Protocol Title: A phase II study of MEDI-551 as maintenance therapy after allogeneic stem cell transplant in patients with newly diagnosed poor-risk or relapsed multiple myeloma

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SCHEMA

Day -6 to -1	Non-myeloablative stem cell conditioning (fludarabine, cyclophosphamide, total body irradiation)
	↓
Day 0	Allogeneic T-cell replete stem cell infusion
	↓
Day +3-180	GVHD prophylaxis (cyclophosphamide Day 3,4 MMF Day 5-35 Tacrolimus Day 5-60)
	↓
Day +60, +90 or +120	Initiation of MEDI-551 maintenance (12 28-day cycles)
	↓
Day +396-465	Discontinue MEDI-551 maintenance
	↓
Day +465-	Assess disease status, GVHD, chimerism

1 INTRODUCTION

1.1 Multiple myeloma

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States and is characterized by the clonal expansion of neoplastic plasma cells.[1] The most common clinical manifestations of the disease include anemia, renal failure, osteopenia, and hypercalcemia. Early treatment paradigms focused on the use of standard cytotoxic chemotherapeutic agents, especially alkylators (e.g., melphalan) in combination with glucocorticoids. More recently several novel drugs with diverse mechanisms of action that include immunomodulatory agents, proteasome inhibitors, histone deacetylase inhibitors, and monoclonal antibodies targeting cell surface antigens have been approved for clinical use in MM. Accordingly, response rates, especially the achievement of complete remissions, has dramatically increased. Unfortunately, MM remains incurable for the vast majority of patients despite these clinical advances. The factors involved in MM relapse are not fully understood, but one possible explanation for the discrepancy between complete remission and cure rates may be that current therapies fail to target tumor cells with the clonogenic growth potential, i.e., MM cancer stem cells (CSCs).[2,3]

1.2 Multiple myeloma cancer stem cells

Mature plasma cells expressing the characteristic plasma cell surface antigen CD138 are the hallmark of MM. However, several groups have identified subpopulations of tumor cells that lack CD138 and instead express B cell surface antigens (CD19 and CD20).[4-16] These cells can be identified in the bone marrow and peripheral blood of all MM patients and are clonally related to the abnormal plasma cells since they harbor identical immunoglobulin idiotypes and somatically hypermutated and rearranged gene sequences. It is clear that mature plasma cells are responsible for the clinical manifestations of MM by virtue of their infiltration of the bone marrow (anemia, hypercalcemia, bone disease) or monoclonal immunoglobulin production (renal failure, immunodeficiency). However, they appear terminally differentiated like their normal counterparts and it has been unclear whether they have the clonogenic growth potential to drive disease initiation or relapse.[17]

In order to better understand the processes involved in disease relapse we have studied the growth potential of MM cells derived from primary clinical specimens. We found that mature CD138+ plasma cells have little tumorigenic potential either *in vitro* or *in vivo*.[18,19] In contrast, clonotypic B cells are capable of generating tumor cell colonies *in vitro* and characteristic MM plasma cells and symptomatic disease in immunodeficient mice. These clonotypic B cells can also be re-isolated from affected animals and maintain the ability to produce disease over the course of serial transplantation. These properties, namely self-renewal and the production of differentiated progeny that recapitulates the original tumor, suggest that clonotypic B cells represent the cancer stem cell (CSC) in MM. Initial clinical responses demonstrate that bulk plasma cells are responsive to standard therapies, but inevitable relapse suggest that tumorigenic CSCs are not inhibited.[2,20] We compared the sensitivity of MM plasma cells and CSCs to standard anti-myeloma agents (dexamethasone, cyclophosphamide, lenalidomide, and bortezomib) and found that MM CSC were relatively resistant to all of these compared to plasma cells.[19] Therefore, the combination of intrinsic drug-resistance and tumorigenic and self-renewal potential implicates MM CSC as the primary mediators of disease relapse, and strategies inhibiting these cells may ultimately improve long-term outcomes. We have identified a number of processes that regulate the self-renewal of MM CSCs, including the Hedgehog signaling pathway and telomerase activity.[21,22] Moreover, we have explored the unique phenotype of MM CSCs using monoclonal antibodies directed against CD19 and CD20 and found that these can inhibit clonogenic MM growth in the laboratory.[23] In this clinical trial, we will examine the clinical activity of a novel anti-

CD19 monoclonal antibody, MEDI-551 in MM patients following allogeneic bone marrow transplantation (alloSCT).

1.3 Clinical experience targeting multiple myeloma cancer stem cells

1.3.1 Rituximab

CD20 is a B cell surface antigen and expressed by MM CSCs, but not mature plasma cells, in most MM patients. To date, three clinical trials have been published examining the activity of the anti-CD20 monoclonal antibody rituximab as a single agent in MM patients.[24-26] None of these trials demonstrated significant clinical activity based on standard response criteria that primarily reflect changes in bulk tumor burden, such as circulating monoclonal immunoglobulin (M protein) levels or the extent of bone marrow plasma cell infiltration. However, rituximab would not be expected to have activity against bulk plasma cells that lack CD20 expression and the elimination of CD20+ MM CSCs would not impact standard response criteria since they constitute a minor fraction of all tumor cells.[27,28] Furthermore, even if the production of new plasma cells was inhibited, it is likely that clinical responses would be delayed since these cells have a long half-life, and longer follow up may have demonstrated an eventual decrease in bone marrow plasmacytosis and M protein levels.

In order to better detect any clinical effects of MM CSC targeting, we examined whether the use of "maintenance" rituximab after induction with conventional therapy could prolong the time to disease progression.[29] We carried out a phase II trial sequentially administering high-dose cyclophosphamide (Cy) to eliminate mature plasma cells followed by rituximab to inhibit MM CSCs.[29] We treated 21 patients, including those with primary refractory disease (n=1), high risk 1st remission defined as β_2M > 5.0 or deletions of chromosome 13 (n=15), and relapsed disease responding to salvage treatment (n=5). Based on uniform response criteria, the following responses were seen: 1 CR, 4 VGPR, 11 PR (or continued PR), and 5 with progressive disease. The median time to progression was 201 days (95% C.I.: 184, 488), and 2 patients remain progression-free (738-1498 days after Cy). The median overall survival was 1194 days (95%C.I.: 919, NA).

In order to understand the clinical relevance of MM CSCs, we determined whether changes in their frequency were associated with clinical outcomes. We quantified the *in vitro* growth of MM CSCs isolated from patients undergoing treatment with high-dose Cy + rituximab using the methods we originally developed to identify MM CSCs.[30] Bone marrow aspirates were collected prior to treatment, following count recovery, and at 2, 3, 6, 9, and 12 months post Cy, and MM CSCs were quantified as MM colony formation in methylcellulose at each time point. We successfully evaluated *in vitro* clonogenic MM growth at all intended time points in 18 (86%) of the 21 patients enrolled on this trial (Fig. 1). Using a time-dependent covariate analysis, we found that the absolute number of colonies at day 90 and 180, was significantly associated with an increased risk of progression with hazard ratios HR=1.46 (95% CI: 1.12, 1.88), p=0.004, and HR=1.69 (95% CI: 1.24, 2.30), p=0.0009, respectively. Furthermore, using all available data (up to one year post-Cy), both the absolute colony count and the change from baseline were significant predictors of time to progression with

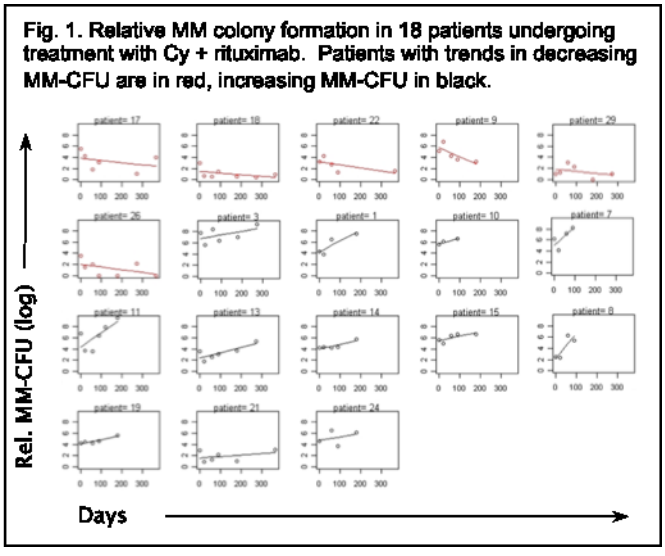

Fig. 1. Relative MM colony formation in 18 patients undergoing treatment with Cy + rituximab. Patients with trends in decreasing MM-CFU are in red, increasing MM-CFU in black.

HR=1.72 (95% CI: 1.26, 2.34), p=0.0006 and HR=1.46 (95% CI: 1.11, 1.93), p=0.007, respectively. Using a simple linear regression model to study changes in colony counts over time, patients were divided into two groups based on whether they had a positive slope (increasing colony numbers) or negative slope (decreasing colony numbers) over the duration of evaluation. Kaplan-Meier curves were generated for each of these groups (Fig. 2), and patients with a positive slope had a higher risk of progression than patients with a negative slope, HR=10.56, 95% CI (2.2, 50.7), p=0.003. For patients with decreasing colony counts (Fig. 2, n=6, solid line), progression-free survival was 640 days as compared to 185 days for those with rising colony counts (n=12, dotted line). We also examined the clinical status of the 12 patients with increasing MM colony numbers and found that all were clinically stable when MM colony counts recovered to pre-treatment baseline levels. However, all 12 patients subsequently clinically progressed on the basis of increasing bone marrow plasmacytosis or serum M protein levels after an average delay of ~100 days (range 30-240 days). We also examine whether MM CSCs were eliminated by rituximab in the circulation, but by flow cytometry found persistent clonotypic B cells with rituximab bound to the cell surface. Therefore, rituximab was able to bind to MM CSCs, but were not eradicated by this monoclonal antibody. The mechanisms by which MM CSCs are resistant to rituximab are unclear but may be mediated by low CD20 expression, inadequate effector cell function, or FCγRIIIa polymorphisms that prevent maximal monoclonal antibody recognition and binding during ADCC.

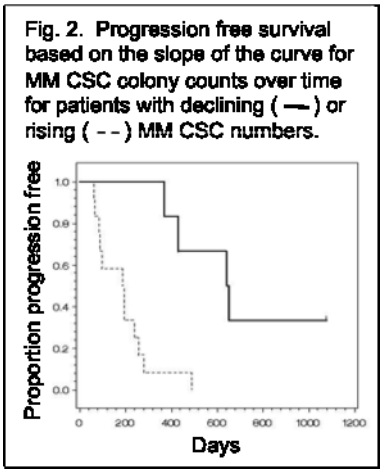

Fig. 2. Progression free survival based on the slope of the curve for MM CSC colony counts over time for patients with declining (—) or rising (- -) MM CSC numbers.

