may be refractory.

Severe graft-versus-host disease: Rarely, GvHD can be severe or deadly. Severe acute GvHD could involve a severe skin rash like a burn, severe vomiting and/or diarrhea, liver failure and infections or bleeding. Severe acute GvHD will be treated with intense immunosuppressive therapy according to standard clinical practice or other experimental protocol. Severe chronic GvHD could involve similar symptoms but may produce other symptoms such as severe skin changes, severe dry eyes and weight loss.

Infections or bleeding: Full recovery of blood counts may take months. Full recovery of the immune system may take months to a few years. For this reason, patients will be at increased risk of infections and bleeding. Medications are given to reduce the chance of those infections. Patients will receive treatment if they do get an infection and most infections can be treated successfully with antibiotics. Patients will stay in the hospital longer or be readmitted if found to have an infection. Patients are watched closely for bleeding and given platelet transfusions to prevent serious bleeding, but minor bleeding may occur.

Serious infections or bleeding: Some infections are very difficult to treat, even with strong antibiotics. Rarely, serious infections can be passed on by the transfusion of blood products. Serious bleeding can happen in spite of platelet transfusions. Rarely infections or bleeding are lethal.

Potential sensitization to murine proteins: Mouse protein (the anti CD34 antibody used in this device is of murine derivation) is used in the CliniMACS processing procedure. Marrow cells are also separated on bovine serum albumin gradients and exposed to sheep red cells to remove rosetting populations. It is possible that patients may have pre-existing immunity to these proteins and may be at risk for allergic reactions during infusion of the processed marrow and/or peripheral blood. No allergic reactions have been noted with infusions of cells processed by the CliniMACS system in clinical studies or from infusion of cells recovered by depletion of SRBC-rosette-positive cells. Precautions for an allergic event will be taken during the infusion of the processed cells.

Pneumocystis jiroveci prophylaxis: The risk of trimethoprim and sulfamethoxazole in the doses given are primarily hypersensitivity reactions and signs of folate deficiency. Any patient with known hypersensitivity to

these compounds will not receive these drugs. The risks of parenteral pentamidine are primarily hypotension and hypoglycemia both of which will be monitored during and following administration of the drug. Hypokalemia or hypomagnesemia associated with prolonged QT syndrome or Torsade de pointe necessitates strict electrolyte monitoring. The risks of aerosolized pentamidine are mild bronchospasm primarily observed in (prior) tobacco abusers and easily managed with bronchodilator therapy.

Risk of a secondary cancer different from multiple myeloma may happen after chemotherapy. The risk of developing a secondary cancer of the skin, cervix, etc., which has been seen in other studies of similar transplants, is less than 5%. There is a special concern in patients who receive a T cell-depleted transplants because there is a risk of having a cancer of the lymph nodes (lymphoma) caused by the Epstein Barr virus (EBV). This virus causes mononucleosis in healthy people. Treatment of EBV lymphoma includes Donor Leukocyte Infusion and Rituximab.

Graft Failure: Bone marrow graft may fail to grow. Past experience suggests that this may occur in about 10% of patients. This number might be higher in patients treated with checkpoint inhibitor like ipilimumab by activating residual host T cells. Although not reported with ipilimumab in the post-llogeneic transplantation setting, this has been observed with PD-1 inhibitors are also immune checkpoint inhibitors (12). If graft failure occurs, it is unlikely that bone marrow will recover and a second transplant with stem cells from the same donor or a different donor will be needed. We will be monitoring T cell chimerism at monthly intervals whist the patients are on ipilimumab therapy starting day 100 – if the absolute lymphocyte count is equal to or greater than 0.5 K/mcL. – until 18 months post alloHSCT or if clinically indicated. T-cell chimerism analysis is not required when a patient's absolute lymphocyte count is less than 0.5 K/mcL.

Progression of Disease and Relapse of Multiple Myeloma is a risk even if the transplant is initially successful. Patients who have relapsed or progressed will be removed from study and be treated as per the investigator choice.

15.2 ASSESSMENT OF SAFETY

Toxicities during the transplant portion of the study will be graded and collected as per MSKCC Adult and Pediatric BMT Adverse Event Reporting Guide.

Ipilimumab Safety

The safety profile of ipilimumab was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with ipilimumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. These events are manageable by available/established treatment guidelines as described in the study protocol.

15.3 Investigational Scan Considerations

Patients on study may have optional biopsies any time after a scan shows response to treatment. Patients undergoing investigational CT guided biopsies are exposed to an additional 0.626 Gy (+/- 0.132) dermatologically, an additional 29.9 mSv in for scan done in helical mode and an additional 18.9 mSv for scans done in axial mode.

It is estimated that each patient with plasmacytoma(s) will have up to 3 additional scans for CT-guided biopsies.

The informed consent will include the necessary risk language on contrast use and low-level radiation.

15.4 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

The reportable serious adverse events during the transplant portion of the study will be defined according to the current MSKCC Adult BMT Adverse Event Reporting Guide.