1.3.2 Lenalidomide + dexamethasone + MEDI-551

To improve MM CSC targeting, we have studied additional monoclonal antibodies targeting B cell surface antigens expressed by these cells. We identified the anti-CD19 monoclonal antibody MEDI-551 (see Section 1.5 for information regarding MEDI-551) as an ideal candidate as it is an affinity-optimized and afucosylated antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC). Moreover, we found that CD19 was typically expressed at higher levels on MM CSCs than CD20. We initiated a clinical trial in newly diagnosed MM patients studying MEDI-551 in combination with lenalidomide and dexamethasone (Rd). In this early phase, single arm, clinical trial, newly diagnosed MM patients received 28 day cycles of Rd. Following two initial cycles of Rd, MEDI-551 was administered during cycle 3 (days 1, 8) and cycle 4 (day 1). Patients with evidence of clinical response continued on Rd.

We enrolled 17 newly diagnosed MM patients on this study with a median age of 65 (range 34- 73) years of age and ISS stage I (n=11), II (n=2), or III (n=4). Seven patients had t(4;14) translocations. Two patients did not receive MEDI-551 due to progressive disease (PD) or noncompliance. Of the 15 evaluable patients clinical responses included very good partial remission (VGPR; n=3), partial remission (PR; n=10), minor response (MR; n=1), and stable disease (SD; n=1) after cycle 2 (Rd). Following the completion of cycle 4 (Rd + MEDI-551), responses consisted of VGPR (n=6), PR (n=8), and MR (n=1). There were no serious adverse events observed. Two patients experienced Grade 2 infusion reactions after the first MEDI-551 dose but no further reactions for subsequent doses. Ten patients who completed Rd + MEDI-551 currently remain on Rd, and responses at the end of cycle 7 include CR (n=1), VGPR (n=8), and PR (n=1).

The frequency of MM CSCs was serially measured by quantifying the growth of MM colonies from bone marrow aspirates or circulating peripheral blood MM CSCs by flow cytometry prior to the initiation of any therapy (baseline), at the end of cycle 2 (Rd alone), and following cycle 4 (Rd + MEDI-551). Bone marrow derived CFU-MM increased by a median of 2.5 fold (range 0.4-7.4) after cycle 2 (Rd) then decreased in 14/15 patients after cycle 4 (Rd+MEDI-551; 0.48 fold, range 0.14-

0.85) relative to baseline levels. In comparison, we also examined changes in MM-CFU in 4 newly diagnosed MM patients receiving standard treatment with Rd alone and found that they continually increased 9.3 fold (range 4-14) at a median of 4 months (range 2-4) despite achieving at least a VGPR in all patients. We also serially quantified circulating MM CSCs and found that they increased in 14/15 patients after cycle 2 (Rd; 1.6 fold, range 0.4-8.6) then fell in 13/15 after cycle 4 (Rd + MEDI-551; 0.6 fold, range 0.01-7.4). Peripheral blood CSCs were also quantified at the end of cycle 5 and cycle 7. At end of cycles 5 and 7 (approximately 55 and 110 days after the last dose of MEDI-551) MM CSCs subsequently increased in 4/10 and 8/10 patients, respectively. Circulating MM CSCs increased by end of cycle 4 in 2 patients, and both experienced PD by end of cycle 7.

Therefore, MM CSCs decreased in most patients following 3 doses of MEDI-551 compared to 33% of patients in our previous clinical trial examining high-dose Cy + rituximab. Furthermore, compared to standard treatment with Rd in which MM CSCs uniformly increase over time, the addition of MEDI-551 was associated with a clear decrease in the frequency of these cells in the majority of patients. MM CSCs subsequently rebounded following the completion of MEDI-551 treatment suggesting that a longer period of treatment may be needed to fully inhibit these cells.

1.4 Allogeneic stem cell transplantation in multiple myeloma

Allogeneic stem cell (AlloSCT) transplantation currently remains the only potentially curative option for MM, but initial studies utilizing standard myeloablative conditioning regimens carried a high degree of transplant related mortality.[31,32] The development of non-myeloablative (i.e., mini) allogeneic transplant (NM-AlloSCT) approaches have significantly decreased morbidity and mortality attributable to high-dose conditioning regimens, but high rates of graft-versus-host disease (GVHD) remained a serious complication impacting long-term outcomes.[32-35]

At Johns Hopkins, we have pioneered the use of high-dose post-transplantation (PTCy) as GVHD prophylaxis that has impacted clinical stem cell transplantation in two major ways.[36-38] First, the potent immunomodulatory impact of PTCy allows HLA-haploidentical alloSCT to be safely carried out with similar outcomes to those seen with fully HLA-identical transplants. This alleviates most donor availability issues as all first-degree and half of second-degree relatives are potentially eligible to donate. Second, it dramatically improves the safety of the procedure with respect to GVHD. Recent CIBMTR analyses have actually shown lower rates of serious Grade III and IV acute GVHD (aGVHD) and chronic GVHD (cGVHD) with haploidentical transplants to those seen with matched transplants, with patients requiring systemic treatment to approximately 5% and 10%, respectively.[39]

We have recently compiled our experience utilizing alloSCT with PTCy in MM.[40] Here, 39 patients underwent alloSCT from 2001-2011, including 9 with myeloablative and 30 with NM conditioning regimens. 32 patients received HLA-identical and 7 received HLA-haploidentical grafts. Similar to our other studies utilizing PTCy, the rates of serious Grade III and IV aGVHD (n=3, 8%, all Grade III), cGVHD requiring treatment (n=3, 8%), and transplant related mortality (n=1, 2.6%) were low. Eight patients (21%) remain in a sustained CR at a median follow up of 82 months. Disease relapse was common and the median progression free survival was 14 (95%CI: 6.2-32.8) months. Therefore, PTCy is effective in reducing transplant related morbidity and mortality, but relapse remains a major issue.

High rates of disease relapse following alloSCT with PTCy are not limited to MM, but can also be seen in most other hematologic malignancies.[36] In order to reduce relapse rates, we have begun to explore the use of maintenance strategies following alloSCT. Growing experience in several hematologic malignancies have demonstrated that disease specific therapies routinely used in the non-transplant setting can dramatically reduce relapse rates when used in the post transplant

setting. These include BCR-ABL tyrosine kinase inhibitors in ALL and CML,[41] sorafenib in FLT3-mutated AML,[42,43] and rituximab in NHL.[44] Therefore, non-curative agents may significantly improve long-term clinical outcomes in the post-transplant setting, and it appears that the new, non-tolerant, non-exhausted transplanted immune system works in tandem with these agents.

1.5 MEDI-551

MEDI-551 is a humanized afucosylated IgG1 kappa monoclonal antibody directed against CD19. Compared to earlier therapeutic monoclonal antibodies directed against B cell surface antigens (e.g., rituximab), MEDI-551 has several modifications to improve its anti-tumor activity. MEDI-551 is an afucosylated antibody, and the lack of fucose from the Fc domain results in a 10-fold increase in binding to human FCγRIIIa compared to the fucosylated counterpart. Moreover, this increased binding affinity negates any impact of FCγRIIIa polymorphisms on antibody binding to effector cells. MEDI-551 also induces little antigen internalization and dissociates slowly from the cell surface to increase recognition by effector cells. These features enhance antibody-dependent cellular cytotoxicity (ADCC), and MEDI-551 displays potent *in vitro* ADCC activity against multiple B-cell leukemia and lymphoma cell lines. Furthermore, the activity of MEDI-551 was equal or superior to the activity of rituximab in 11 of 15 cell lines tested.[45]

The ability of MEDI-551 to target primary human B cells has been tested with peripheral blood mononuclear cells (PBMCs) from healthy donors. The ADCC activity of MEDI-551 compares favorably to the activity of the rituximab in these assays.[46] In addition, MEDI-551 has been tested for its ability to deplete malignant B cells in samples derived from CLL and ALL patients. In 6 of 6 CLL patient samples tested, the activity of MEDI-551 was superior to rituximab. Similarly, MEDI-551 was more potent (lower concentration giving half-maximal response (EC50) values) than rituximab against 4 patient-derived ALL samples. To evaluate antitumor activity *in vivo*, MEDI-551 has been tested in multiple severe combined immunodeficient (SCID) mouse models of human B-cell leukemia and lymphoma. Treatment of Burkitt lymphoma subcutaneous xenografts (Raji, Daudi, Namalwa, and Ramos cells) with MEDI-551 significantly inhibited tumor growth compared to an IgG1 isotype control antibody. The efficacy of MEDI-551 treatment was also noted in DLBCL xenograft models (Toledo, OCI-LY-19) as well as intravenous tumor models (Raji, Daudi, and Namalwa cells).[46]

The clinical development of MEDI-551 is ongoing in oncology and autoimmune disorders (ie scleroderma, multiple sclerosis, and neuromyelitis optica). There are 5 clinical studies of MEDI-551 in subjects with B-cell malignancies; these studies are described below, based on a data cutoff date of 31Mar2015. Collectively, these data indicate that MEDI-551 has anti-tumor activity and a manageable safety profile.

The Phase 1/2 study MI-CP204 enrolled 111 adult subjects with relapsed and refractory advanced B-cell malignancies (CLL, DLBCL, FL, or MM). MEDI-551 was evaluated at doses of 0.5, 1, 2, 4, 8, and 12 mg/kg. Two dose-limiting toxicities (DLTs) occurred at the 4 mg/kg and 12 mg/kg dose levels; both were infusion related reactions. The most commonly reported adverse events (> 20% of subjects) were infusion related reaction, fatigue, cough, and nausea. The most commonly reported related adverse events (AEs) (in ≥ 5% of subjects in the overall study population) were infusion related reaction, nausea, neutropenia, fatigue, and vomiting. Deaths were reported for 27 of 111 (24.3%) subjects in MI-CP204. Progressive disease was the most common cause. All 27 deaths were considered unrelated to MEDI-551. Thirty of 111 subjects (27.0 %) in MI-CP204 experienced objective response (OR), defined as complete response (CR) or partial response (PR). Three subjects, 2 subjects who achieved CR and 1 subject who achieved a very good PR, were retreated following relapse.

Study D2850C00001, is a Phase 1, open-label, dose escalation study of MEDI-551 in adult Japanese subjects with advanced B-cell malignancies. Twenty subjects were enrolled and have

received doses of 2, 4, 8, or 12 mg/kg. The AEs most commonly reported (in ≥ 15% of subjects) were infusion related reaction, hypertriglyceridemia, white blood cell count decreased, leukopenia, nasopharyngitis, lymphocyte count decreased, neutrophil count decreased, and rash. Two DLTs of infusion related reaction occurred at the 12 mg/kg dose; hence the MTD was determined to be 8mg/kg in this population.

Study CD-ON-MEDI-551-1019 is a Phase 2, multicenter, international, randomized, 3-arm, active-control, open label study evaluating the antitumor activity, safety, tolerability, immunogenicity (IM), pharmacokinetics (PK), and pharmacodynamics of MEDI-551 when used in combination with bendamustine versus rituximab in combination with bendamustine in adult subjects with progressive CLL (also known as relapsed or refractory CLL). A total of 150 subjects have been treated with one of 3 regimens: MEDI-551 2 mg/kg, MEDI-551 4 mg/kg, or rituximab, each in combination with bendamustine. A total of 90 subjects have been treated with MEDI-551. The most common AEs reported in the combined MEDI-551 groups (in > 20% of subjects) were infusion related reaction, nausea, fatigue, neutropenia, pyrexia, cough, and constipation. Deaths were reported for 18 of 90 subjects (20.0%) who received MEDI-551 in CD-ON-MEDI-551-1019 (6 of 33 subjects [18.2%] in the 2 mg/kg group and 12 of 57 subjects [21.1%] in the 4 mg/kg group) and in 6 of 60 subjects (10.0%) in the rituximab + bendamustine group. All except for 1 of the deaths (4 mg/kg MEDI-551 + bendamustine group) were considered not related to study drug. Thirty-five of 90 subjects (38.9%) in the combined MEDI-551 groups and 19 of 60 subjects (31.7%) in the rituximab group experienced SAEs. The SAE of infusion related reaction occurred more frequently in the combined MEDI-551 groups (10 of 90 subjects [11.1%]) than in the rituximab group (1 of 60 subjects [1.7%]). Febrile neutropenia occurred more frequently in the rituximab group (7 of 47 subjects [11.7%]) than in the combined MEDI-551 groups (2 of 90 subjects [2.2%]).

Study CD-ON-MEDI-551-1088 is a Phase 2 study of MEDI-551when used in combination with ifosfamide-carboplatin-etoposide (ICE) or dexamethasone cytarabine-cisplatin (DHAP) versus rituximab in combination with ICE or DHAP in adult subjects with relapsed or refractory DLBCL. Subjects were initially assigned to one of3 regimens: MEDI-551 2 mg/kg, MEDI-551 4 mg/kg, or rituximab, each in combination with ICE or DHAP. A total of 119 subjects in CD-ON-MEDI-551-1088 have received at least 1 dose of study treatment, including 71 subjects in the combined MEDI-551 groups. Adverse events reported for > 20% of subjects in the combined MEDI-551 groups were anemia, thrombocytopenia, nausea, fatigue, neutropenia, constipation, vomiting, asthenia, and diarrhea. The most common AEs judged related to MEDI-551 (in > 10% of subjects in the combined MEDI-551 groups) were anemia, thrombocytopenia, nausea, neutropenia, fatigue, and leukopenia. Deaths were reported for 9 of 71 subjects (12.7%) receiving MEDI-551 (7 of 48 subjects [14.6%] in the 2 mg/kg group and 2 of 23 subjects [8.7%] in the 4 mg/kg group) and 8 of 48 subjects (16.7%) receiving rituximab in CD-ON-MEDI-551-1088. Two deaths in the MEDI-551 group and 1 death in the rituximab group were considered to be related to investigational product. Thirty of 71 subjects (42.3%) in the combined MEDI-551 groups and 20 of 48 subjects (41.7%) in the rituximab group experienced SAEs in CD-ON-MEDI-551-1088.

A Phase 1b/2, multicenter, open-label study of MEDI0680, a monoclonal antibody directed against human programmed cell death 1 (PD-1), in combination with MEDI-551, D2852C00004, is evaluating the safety, tolerability, clinical activity, MTD, PK, and anti-drug antibodies (ADA) in subjects with relapsed and refractory aggressive B-cell lymphoma. Eight subjects received MEDI-551 at 12 mg/kg and MEDI0680 at 2.5 mg/kg or 10 mg/kg. Adverse events reported by more than 1 subject were fatigue, constipation, diarrhea, nausea, vomiting, peripheral edema, paresthesia, and rash. Two subjects, both in the MEDI-551 12 mg/kg + MEDI0680 2.5 mg/kg dose group died. Neither death was considered to be related to either study drug. Both deaths were attributed to progressive disease. Serious adverse events were reported for 2 subjects in the MEDI-551 12 mg/kg + MEDI0680 2.5 mg/kg group. One subject suffered Grade 3 hydronephrosis from which he recovered. The verbatim language for the second subject's SAE (not yet coded) was

hospitalization and disease progression.

2 STUDY OBJECTIVES

2.1 Primary objective

Determine the progression free survival of high-risk or relapsed MM patients undergoing non-myeloablative allogeneic stem cell transplantation (NM-AlloSCT) followed by maintenance therapy with MEDI-551.

2.2 Secondary objectives

1. Determine changes in MM CSCs in high-risk or relapsed MM patients receiving MEDI-551 following NM-AlloSCT.

2. Evaluate the safety and toxicity of maintenance therapy with MEDI-551 following NM-AlloSCT in patients with high-risk or relapsed MM.

3. Determine the overall response rate for treatment with MEDI-551 following NM-AlloSCT in patients with high-risk or relapsed MM.

4. Determine the rate of minimal residual disease negativity for treatment with MEDI-551 following NM-AlloSCT in patients with high-risk or relapsed MM.

5. Determine the overall survival of patients with high-risk or relapsed MM patients receiving MEDI-551 following NM-AlloSCT.

6. Determine the pharmacokinetics of MEDI-551 administered as a single agent following NM-AlloSCT in patients with high-risk or relapsed MM.

7. Determine the immunogenicity of MEDI-551 administered as a single agent following NM-AlloSCT in patients with high-risk or relapsed MM.

8. Determine changes in circulating B cell levels in high-risk or relapsed MM patients receiving NM-AlloSCT and MEDI-551.

3 PATIENT SELECTION

3.1 Inclusion criteria

Patient eligibility for the study will be determined when patients are deemed eligible to proceed to AlloSCT. To determine patient eligibility, evaluations for inclusion and exclusion criteria must be performed prior to patient registration. Patients who meet these criteria can then be registered on the trial. All evaluations for inclusion and exclusion criteria must be performed within 30 days prior to registration unless otherwise noted.

At the time of study registration, patients will be eligible if they meet all of the following inclusion criteria:

1. Previous diagnosis of MM based on standard criteria as defined in Appendix A (Diagnostic Criteria for MM). Diagnostic studies need not be performed within 30 days of registration;

2. Patients must meet one of the disease criteria outlined in either a, b, or c:

   a. Patients with newly diagnosed high-risk MM achieving a partial response (PR) or better at the time of enrollment in response to systemic anti-myeloma therapy, which may include autologous hematopoietic stem cell transplant (HSCT).

   High risk is defined by the presence of any one of the following:
   - i. High-risk chromosomal translocations by FISH: t(4;14), t(14;16), t(14;20), del(17p), del(1p), amplification 1q
   - ii. MyPRS GEP-70 high-risk signature either at diagnosis or at time of registration for the study
   - iii. LDH > 300 U/L at diagnosis
   - iv. Plasma cell leukemia
   - v. Relapse from prior therapy within 12 months

   b. Patients with high-risk MM with at least 1 prior progression in PR or better in response to salvage systemic anti-myeloma therapy at the time of enrollment

   c. Patients with standard risk MM with 1 prior progression within 18 months from an autologous HSCT and in VGPR or better in response to salvage systemic anti-myeloma therapy at the time of enrollment.

3. Patients must have a suitable first-degree or second-degree related, HLA-haploidentical or HLA-matched stem cell donor. The donor and recipient must be identical at least one allele of each of the following genetic loci: HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DQB1. A minimum match of 5/10 is therefore required, and will be considered sufficient evidence that the donor and recipient share one HLA haplotype;

4. No previous AlloSCT (syngeneic HSCT permissible);

5. Any previous autologous HSCT must have occurred at least 3 months prior to start of conditioning;

6. ECOG performance status of 0-2;

7. Life expectancy > 6 months;

8. Adequate end organ function as measured by:
   - a. Left ventricular ejection fraction ≥ 35% or shortening fraction > 25%
   - b. Bilirubin ≤ 3.0 mg/dL (unless due to Gilbert's syndrome or hemolysis), and ALT and AST < 5x ULN
   - c. FEV1 and FVC > 40% of predicted

9. Not pregnant or breast-feeding;

10. No uncontrolled infection. Note: Infection is permitted if there is evidence of response to medication;

11. The patient must be able to comprehend and have signed the informed consent.

3.2. Donor eligibility

Donors must be:

1. HLA-haploidentical or HLA-identical first-degree or second-degree relative of the patient based on allele or allele group level typing as defined in Section 3.1;

2. Medically fit to and willing to donate;

3. Lack of recipient anti-donor HLA antibody. Note: In some instances, low level, non-cytotoxic HLA specific antibodies may be permissible if they are found to be at a level well below that detectable by flow cytometry. This will be decided on a case-by-case basis by the PI and one of the immunogenetics directors. Pheresis to reduce anti-HLA antibodies is permissible; however, eligibility to proceed with the transplant regimen would be contingent upon the success of the desensitization.

4. Has not donated blood products to patient.

3.3. Donor prioritization

In the event of multiple potential donors, donors will be prioritized in the following order:

1. Fit to donate;

2. HLA-matched prioritized over HLA-mismatched;

3. Lack of major ABO incompatibility. In order of priority:
    a. Compatible
    b. Minor incompatibility
    c. Major incompatibility

4. CMV serostatus: CMV negative donor preferred, if the patient is CMV negative; CMV positive donor preferred, if the patient is CMV is positive;

5. Avoidance of female donor for male recipient.

Other factors such as donor age and health history will be integrated into the donor selection process per standard practice and may be prioritized over HLA, ABO and CMV status.

3.4. Exclusion criteria

At the time of study registration, patients will be ineligible if any of the following exclusion criteria apply:

1. Diagnosis of any of the following cancers:
    a. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M-protein) and skin changes)
    b. Non-secretory myeloma (no measurable protein on Serum Free Lite Assay)
    c. HTLV1 / HTLV2 positive
    d. Diagnosis of amyloidosis

2. Failed to achieve at least a partial response (PR) to latest therapy;

3. Known history of HIV infection;

4. Systemic infection requiring treatment with antibiotics, antifungal, or antiviral agents

within 7 days of registration;

5. History of malignancy other than MM within 5 years of registration, except adequately treated basal or squamous cell skin cancer;

6. History of serious allergy or reaction to any component of the MEDI-551 formulation that would prevent administration;

7. Active hepatitis B as defined by seropositivity for hepatitis B surface antigen or patients with positive hepatitis B core antibody titers.

8. Patients with hepatitis C antibody will be eligible provided that they do not have elevated liver transaminases or other evidence of active hepatitis.

3.5. Patient eligibility criteria to begin maintenance therapy

In order to be eligible for maintenance therapy with MEDI-551, patients must have sufficiently recovered from NM-AlloSCT. Between Day 60 and Day 120 following NM-AlloSCT, patients will be evaluated to receive MEDI-551. If patients meet the eligibility criteria for initiating maintenance they will continue to be followed per the protocol.