15.5 External AE/SAE Reporting

Adverse Event Reporting

Adverse Event intensity and/or severity will be graded using CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded from CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the event's outcome, including lab abnormalities. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

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

Monitoring, recording and reporting adverse events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to the investigational product should be reported as an AE. An overdose, accidental or intentional, whether it is associated with an AE, should be reported. Any sequela of an accidental or intentional overdose of the investigational product should be reported as an AE. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and as an AE.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 90 days after the last dose of IP and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (SAEs) will be recorded in the subject's source documents. All SAEs must be reported to BMS Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using a redacted MSK SAE Report Form.

Evaluation of adverse events

A qualified Investigator will evaluate all adverse events as to:

Seriousness

A serious adverse event (SAE) is defined in section 15.3

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.

- The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.

- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.

- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.

- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, the SAE Report Form must be completed. For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

Definition of adverse events of special interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for ipilimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with ipilimumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

AESIs observed with ipilimumab include those specified in the IB section 5.5.2.

Assessment of safety parameters

Assessment of severity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as “serious” which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject’s participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

Overdose

Overdose, as defined for this protocol, refers to ipilimumab.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of ipilimumab assigned to a given patient, regardless of any associated adverse events or sequelae.

PO	any amount over the protocol-specified dose

IV 10% over the protocol-specified dose

SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to BMS Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify BMS Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to BMS Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Second Primary Malignancies

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to IP (alloHSCT and ipilimumab), occurring at any time for the duration of the study, from the time of signing the informed consent document for at least 3 years from the date the last subject is randomized into the study. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF (i.e., AE and SPM CRF) and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

Collection and Reporting Information:

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through (100 days) of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

A redacted MSK SAE report will be used to report SAEs to BMS. The BMS Protocol number should be on the SAE form or on the cover sheet with the SAE form transmission.

- The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
    - The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
    - GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
    - The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.
    - ✓ Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from following the subject's written consent to participate in the study.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of (100 days) following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

AEs of Special Interest

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event and complete one of the following forms within 24 hours of awareness of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

16.1 PROTECTION OF HUMAN PARTICIPANTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC IRB guidelines. Patients who do not wish to participate in the study may receive a conventional transplant. The study will protect the rights of all human subjects and an informed consent will clearly define the risks, benefits toxicities and side effects of treatment. We will also thoroughly explain the alternative options for treatment.

The patients will be aware of the potential financial costs and burdens of enrolling on a clinical trial. The patient's health plan/insurance company will need to pay for all of the costs of treatment in this study excluding the ipilimumab and research specimen collection/analysis. The patient will be responsible for the costs of standard medical care, all hospitalizations and any transplant complications. Patients will not be paid for taking part in this study.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

A Clinical Research Coordinator (CRC), a Clinical Research Associate (CRA), and a Research Regulatory Associate (RRA) will be assigned to the study. The responsibilities of these positions will include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolutions, and coordination of the activities of the protocol study team. The data collected for this study will be entered into a secure database: Clinical Research Database (CRDB) and Medidata. Source documentation will be available to support the computerized patient record.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

16.3 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Full sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, and more frequently if indicated.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.0 REFERENCES

1. Giralt S, et al. American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in Patients with Relapsed Multiple Myeloma. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation.2015;21:2039-2051.
2. Giralt S, Koehne G. Allogeneic hematopoietic stem cell transplantation for multiple myeloma: what place, if any? Current hematologic malignancy reports.2013;8:284-290.
3. Smith E, et al. CD34-Selected Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Relapsed, High-Risk Multiple Myeloma. Biol Blood Marrow Transplant.2016;22:258-267.
4. Hoyos V, Borrello I. The immunotherapy era of myeloma: monoclonal antibodies, vaccines, and adoptive T-cell therapies. Blood.2016;128:1679-1687.
5. Armand P. Immune checkpoint blockade in hematologic malignancies. Blood.2015;125:3393-3400.
6. Davids MS, et al. Ipilimumab for Patients with Relapse after Allogeneic Transplantation. N Engl J Med.2016;375:143-153.
7. Davids MS, et al. Optimizing Checkpoint Blockade As a Treatment for Relapsed Hematologic Malignancies after Allogeneic Hematopoietic Cell Transplantation. Blood.2017;130:275-275.
8. Haverkos BM, et al. PD-1 blockade for relapsed lymphoma post-allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. Blood.2017;130:221-228.
9. Bashey A, et al. CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. Blood.2009;113:1581-1588.
10. Brentjens R, Yeh R, Bernal Y, Riviere I, Sadelain M. Treatment of chronic lymphocytic leukemia with genetically targeted autologous T cells: case report of an unforeseen adverse event in a phase I clinical trial. Mol Ther.2010;18:666-668.
11. Kumar S, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol.2016;17:e328-e346.
12. Bryant AR, Perales MA, Tamari R, Peled JU, Giralt S. Severe pembrolizumab-associated neutropenia after CD34(+) selected allogeneic hematopoietic-cell transplantation for multiple myeloma. Bone Marrow Transplant.2018;53:1065-1068.
13. Rowlings PA, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol.1997;97:855-864.
14. Sullivan K, et al. Prednisone and azathioprine compared with prednisone and placebo for treatment of chronic graft-v-host disease: prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation. Blood.1988;72:546-554.

18.0 APPENDICES

Not applicable.