Eligibility criteria for initiating MEDI-551 are as follows:

1. Platelet count ≥ 75,000/mm3;

2. Absolute neutrophil count (ANC) ≥ 1,000/mm3;

3. Total bilirubin ≤ 3.0 mg/dL, except in patients with Gilbert's syndrome;

4. ALT/AST < 3x the upper normal limit;

5. No ≥ Grade 2 visceral (gut or liver) acute GVHD;

6. No ≥ Grade 3 any other acute GVHD;

7. No active treatment for MM;

4 REGISTRATION PROCEDURES

4.1. Registration requirements

Patients will be registered in the CRMS. The following are additionally required:

a. Signed and dated informed consent;
b. Patient eligibility checklist(s).

A registration may be cancelled, provided that protocol treatment has not been begun.

4.2. Accrual goal

We will enroll patients in order to have 30 evaluable subjects. An evaluable subject is defined as one who has received at least 6 months of MEDI-551. We anticipate an enrollment of up to 36 study participants to achieve this number of evaluable subjects. All patients who are enrolled will be evaluated for safety.

5 TREATMENT PLAN

5.1 Transplantation regimen

The preparative regimen in each case consists of fludarabine, cyclophosphamide (Cy), and total body irradiation (TBI), with post-transplantation high-dose Cy (PTCy), mycophenolate mofetil (MMF), and tacrolimus.

5.1.1. Fludarabine

Fludarabine 30mg/m2/day (adjusted for renal function) is administered over a 30-60 minute IV infusion on Days -6 through -2 (maximum cumulative dose, 150 mg/m2).

The body surface area (BSA) for fludarabine dosing is based on actual body weight.

For decreased creatinine clearance (CrCl), fludarabine dosage is reduced as follows or by institutional standard:
CrCl 40-69mL/min, fludarabine = 24mg/m2
CrCl 20-39mL/min, fludarabine = 20mg/m2

CrCl will be estimated by the Cockcroft Formula, based on ideal body weight (IBW):

CrCl = ((140 -age) x IBW (kg)) / Serum creatinine x 0.85 for females

A measured CrCl or a glomerular filtration rate may be substituted to determine CrCl.

Fludarabine dosing is based on the last CrCl prior to the start of conditioning. The estimated CrCl on the day preceding start of conditioning may be used. The fludarabine dose should be the same on Days -6 to -2, even if the creatinine changes. However, adjustment in fludarabine dose due to creatinine changes during conditioning is permitted.

5.1.2. Pre-transplantation cyclophosphamide

Cy 14.5mg/kg/day is administered as a 1-2 hour IV infusion on Days -6 and -5 after hydration. Mesna 11.6mg/kg IV daily on Days -6 and -5 is not required, but may be given.

Cy and mesna are dosed according to ideal body weight unless the patient weighs less than IBW, in which case dose drug according to actual weight.

5.1.3. Total body irradiation (TBI)

200cGy TBI is administered in a single fraction on Day -1. Radiation sources, dose rates, and shielding follow institutional practice.

5.1.4. Day of rest

A day of rest (i.e., after preparative regimen completion and prior to hematopoietic stem cell graft infusion) is not routinely scheduled. Up to two days of rest may be added in this window based on logistical considerations or clinically as indicated. For one day of rest, fludarabine would be administered on Days -7 through -3, pre-transplantation Cy on Day -7

and Day -6, and TBI on Day -2. For two days of rest, fludarabine would be administered on Days -8 through -4, pre-transplantation Cy on Day -8 and Day -7, and TBI on Day -3.

5.1.5. Hematopoietic stem cell graft infusion

The graft will not be manipulated to deplete T cells. Processing for ABO incompatibility follows institutional practices. Guidelines for bone marrow and peripheral blood stem cell infusion are established and outlined in the ABO compatible/minor mismatched AlloSCT or the ABO incompatible AlloSCT standing orders.

5.1.6. Post-transplantation cyclophosphamide (PTCy)

Hydration prior to and following PTCy, management of volume status, and monitoring for hemorrhagic cystitis will follow institutional standards. Mesna will be used with PTCy as per institutional standards.

PTCy 50mg/kg IV, over approximately 1-2 hours (depending on volume), is given on Day 3 post-transplantation (ideally between 60 and 72 hours after marrow infusion) and on Day 4 (approximately 24 hours after Day 3 PTCy).

PTCy and mesna are dosed according to ideal body weight, unless the actual body weight is less, in which case dose drugs according to actual body weight.

It is crucial that no systemic immunosuppressive agents are given from Day 0 until at least 24 hours after the completion of the PTCy. This includes corticosteroids as anti-emetics.

Dose adjustments for PTCy will not be made.

5.1.7. Mycophenolate mofetil (MMF)

MMF begins on Day 5, at least 24 hours after completion of PTCy. The MMF dose is 15mg/kg PO TID (actual body weight) with total daily dose not to exceed 3 grams (i.e., maximum 1g PO TID). Doses are rounded to the nearest strength tablets. Equivalent IV dosing (1:1 conversion) may instead be given.

MMF prophylaxis is discontinued after the last dose on Day 35, or may be continued if there is graft versus host disease (GVHD).

No MMF dose adjustments are required for liver dysfunction. For renal insufficiency, MMF dosing should not be modified unless dialysis is needed, in which case MMF can be reduced to 25-50% of the starting dose.

5.1.8. Tacrolimus

Tacrolimus begins on Day 5, at least 24 hours after completion of PTCy. The tacrolimus starting dose is 2mg PO BID or as per institutional standard. Patients who cannot tolerate PO may be started IV and changed to PO as per institutional standard. Dose is adjusted to maintain a serum trough level of 10-15ng/mL, with a minimum acceptable trough level of 5ng/mL.

In the case of prohibitive toxicities to calcineurin inhibitors, other immunosuppression may be given after case-by-case discussion with the PI or co-PI.

Tacrolimus is discontinued after the last dose on Day 60 or according to standard institutional practices without taper, or may be continued if GVHD has occurred or may be discontinued earlier in the context of relapse, progression, graft failure, or prohibitive toxicity. Patients with suspected graft failure should remain on tacrolimus until at least the ~Day 60 chimerism assessment, although earlier discontinuation is permissible after discussion with the PI or co-PI.

Patients with hepatic or renal insufficiency should receive doses at the lower end of therapeutic concentrations. No dose adjustments are required in patients undergoing hemodialysis.

Due to extreme interactions with voriconazole and posaconazole, the tacrolimus dose should be empirically lowered when these azoles are initiated at steady state levels of tacrolimus. Guidelines are provided in Table 5.1.8. Dose adjustments for therapy with other azoles may be indicated. However, the initial tacrolimus dose (on Day 5) remains fixed. Of note, reversal of azole-mediated inhibition of CYP3A4 (and others) and P-glycoprotein is gradual when azoles are stopped. Therefore, immediate significant dose increases in tacrolimus are not advised when azoles are stopped. Rather, tacrolimus dose increases should be cautious and based on more frequent monitoring of levels as appropriate

5.1.9 Growth factors

GCSF (filgrastim) begins on Day 5 at a dose of 5mcg/kg/day (actual body weight) IV or subcutaneously (rounding to the nearest vial dose is allowed), until the absolute neutrophil count (ANC) is ≥ 1,000/mm^3 over the course of three days.

5.2 MEDI-551 maintenance therapy

Medi-551 maintenance therapy will be initiated on Day 60 (±7 days), Day 90 (±7 days), or Day 120 (±7 days) of NM-AlloSCT based on the eligibility criteria for the initiation of maintenance therapy as described in Section 3.1. MEDI-551 will be administered on 28-day cycles at a dose of 4mg/kg, as an IV infusion over 60 ±15 minutes. Infusion sets must contain a 0.2 micron in-line filter. MEDI-551 will be administered on days 1, 8, 15, and 22 of cycle 1, then 4mg/kg IV on day1 of cycles 2 through 12. Treatment may be stopped earlier if there is unacceptable toxicity, development of Grade 3 or 4 GVHD, documentation of disease progression, or patient withdrawal for other reasons.

Patients will be monitored during and after MEDI-551 infusions with assessment of vital signs (temperature, blood pressure, pulse rate, respiratory rate, and pulse oxymetry) every 30 minutes during infusion, at the end of infusion, and 30 and 60 minutes after infusion. In the event of an infusion-related reaction, the infusion of MEDI-551 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. Acetaminophen and/or an antihistamine (e.g., diphenydramine), or institutional equivalents, may be administered at the discretion of the investigator. If the infusion reaction is severe or prolonged, methylprednisolone 100 mg (or the equivalent) may be administered as well. For subsequent infusions in patients who experience an infusion reaction and do not require discontinuation of MEDI-551, acetaminophen and an antihistamine may be administered prior to initiation of the MEDI-551 infusion according to standard of care. As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

No dose reductions of MEDI-551 are allowed. Patients should permanently discontinue treatment for any toxicity Grade ≥ 3 unless any of the following conditions exist:

1. Grade 3 fever that lasts ≤ 24 hours with or without medical therapy and is not considered an SAE;

2. Transient Grade 3 rigors or chills that are clearly attributable to MEDI-551 and respond to optimum therapy;

3. Any Grade 3 or 4 electrolyte alteration that is reversible to Grade ≤ 1 (or patient's baseline) within 24 hours after it occurs;

4. Any Grade 3 liver function test elevation that resolves to Grade ≤ 1 or patient's baseline within 7 days after it occurs.

5. Transient increase in lactate dehydrogenase (LDH) levels that resolve to within normal levels within 7 days after it occurs;

Treatment may be continued after any of the following hematologic toxicities, regardless of causality:

1. Grade ≥ 3 lymphopenia or leukopenia in the absence of neutropenia;

2. Grade ≤ 4 neutropenia (in the absence of fever) that resolves to ≤ Grade 2 or patient's baseline within 5 days;

3. Grade ≤ 4 thrombocytopenia that resolves to Grade ≤ 2 or patient's baseline within 5 days;

4. Grade ≤ 4 anemia in a patient who was transfusion dependent at study entry, or had a history of hemolysis.

Treatment will continue until maximal duration of maintenance therapy is reached (twelve 28-day cycles), or the occurrence of any of the following events:

1. Disease progression.

2. Adverse event(s) that, in the judgment of the PI/medical monitor, may cause severe or permanent harm or which rule out continuation of MEDI-551;

3. Graft failure;

4. Development of Grade III-IV acute GVHD;

5. Development of severe chronic GVHD;

6. Suspected pregnancy;

7. Inability to start planned cycle of MEDI-551 within 56 days of intended start date of each cycle;

8. Major violation of the study protocol (to include subject noncompliance with study medications or protocol-specified procedures) at the discretion of the Protocol Officer;

9. Withdrawal of consent;

10. The subject is lost to follow up;

11. Death

12. Patient is unable to complete 12 cycles of maintenance therapy within 18 months of initiating maintenance therapy.

5.3 Supportive care

5.3.1 Patients will receive transfusions, nutritional support, infection prophylaxis and treatment, and other supportive care according to standard of care and institutional guidelines.

5.3.2 Anti-ovulatory treatment

Menstruating females should begin an anti-ovulatory agent before starting the preparative regimen.

5.3.3 Intravenous access

A central venous catheter is required for administration of IV medications and blood products.

5.3.4 Infection prophylaxis

Patients will receive infection prophylaxis and treatment according to institutional guidelines. Infection prophylaxis should include agents or strategies to prevent herpes simplex, CMV, Pneumocystis jirovecii, fungal infections, and infections from oral flora secondary to mucositis.

Post-transplantation immunizations will be given per institutional standard.

5.3.5 Antiemetics

Note that steroids should not be used as an antiemetic agent after the graft is infused, until at least 24 hours after the completion of all PTCy. The use of steroids as antiemetics after this time frame is discouraged in the absence of relapsed/progressive disease.

6 MEASUREMENT OF EFFECT

6.1 Disease and survival endpoints

6.1.1 Survival outcomes

Progression-free survival (PFS): Interval from NM-AlloSCT Day 0 to date of first objective disease progression or relapse, unplanned treatment for disease persistence, or death from any cause. Patients without these failures will be censored at the last date they were assessed and deemed failure-free. Disease persistence in the absence of progression is not considered a PFS failure unless it leads to treatment.

Disease-free survival (DFS): Interval from NM-AlloSCT Day 0 to date of first objective detection of disease persistence, progression or relapse, or death from any cause.

Patients without such failures will be censored at the last date they were assessed and deemed failure-free. Disease persistence posttransplantation, followed by disappearance of detectable disease in the absence of treatment, is not considered a DFS failure.

Overall survival (OS): Interval from NM-AlloSCT Day 0 to date of death from any cause or last patient contact.

Nonrelapse mortality (NRM): Death without evidence of disease progression or relapse. Relapse/progression is a competing risk for NRM.

6.1.2 Disease response

Response will be assessed using the International Myeloma Working Group Uniform Response Criteria.[50] Until disease progression, all disease classifications are relative to the patient's disease status prior to NM-AlloSCT. At each time point where response is assessed, patients will undergo serum protein electrophoresis, 24 hour urine protein electrophoresis and serum light chain analysis. If electrophoresis is negative, immunofixation will be performed and if negative, an additional bone marrow aspiration and biopsy will be performed as clinically indicated to assess response.

MEDI-551, like other monoclonal antibody therapeutics, has the potential to interfere with serum protein electrophoresis and immunofixation assays. Reflex assays may be conducted to differentiate MEDI-551 from M protein.

Stringent complete remission (sCR): Requires all of the following:

a. All criteria for complete remission (CR) listed below with the addition of normal serum free light chain ratio;
b. Absence of clonal plasma cells on bone marrow as demonstrated by immunohistochemistry or flow cytometry

Complete remission (CR): Requires all of the following:

a. Negative serum and urine electrophoresis and immunofixation;
b. Disappearance of any soft tissue plasmacytomas;
c. ≤5% plasma cells on bone marrow aspiration and biopsy

Very good partial remission (VGPR):

Serum and / or urine M protein detectable by immunofixation but not electrophoresis or ≥ 90% reduction in serum M protein and urine M protein ≤ 100mg per 24 hours

Partial remission (PR): Requires:

a. ≥ 50% reduction in serum M protein and reduction in urine M protein is ≥ 90% or to ≤ 200mg per 24 hours;
b. If the serum M protein is ≤ 1g/dL and urine M protein ≤ 200mg per 24 hours, subjects must have a > 50% decrease in the difference between involved and uninvolved serum light chain levels to be deemed a partial remission;
c. If the serum M protein is ≤1 g/dL and urine M protein ≤200 mg per 24 hours and serum light chain levels are ≤100mg/L of the involved light chain, then ≥ 50% reduction in plasma cells on bone marrow biopsy is required to classify a partial remission. This criterion may only be used if ≥ 30% plasma cells are present on the baseline bone marrow biopsy;
d. In addition, if present, a ≥ 50% reduction in the size of soft tissue plasmacytomas is required.

Stable disease (SD):

Not meeting criteria for sCR, CR, VGPR, PR or progressive disease

Progressive disease (PD) for patients not achieving a complete remission (CR): Any one or more of the following:

a. ≥ 25% rise in serum M protein with an absolute rise of a least 0.5g/dL;
b. ≥ 25% rise in urine M protein with an absolute rise of a least 200mg per 24 hours;
c. ≥ 25% rise in bone marrow plasma cell percentage with an absolute value of at least 10%;
d. Definite development of new bone lesions or plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas;
e. Development of hypercalcemia (calcium > 11.5mg/dL) that definitely be attributed to the plasma cell neoplasm.

Relapse from complete remission (CR): Any one or more of the following:

a. Reappearance of serum or urine M protein by electrophoresis or Immunofixation;
b. Development of ≥ 5% plasma cells on bone marrow biopsy;
c. Appearance of any other sign of progression (plasamcytoma, new bone lesions, hypercalcemia)

6.2 Transplant related outcomes

6.2.1 Graft-versus-host disease (GVHD)

1. Acute GVHD:

Acute GVHD is graded by standard criteria. All suspected cases of acute GVHD must be confirmed histologically by biopsy of an affected organ (e.g., skin, liver, or gastrointestinal tract). Date of symptom onset, date of biopsy confirmation of GVHD, maximum clinical Grade, sites affected, and dates and types of treatment will be recorded. Dates of symptom onset of initial diagnosis of GVHD (even if non-severe) and Grade III-IV GVHD will be recorded.

The cumulative incidences of acute Grade 3-4 and Grade 3-4 chronic GVHD will be determined through competing risk analysis. Treatment of disease relapse/progression/persistence (with the exception of planned maintenance or consolidative therapy), graft failure, and death are considered competing risks for GVHD for study purposes.

2. Chronic GVHD:

Chronic GVHD is graded by both NIH consensus criteria and Seattle criteria. Date of onset, date of biopsy confirmation (if any), dates and types of treatment, and extent will be recorded. The cumulative incidence of chronic GVHD (overall and according to extent) will be determined through competing risk analysis.

6.2.2 Toxicity

All Grades ≥ 3 toxicities according to CTCAE, version 4 will be tabulated.

6.3 Quantification of myeloma precursors

Studies will be performed to assess the relative burden of MM CSCs prior to MEDI-551 treatment (at Day +30, +60, +90, and +120 post-NM-AlloSCT, until MEDI-551 treatment is initiated), over the course of MEDI-551 treatment, (start of cycles 2, 4, 6, and 12), and at the 18 month post-transplant follow-up visit. MM CSCs will be quantified by flow cytometry of the peripheral blood. Peripheral blood mononuclear cells (PBMCs) will be isolated by density centrifugation, then stained with the Aldefluor reagent (Stem Cell Technologies) to detect relative ALDH activity and monoclonal antibodies directed against CD19, CD27 and kappa or lambda Ig light chains. A control staining reaction using the specific inhibitor of ALDH, diethylaminobenzaldehyde (DEAB), will be used to set the acquisition gate containing ALDH+ cells. Cells that express the putative MM CSC phenotype (CD19+CD27+ALDH+) will be gated and analyzed for clonality by evaluating surface immunoglobulin light chain expression.

Peripheral blood B cell counts will be evaluated at the same time points.

6.4 MEDI-551 pharmacokinetic evaluation

Samples for MEDI-551 serum concentration will be collected pre dose on cycle 1 day 1, 8, 15, and 22, as well as pre dose on the first day of cycles 2, 4, 6, and 12.

Serum samples will be measured for MEDI-551 levels by MedImmune or an approved vendor using a validated immunoassay.

6.5 MEDI-551 anti-drug antibody evaluation

Samples for MEDI-551 anti-drug antibodies will be collected prior to dosing on cycle 1 day 1, prior to dosing in cycles 2, 6, and 12, and at the 18 month post-transplant follow-up visit.

Samples will be assessed for the presence of anti-MEDI-551 antibodies by MedImmune or an approved vendor using a validated drug-tolerant solution-phase bridging assay. Tiered analysis will be performed to include screening, confirmatory and titer assay components.

7 STUDY MONITORING AND DATA COLLECTION

7.1 Pre-transplant evaluations and requirements

The following observations will be made ≤ 1 month before initiation of conditioning, except where noted (Appendix, Table 7.1):

1. History and physical examination, height and weight;

2. ECOG performance status;

9. HLA Typing (donor and recipient) as described in Sections 3.2 and 3.3 (may occur anytime prior to conditioning);

3. CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, AST and ALT;

4. Estimated creatinine clearance, using the Cockcroft-Gault formula and actual body weight;

5. Infectious disease markers to include: CMV antibody, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV

I/II antibody, and varicella zoster;

6. EKG and LVEF (may be performed ≤ 12 weeks before enrollment);

7. Pulmonary function tests, including DLCO and FEV1 (may be performed ≤ 12 weeks prior to conditioning);

8. Radiological evaluation of sinuses by CT scan or MRI;

9. Pregnancy test per institutional practices for females of child-bearing potential. NOTE: pregnancy test must be performed ≤ 14 days before enrollment;

10. Laboratory disease evaluation:
    a. Quantitative serum immunoglobulin levels;
    b. Serum protein electrophoresis (SPEP);
    24 hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP);
    c. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    d. Serum free light chain ratios (FLC);
    e. Skeletal bone survey or CT scan to include cranium, axial skeleton and proximal long bones

11. Bone marrow evaluation: unilateral bone marrow biopsy and aspirate are indicated to assess disease status prior to transplantation that may include assessment of minimal residual disease (MRD);

12. Lymphocytotoxic antibody screen

13. Donor peripheral blood for VNTR or RFLP analysis (may occur anytime prior to conditioning).

Results of evaluations performed before study entry as standard of care may be used for research purposes and to fulfill study requirements.

7.2 Post-transplant evaluations and requirements

The following evaluations will be done ≤14 days prior to initiation of maintenance therapy with MEDI-551 (see Table 7.2).

1. Physical examination and appropriate lab evaluations to assess GVHD and other morbidity;

2. ECOG performance score;

3. CBC with differential and platelet count;

4. Liver function test and blood chemistries: Serum sodium, potassium, chloride, CO2, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT;

5. Thyroid stimulating hormone (TSH);

6. Pregnancy test, serum HCG (sensitivity of at least 50mIU/mL);

7. Laboratory disease evaluation: Laboratory disease evaluations performed at Day 60 and Day 120 post-transplant can be used as evaluations prior to maintenance therapy if they are ≤ 14 days prior to the initiation of maintenance therapy
    a. Quantitative serum immunoglobulin levels;
    b. Serum protein electrophoresis (SPEP);
    c. 24 hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP). UPEP can be done with a spot urine if the patient has no measurable disease in the urine at diagnosis;
    d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    e. Serum free light chain ratios (FLC);

8. Bone marrow evaluation: unilateral bone marrow biopsy and aspirate for pathological evaluation and minimal residual disease testing by next generation sequencing (for those patients in a CR).

9. Skeletal bone survey or CT scan to include cranium, axial skeleton and proximal long bones.

10. Research peripheral blood specimens for correlative studies including quantification of MM CSCs and total B cells will be carried out every 25-30 days starting on Day +30 of NM-AlloSCT until the initiation of MEDI-551 maintenance. Samples will be collected just prior to the initiation of maintenance therapy with MEDI-551 unless carried out within the prior 14 days.

7.3 Pre-maintenance evaluations and requirements

The following evaluations will be done ≤14 days prior to initiation of maintenance therapy with MEDI-551 (see Table 7.2).

1. Physical examination and appropriate lab evaluations to assess GVHD and other morbidity;

2. ECOG performance score;

3. CBC with differential and platelet count;

4. Liver function test and blood chemistries: Serum sodium, potassium, chloride, CO2, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT;

5. Viral hepatitis tests if a history of hepatitis B or C

6. Thyroid stimulating hormone (TSH);

7. Pregnancy test, serum HCG (sensitivity of at least 50mIU/mL);

8. Laboratory disease evaluation: Laboratory disease evaluations performed at Day 60 and Day 120 post-transplant can be used as evaluations prior to maintenance therapy if they are ≤ 14 days prior to the initiation of maintenance therapy
    a. Quantitative serum immunoglobulin levels;
    b. Serum protein electrophoresis (SPEP);

c. 24 hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP). UPEP can be done with a spot urine if the patient has no measurable disease in the urine at diagnosis;
d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
e. Serum free light chain ratios (FLC);

9. Bone marrow evaluation: unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients.

10. Skeletal bone survey or CT scan to include cranium, axial skeleton and proximal long bones.

11. Research peripheral blood specimens for correlative studies including quantification of MM CSCs, total B cells, just prior to the initiation of maintenance therapy with MEDI-551 unless carried out within the prior 14 days.

7.4 Evaluations during maintenance therapy with MEDI-551

Upon initiation of maintenance with MEDI-551, weekly laboratory monitoring and GVHD assessment is required during cycles 1 and 2. Laboratory monitoring is required once every cycle for all cycles thereafter. Patient visits are mandatory for planned cycles 1-12 and 28 days after the last dose of MEDI-551, unscheduled visits and laboratory monitoring may take place as needed. Evaluations may occur within one calendar day before or after the planned visit date for cycles 1 and 2, and within seven calendar days before or after the planned visit date for cycles 3 through 12.

The following required observations are after initiation of maintenance therapy. These evaluations will occur as indicated below and in Tables 7.3a, 7.3b, and 7.3c.

1. Physical examination and appropriate lab evaluations to assess acute and chronic GVHD and other morbidities monthly;

2. CBC with differential, platelet count weekly for cycle 1, every other week for cycle 3, and monthly otherwise;

3. Liver function test and blood chemistries: Serum sodium, potassium, chloride, CO2, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT for cycle 1 and monthly otherwise;

4. Laboratory disease evaluation required every 2 months:
a. Quantitative serum immunoglobulin levels;
b. Serum protein electrophoresis (SPEP);
c. 24 hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP). UPEP can be done with a spot urine if the patient has no measurable disease in the urine at diagnosis;
d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
e. Serum free light chain ratios (FLC);

5. Bone marrow evaluation: unilateral bone marrow biopsy and aspirate for pathological evaluation and minimal residual disease testing by next generation sequencing (for those patients in a CR) at 60, 180, 365 days post-transplant.

6. Thyroid stimulating hormone (TSH) to be obtained at Cycles 1, 4, 7, 10, and the EOT.

7. Skeletal survey or CT scan to include cranium, axial skeleton and proximal long bones is required ≤ 28 days of the last dose of maintenance, but otherwise may be performed as clinically indicated during the course of the study at the discretion of the transplant physician.

8. Sorted or unsorted chimerism analysis (peripheral blood or bone marrow) every six months during treatment with maintenance study drug, and as otherwise clinically indicated, at the discretion of the physician. (The chimerism analysis technique (sorted or unsorted) is at the discretion of the attending physician but must be utilized consistently while on MEDI-551).

9. Assessment and appropriate lab evaluations for toxicities at Cycles 1, 2, 3, 4, 6, 9, 12 and ≤ 28 days after the last dose of MEDI-551.

10. Research peripheral blood specimens for correlative studies including quantification of MM CSCs and total B cells at the beginning of cycle 2, 3, 5, 7, and 10, and the EOT.

11. MEDI-551 PK: pre-dose on Cycle 1 Day 1, Day 8, Day 15, and Day 22; pre-dose at the start of Cycles 2, 4, 6, and 12.

12. MEDI-551 anti-drug antibodies (ADA): prior to the first dose on Cycle 1 Day 1, pre-dose at the start of Cycle 2, 6, and 12.

7.5 Evaluations post-maintenance therapy with MEDI-551

The following evaluations will occur after cycle 12 of MEDI-551 maintenance as indicated below and in Table 7.4. Evaluations may occur within one week before or after the planned visit date.

1. Physical examination and appropriate lab evaluations to assess acute and chronic GVHD at 18 months, and 2 years post-transplant;

2. CBC with differential, platelet count at 6 months, 18 months, and 2 years post-transplant;

3. Laboratory disease evaluation:
    a. Quantitative serum immunoglobulin levels;
    b. Serum protein electrophoresis (SPEP);
    c. 24 hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP). UPEP can be done with a spot urine if the patient has no measurable disease in the urine at diagnosis;
    d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    e. Serum free light chain ratios (FLC);
    f. Skeletal bone survey or CT scan to include cranium, axial skeleton and proximal long bones

4. Bone marrow evaluation: unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients that will include minimal residual disease testing.

5. Assessment for toxicities.

6. Research peripheral blood specimens for correlative studies including quantification of MM CSCs and B cells at 18 and 24 months post-transplant.

7.6 Study monitoring

This is a JHU-investigator-sponsored IND or IDE trial, DSMP Level III per the JHU SKCCC DSMP. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally at SKCCC by the principal investigator and the SKCCC CRO in accordance with SKCCC guidelines. The SKCCC Safety Monitoring Committee requires all DSMP Level I-IV study teams to maintain a study-specific master adverse event log and a protocol deviation log in Excel format. Templates available here: http://cro.onc.jhmi.edu/.

The PI/sub-investigator or his designee will be responsible for completing, in a timely manner, an electronic Case Report Forms (eCRFs) for each patient who is registered to participate in this study. eCRFs should be completed within 10 days after the date of study visit, or as information becomes available. The PI or a sub-investigator will sign and date the indicated places on the eCRF. This signature will indicate that a thorough inspection of the audited data therein has been made and will thereby certify the contents of the form.

The PI is responsible for internally monitoring the study and establishing additional external data & safety monitoring oversight, as required. The PI will also monitor the progress of the trial, review safety reports, and confirm that the safety outcomes and response assessments favor continuation of the study.

8 RISK and REPORTING REQUIREMENTS

8.1 Possible adverse effects of medications

8.1.1 Cyclophosphamide (Cytoxan®)

Cyclophosphamide is an alkylating agent whose metabolites form cross-links with DNA resulting in cell cycle-nonspecific inhibition of DNA synthesis and function. Cyclophosphamide side effects include: nausea, vomiting, diarrhea, headache, dizziness, hemorrhagic cystitis, fluid weight gain/edema, SIADH, transaminitis, cardiomyopathy, pericarditis, rash, mucositis, alopecia, cytopenias, sterility, and rarely, secondary myelodysplastic syndrome and anaphylaxis.

8.1.2 Mesna (sodium-2-mercapto ethane sulphonate)

Mesna is a prophylactic agent used to prevent hemorrhagic cystitis induced by the oxasophosphorines (cyclophosphamide and ifosphamide). It has no intrinsic cytotoxicity and no antagonistic effects on chemotherapy. Mesna binds with acrolein, the urotoxic metabolite produced by the oxasophosphorines, to produce a non-toxic thioether and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxasophosphorines.

The total daily dose of mesna is equal to 80% of the total daily dose of cyclophosphamide. At the doses used for uroprotection, mesna is virtually non-toxic. However, potential adverse effects include nausea and vomiting, diarrhea, abdominal pain, altered taste, rash, urticaria, headache, joint or limb pain, hypotension, and fatigue.

8.1.3 Fludarabine (Fludara)

Fludarabine is a purine analog antimetabolite. Side effects of fludarabine include:

a. Neurotoxicity: Agitation or confusion, blurred vision, loss of hearing, peripheral neuropathy or weakness have been reported. Severe neurologic effects, including blindness, coma, and death may occur; severe CNS toxicity is rarely seen with doses in the recommended range for non-transplant therapy. The dose used in this study is approximately 1.5 times the usual one-course dose given in non-transplant settings. Doses and schedules similar to those used in this study have been used in adult and pediatric patients without observed increase in neurotoxicity.

b. Anemia: Life-threatening and sometimes fatal autoimmune hemolytic anemia has been reported after one or more cycles of therapy in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test and who may or may not be in remission. Corticosteroids may or may not be effective in controlling these episodes. The majority of patients re-challenged developed a recurrence of the hemolytic process.

c. Cardiovascular: Deep venous thrombosis, phlebitis, transient ischemic attack, and aneurysm (1%) are reported.

d. Fever: 60% develop fever.

e. Rash: 15% develop a rash, which may be pruritic.

f. Gastrointestinal side effects include: nausea/vomiting (36%), diarrhea (15%), stomatitis (9%), anorexia (7%), GI bleeding and esophagitis (3%), mucositis (2%), liver failure, abnormal liver function test, constipation, dysphagia (1%) and mouth sores.

g. Other effects include: Chills (11%), peripheral edema (8%), myalgias (4%), osteoporosis (2%), pancytopenia, arthralgias (1%), dysuria (4%), urinary tract infection and hematuria (2%); renal failure, abnormal renal function test, and proteinuria (1%); and, very rarely, hemorrhagic cystitis and pulmonary toxicity.

8.1.4 Total Body Irradiation (TBI)

TBI can cause: nausea and vomiting, diarrhea, parotitis (rapid onset within 24-48 hours, usually self-limited), generalized mild erythema (usually within 24 hours, resolving in 48-72 hours), hyperpigmentation, fever, mucositis, alopecia, and pancytopenia. Late effects include: cataracts (10- 20%), hypothyroidism, nephropathy, interstitial pneumonitis, veno-occlusive disease, carcinogenesis, and sterility.

8.1.5 Mycophenolate Mofetil (MMF, Cellcept®)

MMF is an ester prodrug of the active immunosuppressant mycophenolic acid.
Side effects include: pancytopenia, infection (including sepsis, CMV, HSV, VZV, and Candida), nausea, vomiting, diarrhea, allergic reactions, hypertension, headache, dizziness, insomnia, hyperglycemia, electrolyte imbalances, rash, and leg cramps/bone pain.

Drug interactions: MMF activity is decreased with oral antacids and cholestyramine.

There are no pharmacokinetic interactions with cotrimoxazole, oral contraceptives, or cyclosporine. Acyclovir or ganciclovir blood levels may increase due to competition for tubular secretion. High doses of salicylates or other highly protein-bound drugs may increase the free fraction of MPA and exaggerate the potential for myelosuppression.

8.1.6 Tacrolimus (FK-506, Prograf®)

Tacrolimus is a macrolide immunosuppressant that inhibits lymphocytes through calcineurin inhibition. There is a spectrum of well-described toxicities of tacrolimus, including: renal insufficiency, hypertension, hyperglycemia, hypomagnesemia, hypokalemia, nausea, diarrhea, headache, neurologic toxicity including tremor and leukoencephalopathy, infection, and rarely thrombotic thrombocytopenic purpura (TTP).

Drug interactions: Tacrolimus is well absorbed orally. Tacrolimus is extensively metabolized by the cytochrome P-450 (CYP3A4) system and metabolized products are excreted in the urine. Drugs that may increase tacrolimus levels include tri-azole drugs (especially voriconazole and posaconazole), nephrotoxic drugs, calcium channel blockers, cimetidine and omeprazole, metoclopramide, macrolide antibiotics, quinupristin/dalfopristin, danazol, ethinyl estradiol, methylprednisolone, and HIV protease inhibitors. Drugs that may decrease tacrolimus levels include some anticonvulsants (phenobarbital, phenytoin, carbamazepine), caspofungin, rifamycins, and St. John's wort.

8.1.7 MEDI-551

MEDI-551 is a humanized afucosylated IgG1 kappa monoclonal antibody directed against CD19. The potential risks of MEDI-551 include hypersensitivity, tumor lysis syndrome, cytopenias (neutropenia, thrombocytopenia, anemia), serious infections (viral reactivation, opportunistic infections, progressive multifocal leukoencephalopathy [PML]) and, for combination with chemotherapy, intestinal obstruction and perforation. Infusion-related reaction is an identified risk of MEDI-551.

8.2 Toxicity grading

Toxicities are graded using the NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

8.3 Toxicity reporting

The agents used during NM-AlloSCT have well-defined toxicity profiles (see Section 8). In addition, there are many expected toxicities of NM-AlloSCT. The following are examples of toxicities that are serious but not unexpected: Grade 4 cytopenias, neutropenic fever and sepsis, bacterial, fungal, or viral (including CMV, BK virus) infection, severe mucositis, severe GVHD, hepatic veno-occlusive disease, pulmonary toxicities, hemorrhagic cystitis, bleeding without hemodynamic compromise.

For study purposes, the following will be recorded and reported in accordance with IRB requirements:

1. Any hospitalization and its reason in the first year of transplant, with the exception of hospitalizations related to relapsed disease or second HSCTs;
2. Neutropenic fever is an expected, common complication; as such, hospitalizations for

Grade 4 neutropenic fever will be reported in real-time to the IRB with hospitalizations for lesser Grade neutropenic fever routinely reported on a yearly basis;

3. Any death before Day +200 following NM-AlloSCT, and any later death which is potentially transplant-related;
4. Any unexpected, serious events deemed significant by the PI.

In addition, the following toxicities will be tracked for study purposes and reported on a yearly basis to the IRB, or earlier if warranted:

1. Clinically significant infections during the first year of transplant, with the exception of uncomplicated, culture-negative neutropenic fever. This includes CMV disease, other clinically significant documented viral infections, bacterial infections, and proven or probable invasive fungal infections;
2. CMV reactivation (including asymptomatic reactivation);
3. Hepatic veno-occlusive disease;
4. Grade 3 or greater pulmonary toxicity during the first year of transplant that is potentially transplant-related;

Additional complications and toxicities may be tracked. This is in addition to evaluating hematologic parameters, GVHD, and disease and survival endpoints outlined in Section 6.

8.3.1 FDA Reporting of Adverse Events

All FDA reporting of adverse events will be conducted in accordance with 21 CFR part 312 and 21 CFR part 320.

Unexpected Adverse Event: An AE is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Unexpected fatal or life-threatening suspected adverse reactions will be reported to the FDA with MedWatch Form 3500A within 7 calendar days of initial receipt of the event information.

Any other suspected adverse reactions to MEDI-551 will be reported to the FDA within 15 calendar days of initial receipt of the event information.

8.3.2 Reporting of Adverse Events to AstraZeneca

The sponsor is responsible for submission of adverse events to AstraZeneca in accordance with the following guidelines. All event reporting is done via paper correspondence with AstraZeneca.

Suspected Unexpected Serious Adverse Events (SUSARs) will be reported to AstraZeneca simultaneously with regulatory submission to the FDA.

Serious Adverse Events (SAEs) will be reported to AstraZeneca on a yearly basis along with an annual report.

9. STATISTICAL CONSIDERATIONS

9.1 Study design and objectives

The study is designed as a Phase II, non-randomized, single institution prospective study of MEDI-551 maintenance therapy following NM-AlloSCT for high-risk or relapsed MM. The premise is that MEDI-551 will increase progression-free survival in patients as compared to our historical data in MM patients receiving PTCy. Patients will be enrolled prior to initiation of the conditioning regimen. Patients who are eligible at 60-120 days post-transplant will receive MEDI-551 maintenance therapy and evaluated for the primary endpoint of progression-free survival. Patients who are transplanted but do not receive MEDI-551 will be followed for secondary endpoints. The target sample size is 36 patients. We assume that 10% of patients will fail to meet criteria to initiate maintenance MED-551 and so plan to enroll 40 patients receiving NM-AlloSCT in order to achieve the targeted number of evaluable patients.

9.2 Accrual

It is estimated that two years of accrual will be necessary to enroll the targeted sample size.

9.3 Primary endpoint

Determine the progression free survival (PFS) of high-risk or relapsed MM patients undergoing non-myeloablative bone marrow allogeneic transplantation (NM-AlloSCT) followed by maintenance therapy with MEDI-551. We will estimate the median PFS using the method of Kaplan and Meier and derive 90%CI with Bookmeyer-Crowley. To estimate whether treatment with MEDI-551 improves PFS we will determine whether the lower interval of the 90%CI excludes the null value for median PFS.

9.4 Sample size and power calculation

We calculated sample size using the formula described in Lawless: equation 3.2.7 (page 108) of Lawless (1982) (*Statistical Models and Methods for Lifetime Data*, John Wiley and Sons). Sample size calculation is based on the assumptions of uniform accrual over time, no loss to follow-up, exponentially distributed event times, and use of the exponential MLE test.

We assumed the following values for calculating sample size using a one-sided test:
Length of accrual period = 24 months
Length of follow-up period-time from end of accrual to analysis = 24 months
Type-I error = .10
Type-II error = .20

Median PFS for the historical rate (Null) = 14 months
Median PFS under the new treatment (alternative hypothesis) = 21 months

We calculated a sample size of 37 subjects.

9.5. Analysis of secondary endpoints

In addition to primary endpoint of PFS, we will also estimate the 3-year overall survival (OS) using Kaplan-Meier (KM) method. Cumulative incidences of relapse and non-relapse mortality will be estimated separately using Gray's method for competing risks.

9.6. Toxicities

The cumulative incidence of acute (grade II-IV, grade III-IV) and chronic GVHD (overall, and by extent) will be estimated through competing-risk analysis, wherein treatment of relapse/progression, graft failure, and death are competing risks for GVHD. These will be reported overall and according to HLA match or mismatch status. We also plan to report the cumulative incidence of GVHD with only graft failure and death regarded as competing risks. The cumulative incidence of systemic steroid initiation, the cumulative incidence of non-steroid immunosuppression use, and the cumulative incidence of discontinuation of systemic immunosuppression for GVHD treatment will be similarly estimated using competing-risk analyses, wherein graft failure and death, or graft failure, death and treatment of relapse/progression, are considered competing risks. The number and types of systemic immunosuppression used for GVHD treatment will be reported descriptively. Toxicities will be monitored until the end of the MEDI-551 treatment period.

9.7. Early stopping guidelines for toxicity

Toxicity will be monitored after each transplant recipient up to a maximum of 36 patients. A patient who experiences wither GVHD or does before relapsing would be counted towards toxicity. The stopping rule for toxicity will hold enrollment if the posterior probability of toxicity being > 30% exceeds 0.70. The prior for this toxicity monitoring rule is a beta(1,5) distribution. This means that our prior guess at the proportion of severe toxicities is 16.7%, and there is a 90% probability that this proportion is between 1.0% and 45.1%. Table 9.1 shows the results of this rule. For example, the rule calls for pausing the study if, for example, 3 out of the first 3 patients, or 4 out of the first 5 to 7 patients develop toxicity.

Table 9.1 Stopping rules for toxicity

Number of patients with toxicity	Number of evaluable patients
3	3-43-4
4	5-7
5	8-10
6	11-13
7	14-16
8	17-19
9	20-22
10	23-25
11	26-28
12	29-31
13	32-35
14	36

Table 9.2 shows the percent of time that the stopping rule will terminate the study under different hypothetical risks of toxicity. These calculations are based on 10,000 simulations.

Table 9.2 Operating characteristics of safety monitoring rules	
True proportion with the toxicity	Probability of stopping
20%	9.3%
25%	21%
30%	40%
35%	62%
40%	80%
50%	98%

10 PATHOLOGY REVIEW

Specimens diagnostic of MM (from the original diagnosis and/or relapse) must be reviewed by the Johns Hopkins Department of Pathology prior to starting protocol therapy.

11 RECORDS TO BE KEPT

Records to be filed include the following:

1. Patient consent form;
2. Registration form;
3. Eligibility checklist(s);
4. Case report forms;
5. Adverse event report form(s);
6. Follow-up assessments

The principal investigator will review case report forms on a regular basis. Case report forms will be supported by primary source documents.

12 PATIENT CONSENT AND PEER JUDGMENT

Current federal, NCI, state, and institutional regulations regarding informed consent will be followed. More frequent monitoring of disease status, vital status, and toxicities may be performed for study purposes including through collection of outside records and patient and physician contact. Patients who relapse or progress will continue to be followed on study unless consent is withdrawn.

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14 APPENDICES

14.1 Appendix A. Diagnostic criteria for multiple myeloma[51]

Clonal bone marrow plasma cells ≥10% of biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:

- Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcemia: serum calcium > 0.25mmol/L (> 1mg/dL) higher than the upper limit of normal or > 2.75mmol/L (>11mg/dL)
  - Renal insufficiency: creatinine clearance < 40mL per min or serum creatinine > 177μmol/L (> 2mg/dL)
  - Anemia: hemoglobin value of > 20g/L below the lower limit of normal, or a hemoglobin value < 100g/L
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage ≥ 60%
  - Involved:uninvolved serum free light chain ratio ≥100
  - >1 focal lesions on MRI studies

14.2 TABLES

Table 7.1

Study Assessments/Testing	Within 28 days of start of conditioning unless indicated otherwise
Medical history	X
Physical exam, weight and height	X
ECOG performance status	X
Hematology [1]	X
Blood chemistries [2]	X
Estimated creatinine clearance [3]	X
Infectious disease markers [4]	X
Cardiac function analysis (EKG and LVEF) [5]	X
Lung function analysis (DLCO and FEV) [5]	X
Pregnancy test [6]	X
Transplant compatibility	
HLA typing (donor and recipient)	X
Lymphocytotoxic antibody screen	X
Disease evaluation	
Quantitative serum immunoglobulins	X
SPEP and immunofixation	X
24 Hour Urine for UPEP, protein excretion and immunofixation	X
Serum free light chain ratio	X
Skeletal survey or CT scan	X
Bone marrow aspirate and biopsy	X

[1]CBC with manual differential and platelet count.
[2]Includes serum sodium, potassium, chloride, CO2, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT.
[3]Estimated creatinine clearance is calculated using the Cockcroft-Gault formula and actual body weight.
[4]Infectious disease titers include: CMV, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV I/II antibody, and varicella zoster.
[5]May be performed within 12 weeks of enrollment.
[6]Pregnancy test must be performed < 14 days from enrollment. Pregnancy test is required for females of child-bearing potential and may be performed per institutional practices.

Table 7.2

Study Assessments/Testing[1]	Weeks Post Transplant (prior to starting maintenance only)											
	1	2	3	4	5	6	7	8	10	12	16	24
Physical exam (focused)		X	X	X	X	X	X	X		X	X	X
Assessment of GVHD		X	X	X	X	X	X	X	X	X	X	X
ECOG performance status		X	X	X	X	X	X	X	X	X	X	X
Evaluate eligibility to begin MEDI-551 maintenance								X		X	X	X
Hematology[2]	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistries[3]	X	X	X	X	X	X	X	X	X	X	X	X
Viral hepatitis tests[4]												
Thyroid stimulating hormone[5]								X			X	X
Pregnancy test[6]								X			X	X
Disease evaluation												
Quantitative serum immunoglobulins								X			X	X
SPEP and immunofixation								X			X	X
24 Hour Urine for UPEP, protein excretion and immunofixation								X			X	X
Serum free light chain ratio								X			X	X
Skeletal bone survey or CT scan								X			X	X
Whole blood for chimerism				X				X				X
Bone marrow aspirate and biopsy for chimerism and MRD analysis								X				X
Blood sample for MM CSCs and B cells				X				X		X	X	X

[1]Post transplant evaluation will occur until eligibility criteria for initiation of MED-551 are met. Subsequent evaluation will take place according to MEDI-551 evaluation table.
[2]CBC with manual differential and platelet count to be performed weekly from Day 0 until engraftment. CBCs will be performed per institutional guidelines from the time of engraftment through randomization.
[3]Includes serum sodium, potassium, chloride, CO2, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT.on weeks 8 and 16.
[4]If history of hepatitis B or C.
[5]Required once prior to initiation of MEDI-551 maintenance.
[6]Required once prior to initiation of MEDI-551 maintenance for females of child-bearing potential and may be performed per institutional practices.

Table 7.3a

Study Assessments/Testing[1]	Weeks Post Transplant																			
	8	9	10	11	12	13	14	15	16	20	24	26	28	32	36	40	44	48	52	56
	MEDI-551 Cycle (C) and Day (D)																			
	C1 D1	C1 D8	C1 D15	C1 D22	C2 D1	C2 D8	C2 D15	C2 D22	C3 D1	C4 D1	C5 D1	C5 D15	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	EOT
Physical exam (focused)	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Vitals[2]	X	X	X	X	X				X	X	X		X	X	X	X	X	X	X	
Assessment of GVHD	X	X	X	X	X	X	X	X	x											
Physical exam (focused)	X				X				X	X			X		X	X	X	X	X	X
ECOG performance status[2]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Hematology[3]	X	X	X	X	X		X		X	X	X		X	X	X	X	X	X	X	X
Blood chemistries[4]	X				X				X	X			X			X			X	X
Thyroid stimulating hormone	X									X				X			X			X
Disease evaluation																				
Quantitative serum immunoglobulins	X								X		X			X		X		X		X
SPEP and immunofixation	X								X		X			X		X		X		X
24 Hour Urine for UPEP, protein excretion and immunofixation	X								X		X			X		X		X		X
Serum free light chain ratio	X								X		X			X		X		X		X
Skeletal bone survey or CT scan[5]	X										X									X
Whole blood for chimerism[6]	X													X						X
Bone marrow aspirate and biopsy for chimerism and MRD analysis	X											X							X	
Blood sample for MM CSCs and B cells	X				X				X		X			X			X			X
Serum for MEDI-551 PK[7]	X	X	X	X	X					X			X						X	X
Serum for MEDI-551 ADA	X				X								X							X

[1]For C1D1 assessments and testing are not required if carried out in the past 7 days.
[2]Temperature, blood pressure, pulse rate, respiratory rate, pulse ox pre-dose, every 30 min during infusion, end of infusion, and 30 and 60 minutes post end of infusion.
[3]CBC with manual differential and platelet count to be performed weekly for the first cycle then monthly.
[4]Includes serum sodium, potassium, chloride, CO2, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT.
[5]Required at EOT; otherwise perform when indicated clinically.
[6]Every 6 months during treatment or when clinically indicated.
[7]Pre-dose only.

Table 7.3b

Study Assessments/Testing[1]	Weeks Post Transplant																			
	16	17	18	19	20	21	22	23	24	28	32	34	36	40	44	48	52	56	60	64
	MEDI-551 Cycle (C) and Day (D)																			
	C1 D1	C1 D8	C1 D15	C1 D22	C2 D1	C2 D8	C2 D15	C2 D22	C3 D1	C4 D1	C5 D1	C5 D15	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	EOT
Physical exam (focused)	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Vitals[2]	X	X	X	X	X				X	X	X		X	X	X	X	X	X	X	
Assessment of GVHD	X	X	X	X	X	X	X	X	x											
Physical exam (focused)	X				X				X	X			X		X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Hematology[3]	X	X	X	X	X		X		X	X	X		X	X	X	X	X	X	X	X
Blood chemistries[4]	X				X				X	X			X			X			X	X
Thyroid stimulating hormone	X									X				X			X			X
Disease evaluation																				
Quantitative serum immunoglobulins	X								X		X			X		X		X		X
SPEP and immunofixation	X								X		X			X		X		X		X
24 Hour Urine for UPEP, protein excretion and immunofixation	X								X		X			X		X		X		X
Serum free light chain ratio	X								X		X			X		X		X		X
Skeletal bone survey or CT scan[5]	X										X									X
Whole blood for chimerism[6]	X													X						X
Bone marrow aspirate and biopsy for chimerism and MRD analysis	X											X							X	
Blood sample for MM CSCs and B cells	X				X				X		X			X			X			X
Serum for MEDI-551 PK[7]	X	X	X	X	X					X			X						X	X
Serum for MEDI-551 ADA	X				X								X							X

[1]For C1D1 assessments and testing are not required if carried out in the past 7 days.
[2]Temperature, blood pressure, pulse rate, respiratory rate, pulse ox pre-dose, every 30 min during infusion, end of infusion, and 30 and 60 minutes post end of infusion.
[3]CBC with manual differential and platelet count to be performed weekly for the first cycle then monthly.
[4]Includes serum sodium, potassium, chloride, CO2, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT.
[5]Required at EOT; otherwise perform when indicated clinically.
[6]Every 6 months during treatment or when clinically indicated.
[7]Pre-dose only.

Table 7.3c

Study Assessments/Testing[1]	Weeks Post Transplant																			
	24	25	26	27	28	29	30	31	32	36	40	42	44	48	52	56	60	64	68	72
	MEDI-551 Cycle (C) and Day (D)																			
	C1 D1	C1 D8	C1 D15	C1 D22	C2 D1	C2 D8	C2 D15	C2 D22	C3 D1	C4 D1	C5 D1	C5 D15	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	EOT
Physical exam (focused)	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Vitals[2]	X	X	X	X	X				X	X	X		X	X	X	X	X	X	X	
Assessment of GVHD	X	X	X	X	X	X	X	X	x											
Physical exam (focused)	X				X				X	X			X		X	X	X	X	X	X
ECOG performance status[7]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Hematology[3]	X	X	X	X	X		X		X	X	X		X	X	X	X	X	X	X	X
Blood chemistries[4]	X				X				X	X			X			X			X	X
Thyroid stimulating hormone	X									X				X			X			X
Disease evaluation																				
Quantitative serum immunoglobulins	X								X		X			X		X		X		X
SPEP and immunofixation	X								X		X			X		X		X		X
24 Hour Urine for UPEP, protein excretion and immunofixation	X								X		X			X		X		X		X
Serum free light chain ratio	X								X		X			X		X		X		X
Skeletal bone survey or CT scan[5]	X										X									X
Whole blood for chimerism[6]	X													X						X
Bone marrow aspirate and biopsy for chimerism and MRD analysis	X											X							X	
Blood sample for MM CSCs and B cells	X				X				X		X			X			X			X
Serum for MEDI-551 PK[7]	X	X	X	X	X					X			X						X	X
Serum for MEDI-551 ADA	X				X								X							X

[1]For C1D1 assessments and testing are not required if carried out in the past 7 days.
[2]Temperature, blood pressure, pulse rate, respiratory rate, pulse ox pre-dose, every 30 min during infusion, end of infusion, and 30 and 60 minutes post end of infusion.
[3]CBC with manual differential and platelet count to be performed weekly for the first cycle then monthly.
[4]Includes serum sodium, potassium, chloride, CO2, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT.
[5]Required at EOT; otherwise perform when indicated clinically.
[6]Every 6 months during treatment or when clinically indicated.
[7]Pre-dose only.

Table 7.4

Study Assessments/Testing[1]	Time Post Transplant (post maintenance EOT only)	
	18 months	2 years[1]
Physical exam (focused)	X	X
Assessment of GVHD	X	X
Assessment of toxicity	X	X
ECOG performance status	X	X
Hematology[2]	X	X
Blood chemistries[3]	X	X
Disease evaluation		
Quantitative serum immunoglobulins	X	X
SPEP and immunofixation	X	X
24 Hour Urine for UPEP, protein excretion and immunofixation	X	X
Serum free light chain ratio	X	X
Skeletal bone survey or CT scan	X	X
Bone marrow aspirate and biopsy for chimerism and MRD analysis	X	X
Blood sample for MM CSCs and B cells	X	

[1]Follow up evaluations to be carried out every 6 months after two years.
[2]CBC with manual differential and platelet count to be performed weekly for the first cycle then monthly.
[3]Includes serum sodium, potassium, chloride, CO2, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT.