TITLE: A Phase II Trial of Vaccination with Dendritic Cell (DC)/Myeloma Fusions in Combination with Nivolumab in Patients with Relapsed Multiple Myeloma

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1. OBJECTIVES

1.1 Study Design

The study is a phase II study to evaluate vaccination with DC/myeloma fusions/GM-CSF and nivolumab in patients diagnosed with relapsed multiple myeloma previously treated with a proteasome inhibitor, IMiD, and anti-CD38 mAb therapy. Patients meeting initial eligibility will be enrolled and vaccine production will be initiated via the harvesting of autologous tumor cells and generation of DCs from adherent mononuclear cells. During the period of vaccine generation, patients will undergo therapy with 1-2 cycles of standard of care therapy. Patients without disease progression will then undergo monthly vaccination with DC/MM fusions for cycles 1, 2, and 3 in conjunction with nivolumab administered on day 1 and 15 and will then receive nivolumab alone for 3 addition cycles, for a total of 6 cycles of treatment.

1.2 Primary Objectives

1.2.1 Primary Immunologic Endpoint

The primary endpoint is to define the immunologic response to nivolumab and the DC/MM fusion vaccine with respect to the induction of myeloma-specific immunity in patients with relapsed disease after prior proteasome inhibitor, IMiD, and anti-CD38 mAb therapy. Specifically, we will quantify the expansion of treatment-induced myeloma-specific T cells in the circulation as measured by pre-therapy and peak post-treatment levels of CD4 and CD8 T cells expressing IFNγ following ex-vivo exposure to autologous tumor lysate. The percentage of patients achieving at least a 3 and 10-fold expansion of myeloma-specific T cells will be determined.

1.3 Secondary Objectives

1.3.1 Secondary Immunologic Endpoints

We will determine the effect of therapy on the percent of marrow-infiltrating myeloma-specific T cells as measured by pre-therapy and peak post-treatment levels of CD4 and CD8 T cells expressing IFNγ following ex vivo exposure to autologous tumor lysate. We will also quantify T cells specific to shared myeloma antigens potentially including MUC1, NY-ESO, PRAME, Survivin, XPB-1, SOX2, and WT1 by pentamer analysis. Assessment of the immune landscape will consist of quantifying T cell subsets in the circulation and marrow, presence of MDSCs, PD-1 expressing T cells, Tregs, and immunoregulatory microRNAs and will be correlated with immunologic response.

1.3.2 Secondary Clinical Endpoints

To determine the clinical response and safety of nivolumab and the DC/MM fusion vaccine in patients with relapsed disease. The percentage of patients achieving complete, very good partial and partial response will be quantified. Minimal residual disease (MRD) status will be determined. Progression free survival (PFS) will be assessed.

2. BACKGROUND

2.1 Therapeutic approaches in Multiple Myeloma

Despite major recent advances in therapeutic options for patients with multiple myeloma (MM), curative outcomes remain elusive. While the introduction of IMIDs, proteasome inhibitors, and antibody-mediated therapies have dramatically improved progression free and overall survival in MM patients, progressive resistance to biologic agents ultimately develops and often results in disease-associated mortality.[1] Novel approaches are needed to improve patient outcomes. Cancer therapeutics has undergone a dramatic change with the observation that cellular

immunotherapy results in sustained disease response in a subset of patients with previously incurable disease.[2] This approach potentially harnesses native immunity to provide specific targeting of tumor cells and the development of memory responses critical to prevent relapse.

2.2 Vaccine Therapy for Multiple Myeloma

Immune therapy has emerged as a leading area of cancer therapeutics due to its potential to recruit multiple effectors that broadly target malignant cells and overcome mechanisms of resistance.[3,4] Multiple myeloma (MM) is characterized by the loss of critical mediators of immune surveillance, resulting in the suppression of antigen-presenting and effector cell function and the development of an immunologic milieu that fosters disease progression.[5–7] We have developed a tumor vaccine in which patient-derived myeloma cells are fused with autologous dendritic cells (DCs), such that a broad array of myeloma antigens are presented in the context of DC-mediated costimulation.[8–10] In diverse tumor models that include MM, vaccination of animals with DC/tumor fusions results in protection from an otherwise lethal challenge of malignant cells and, more significantly, eradication of disease in the setting of advanced metastatic involvement.[11] In a phase I study, 17 patients with advanced myeloma (median of 4 prior regimens) underwent vaccination with DC/MM fusions in conjunction with 4 days of GM-CSF administered at the vaccine site. In this study, MM cells were isolated from bone marrow aspirates and fused with autologous DCs generated from adherent mononuclear cells cultured with GM-CSF, IL-4, and TNFα.[8] Vaccine production was successful in all patients and was well-tolerated without evidence of clinically significant autoimmunity. Vaccination resulted in a mean 10-fold expansion of CD4 and CD8 myeloma-specific T cells, as determined by the percentage of cells expressing IFNγ in response to *ex-vivo* exposure to autologous tumor lysate. Similarly, vaccination resulted in the development of myeloma-specific antibody responses as documented by SERAX analysis.[8]

2.3 Vaccination with DC/Myeloma fusion cells following autologous transplant

Vaccination with DC/Myeloma fusion cells following autologous transplant is associated with potent immune response and conversion from PR to CR in a subset of patients.[10] We completed a clinical trial in which MM patients were vaccinated with DC/MM fusion cells in conjunction with autologous transplantation (ASCT).[8,10] In the first cohort of the study, twenty-four patients received serial vaccinations following post-transplant hematopoietic recovery. A second cohort of 12 patients received a pre-transplant vaccine followed by post-transplant vaccinations. Vaccine preparation was successful in all patients. Mean yield of the DC and MM cells was 1.74×10^8 and 6.5×10^7 cells, respectively. Mean fusion efficiency, as determined by the percentage of cells that co-expressed unique DC (CD80, CD86, and/or CD83) and MM (CD38 and/or CD138) antigens, was 38%. The mean dose administered was 3.6×10^6 fusion cells. Mean viability of the DC, myeloma, and fusion preparations was 87%, 87%, 79%, respectively. The DC/MM fusion preparations exhibited potent antigen presenting capacity, as evidenced by their stimulation of allogeneic T cell proliferation, with a mean stimulation index of 36.6, similar to that observed with the DC preparation prior to fusion (mean stimulation index of 52.3). In contrast, the unfused myeloma cells demonstrated minimal capacity for T cell stimulation (mean stimulation index of 13.7). All vaccine-associated toxicities were of grade I-II intensity. The most common toxicity was erythema and induration at the vaccine injection site associated with T cell infiltration on biopsy. The other common side effects were transient pruritus, rash, fatigue, fever, and myalgias. One patient had a transiently elevated ANA level without clinical evidence of autoimmunity. One patient developed transient grade 2 leukopenia, but no evidence of graft compromise was observed following vaccination.

Consistent with prior reports, the post-transplant period was associated with the relative suppression of general measures of cellular immunity as manifested by decreased T cell proliferative responses to mitogen or recall antigens. In contrast, the period of post-transplant lymphopoietic reconstitution was associated with the expansion of myeloma-specific T cells that was further boosted following vaccination, as determined by percentage of CD4+ and CD8+ T cells expressing IFNγ in response to *ex-vivo* exposure to autologous tumor lysate. In the first cohort that received only post-transplant vaccination, the mean log10-fold increase in myeloma-specific CD4+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 3.55 (95% CI 0.81;15.49) and 10.72 (95% CI 3.89;29.51), respectively. Similarly, the mean log10-fold increase in myeloma-specific CD8+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 6.76 (95% CI 3.02;15.49) and 11.48 (95% CI 4.17;32.36), respectively. A smaller subset of patients underwent a single pre-

transplant vaccination followed by post-transplant boosting. Of note, no difference in peak levels of CD4+ or CD8+ circulating myeloma-specific T cells was observed between the cohort receiving a pre-transplant vaccine and that undergoing post-transplant vaccination alone (p=0.185 and p=0.689, respectively). For the entire study population, the mean log10-fold increase in myeloma-specific CD4+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 3.55 (95% CI 1.58;8.13) and 9.55 (95% CI 5.37;16.98), respectively. The mean log10 fold increase in myeloma-specific CD8+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 4.37 (95% CI 2.40;7.76) and 8.32 (95% CI 4.68;15.14), respectively. Notably, vaccination was associated with the expansion of T cells targeting the myeloma-specific antigen, MUC1, as determined by tetramer analysis. In a cohort of patients who were HLA-A2, the median percentage of MUC1-specific T cells was 0.12 pre-transplant and increased to 1.84 at 3 months after completion of vaccination ($p<0.05$), representing a median fold increase of 17.5. The expansion of T cells targeting MUC1 in response to vaccination is of particular interest, as we have identified a population of CD34+/MUC1+ cells in the bone marrow of patients with myeloma that demonstrate myeloma-initiating capacity. Seventy-eight percent of patients achieved a CR or VGPR (47% CR/nCR; 31% VGPR). Thirty-one percent achieved a CR/nCR in the early post-transplant period, whereas an additional 17% (6 patients: 4 from VGPR, 2 from PR) achieved CR/nCR as best response only after day 100 post- transplant and after undergoing vaccination. The presence of late responses several months after ASCT is consistent with an impact of vaccine therapy on post-transplant residual disease.

2.4 Checkpoint Blockade

A remaining challenge to develop sustained and clinically effective immune therapy for myeloma involves overcoming the immunosuppressive milieu characteristic of the tumor microenvironment.[12] A critical component of this tolerizing environment is the upregulation of negative costimulatory molecules such as programmed death receptor 1 (PD-1) that induced a state of T cell exhaustion.[3,13,14] Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphatase.[15] In health, ligation of PD-1 is associated with protection from autoimmune sequelae of immune overstimulation. For example, PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6)[16] and cardiomyopathy (BALB/c)[17]. In the setting of malignancy, upregulation of PD-L1 on tumor cells and ligation of PD-1 on tumor associated lymphocytes results in a state of immune tolerance and escape facilitating tumor growth. In contrast, blockade of the PD-1/PD-L1 pathway has been associated with dramatic and sustained disease responses in a subset of patients with malignancy including malignant melanoma, Hodgkin disease, renal, lung, bladder, and head and neck cancer.[2,18]

2.5 Nivolumab

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an "exhausted" phenotype. Nivolumab binds to cynomolgus monkey PD-1 but not mouse, rat, or rabbit molecules. Clinical activity of nivolumab has been observed in patients with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and recently in hematologic malignancies. This clinical experience has demonstrated that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. It is not yet clear what factors with respect to the tumor cells, their surrounding microenvironment, and the nature of immune dysregulation are determinative of response to the class of checkpoint inhibitors.

2.5.1 Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Investigator Brochure, 2015). Nivolumab bound specifically to PD-1 (and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA) with a Kd = 3.06 nM. A surrogate rat anti-mouse PD-1 antibody (4H2) was derived and expressed as chimeric IgG1 murine antibody. Antitumor activity was seen for several tumor

models, including colon carcinoma and fibrosarcoma.

2.5.2 Clinical Development of Nivolumab

Nivolumab is being evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), gastrointestinal (GI) malignancies including microsatellite instability (MSI) in colorectal cancer, and triple- negative breast cancer (TNBC) with an expanding group of indications in hematologic malignancies (Investigator Brochure, 2015). Investigator-sponsored trials (ISTs) of nivolumab in combination with a peptide vaccine in melanoma are being conducted in the adjuvant setting and advanced disease.

2.5.3 Pharmacokinetics

Pharmacokinetics (PK) of nivolumab was linear in the range of 0.3 to 10 mg/kg, with dose-proportional increases in maximum serum concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC0-∞), with low to moderate inter-subject variability observed at each dose level (Investigator Brochure, 2015). Clearance of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of BMS-936558 is 17 to 25 days consistent with the half-life of endogenous IgG4.

2.5.4 Efficacy

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study, the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. Ors were observed at all doses.[18] Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Median OS across all dose cohorts was 9.2 months and 9.6 months for squamous and non-squamous NSCLC, respectively.[19] In the RCC cohort, median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥1 year.

2.5.5 Toxicology

A maximum tolerated dose (MTD) of nivolumab was not defined.[18] Serious adverse events (SAEs) occurred in 32 of 296 patients (11%) similar to the immune-related inflammatory events seen with ipilimumab: pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (with noted pulmonary toxicity resulting in 3 deaths. Renal failure, symptomatic pancreatic and DM, neurologic events, and vasculitis have also been reported.).

2.6 Checkpoint Blockade in Myeloma

PD-1 expression is upregulated on T-cells isolated from patients with MM,[14,20,21] suggesting that this pathway is of importance in mediating the immunosuppressive state in this patient population. However, PD-1 blockade has demonstrated minimal single agent activity in MM due to the lack of the intrinsic anti-tumor immunity in this setting.[3,22,23] Efforts are underway to assess the activity of combination therapy with immunomodulatory agents and PD-1 antibody.[24] Phase II studies demonstrated that PD-1 blockade in conjunction with IMID therapy resulted in clinical activity in a subset of patients with advanced disease who were refractory to single agent therapy with IMIDs. However, a randomized trial demonstrated increased morbidity and mortality was noted in patients treated with combination IMID therapy and PD-1 blockade. We postulate that the DC/MM fusion vaccine will act synergistically with checkpoint blockade by inducing the expansion of myeloma specific T cells that can be further activated by exposure to checkpoint blockade. Indeed, preclinical studies from our laboratory demonstrated that PD-1 blockade enhances T-cell response to DC/MM fusions in vitro.[25]

2.7 Rationale

MM is associated with immune suppression, including defects in antigen presentation and effector cell function that are thought to play a role in disease progression. Although the outcomes for myeloma patients have improved greatly over the past decade, the majority of patients relapse even after autologous stem cell transplant and post-transplant maintenance therapy with lenalidomide. We have demonstrated that vaccination with DC-MM fusions induces the expansion of myeloma reactive T cells and is associated with the conversion of partial to complete responses following high dose chemotherapy with stem cell rescue. We are currently conducting a national randomized multicenter trial under the auspices of the CTN cooperative oncology group, to assess the clinical and immunologic impact of vaccination with lenalidomide maintenance as compared to maintenance alone in myeloma patients undergoing autologous stem cell transplantation.

In a phase 1 trial published in 2011, we previously studied the role of personalized DC/MM fusion vaccination in the setting of relapsed MM. In this patient experience, we did observe an encouraging immunologic signal. However, only a subset of these relapsed MM patients had stable disease post-vaccination and no patient demonstrated a reduction in disease burden.[8] For this reason, we postulate that in the relapsed MM disease setting, the combination of vaccination along with a second immunologic agent may yield disease response in addition to immunologic activation against MM. In the present proposal, we hypothesize that the efficacy of checkpoint blockade in myeloma is dependent on the initial expansion of myeloma-reactive T cells in the immune repertoire that can then be further activated and expanded in the context of nivolumab therapy. We propose a clinical trial to examine the toxicity, immunologic effect and clinical response of nivolumab administered in conjunction with the DC/MM vaccine, as vaccination alone in this patient population has not previously yielded clinical disease response. We hypothesize that the study will illuminate the nature of the immunologic response to a therapeutic strategy that incorporates vaccine-mediated expansion of myeloma specific T cell immunity and antibody-mediated targeting of negative checkpoints that will alter the tumor microenvironment and favor the generation of a productive immune response targeting myeloma cells.

2.8 Correlative Studies Background

2.8.1 Impact of therapy on the immunologic response in the peripheral blood and bone marrow

The primary immunologic endpoint is to define the immunologic response to nivolumab and the DC/MM fusion vaccine with respect to the induction of peripheral blood myeloma-specific immunity in patients with relapse disease after prior proteasome inhibition, IMiD, and anti-CD38 mAb therapy. Specifically, we will compare the expansion of
treatment-induced myeloma-specific T cells in the circulation as measured by pre-therapy and peak post-treatment levels of CD4 and CD8 T cells expressing IFNγ following ex-vivo exposure to autologous tumor lysate. Similarly, as a secondary endpoint and correlative study, we will quantify the percentage of myeloma-reactive lymphocytes in the bone marrow prior to cycles 1, 3, 6 and at the off-treatment time. The expansion of myeloma-specific T cells in the circulation and bone marrow will be calculated individually for each patient so that the specific baseline levels prior to vaccination will serve as an internal control value for each patient. To control for intrinsic variability of the assay, samples are cryopreserved and all time points are analyzed in a single experiment. To control for nonspecific reactivity against normal marrow elements, T cell expression of IFNγ will be measured following pulsing with lysate from CD38- BMMCs (when feasible). We will determine the mean fold increase in myeloma-specific T cells and the percentage of patients demonstrating 3 and 10 fold threshold increases in response to vaccination in the circulation and the bone marrow.

We hypothesize that patients will demonstrate enhanced myeloma-specific immunity following exposure to vaccine plus nivolumab as compared to the pre-treatment time point. In a prior study, we observed that patients with multiple myeloma exposed to a MM/DC fusion vaccine had a mean log10-fold increase in myeloma-specific CD4+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 3.55 (95% CI 1.58;8.13) and 9.55 (95% CI 5.37;16.98), respectively. The mean log10 fold increase in myeloma-specific CD8+ T cells from pre-mobilization to post-transplant and from pre-mobilization to peak post-vaccination was 4.37 (95% CI 2.40;7.76) and 8.32 (95% CI 4.68;15.14), respectively.[8,10] Similarly, in an early phase clinical trial of AML patients receiving AML/DC fusion vaccination following a chemotherapy-induced remission, we also observed enhanced leukemia-specific immunity as evidenced by increased circulating lymphocytes targeting leukemia cells.[26]

2.8.2 Effect of treatment on circulating T cells binding the MUC1, NY-ESO, Survivin, PRAME, WT1 tetramers in HLA-A2.1 patients

We have previously observed enhanced antigen-specific reactivity in patients treated with personalized dendritic cell fusion vaccine therapy.[10,26] We will examine antigen-specific reactivity by tetramer analysis in prior to and after exposure to the vaccine and nivolumab in HLA-A2.1 positive patients. This assay utilizes tetrameric proteins to detect and quantify T-cells that are specific for a given antigen within a peripheral blood sample. We hypothesize that patients treated with the combination of vaccine and nivolumab will elicit immune-specific responses against myeloma cells and thereby, we will observe increased T cells against common myeloma antigens including WT-1 and MUC-1. Functional characteristics of the pentamer positive cells will be determined by quantifying expression of IFNγ, granzyme B, IL-4, and IL-10 expression by intracellular FACS staining.

2.8.3 Immune microenvironment including T cell subsets, T cell checkpoint receptors and myeloid-derived suppressor cells (MDSCs)

We plan on quantifying T cell subsets, T cell checkpoint receptors, and MDSCs via flow cytometry. Bone marrow aspirate and peripheral blood samples will be obtained prior to and after initiating immunotherapy and the microenvironment will be assessed with respect to the presence of Tregs, PD-1 expressing T cells, central memory (CD4/CD62L/CD27), effector memory (CD4/CD62L/CD27), and naïve T cells and granulocytic (CD11B+ CD33+ HLADRLOW/ CD15+) and monocytic (CD11B+ CD33+ HLADRLOW/ CD15-) MDSCs. We hypothesize that exposure to vaccine and PD-1 blockade with nivolumab will shift T cells from an immunoregulatory into an immune-activated phenotype and will also decrease MDSC burden in the microenvironment.

2.8.4 Optional Vaccine Site Biopsy

In patients who develop a vaccine site reaction, an optional biopsy of the vaccine site may be performed. Biopsy of the vaccine injection site will undergo immunohistochemical staining to assess for infiltrating lymphocytes which will be further characterized by mechanical disruption and flow cytometry to quantify recruitment of myeloma and antigen specific T cells. Presence of effector (CD62L/CD27) and central memory cells (CD62L/CD27) within the myeloma-specific and pentamer+ T cell populations will be determined by multichannel flow cytometry.

2.8.5 Optional Aspirate and Peripheral Blood Samples for future research

In patients who consent to optional bone marrow aspirate and peripheral blood samples, we will cryopreserve these samples in the Avigan laboratory for future possible use in biomarker discovery and correlative studies including genomic analysis, whole exome sequencing, RNA sequencing, neoantigen discovery, proteomics, microRNA profiling, as well as additional immunologic assays.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participant must have multiple myeloma and have relapsed following or are refractory to proteasome inhibitors, IMiDs and anti-CD38 mAb therapy

3.1.2 Participant must have at least 3 prior lines of therapy

3.1.3 Age ≥18 years.

3.1.4 ECOG performance status ≤2

3.1.5 Participant must have > 20% plasma cells in the bone marrow core or aspirate differential <30 days prior to enrollment.

3.1.6 ANC > 1K/uL; Platelets > 50 K/uL without transfusional support

3.1.7 Participant must have normal organ function as defined below:

- total bilirubin ≤1.5 × institutional upper limit of normal
- AST(SGOT) ≤3 × institutional upper limit of normal
- ALT(SGPT) ≤3 × institutional upper limit of normal
- creatinine clearance ≥40 mL/min for participants with creatinine levels above institutional normal.

3.1.8 The effects of DC/MM fusion and nivolumab on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 5 months after completion of treatment.

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

3.2 Exclusion Criteria

3.2.1 Participants who are receiving any other investigational agents.

3.2.2 Participants with purely non-secretory MM [absence of a monoclonal protein (M protein) in serum as measured by electrophoresis and immunofixation and the absence of Bence-Jones protein in the urine defined by use of conventional electrophoresis and immunofixation techniques and the absence of involved serum free light chain >100 mg/L]. Patients with light chain MM detected in the serum by free light chain assay are eligible.

3.2.3 Participants with Plasma Cell Leukemia

3.2.4 Because of compromised cellular immunity, patients who have a known human immunodeficiency virus (HIV), active hepatitis C virus (HCV) or active hepatitis B virus (HBV).

3.2.5 Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure (see Appendix H), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening will be documented by the investigator as not medically relevant.

3.2.6 Active or prior documented autoimmune or inflammatory disorders including but not limited to the following:

- GI Disorders: (including inflammatory bowel disease [e.g. ulcerative colitis, Crohn's disease], diverticulitis (with the exception of a prior episode that has resolved), celiac disease, or other serious gastrointestinal chronic conditions associated with diarrhea.
- Systemic lupus erythematosus
- Wegener's syndrome [granulomatosis with polyangiitis]
- Myasthenia gravis
- Graves' disease
- Rheumatoid arthritis
- Hypophysitis
- Uveitis

The following are exceptions to this criterion: subjects with vitiligo or alopecia; subjects with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement; or subjects with psoriasis not requiring systemic treatment.

3.2.7 Individuals with a history of a different malignancy are ineligible except for the following circumstances. Note: Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: non-invasive cancer (such as, any in situ cancers) and basal cell or squamous cell carcinoma of the skin.

3.2.8 Female patients who are pregnant (positive β-HCG) or breastfeeding

3.2.9 Prior organ transplant requiring immunosuppressive therapy.

3.2.10 Patients who previously received PD-1 antibody and have experienced toxicities resulting in treatment discontinuation.

3.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.3 Eligibility Prior to Vaccination with DC/MM fusions and nivolumab

3.3.1 Resolution of all chemotherapy related grade 3-4 toxicity as per CTC criteria 4.0

3.3.2 Successful production of at least 2 vaccines of a minimum of 1 $x10^6$ fusion cells

3.3.3 Absence of disease progression to standard of care therapy during the period of vaccine generation.

3.3.4 ECOG performance status ≤2

3.3.5 Participants must have normal organ function as defined below:

- total bilirubin ≤1.5 × institutional upper limit of normal
- AST(SGOT). ≤3 × institutional upper limit of normal
- ALT(SGPT) ≤3 × institutional upper limit of normal
- creatinine clearance ≥40 mL/min for participants with creatinine levels above institutional normal.

3.3.6 No myeloma therapy within 7 days of initiation of study treatment with the exception of steroids

3.4 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

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

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

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5. TREATMENT PLAN

On this study, patients will be enrolled and undergo tumor collection and dendritic cell collection per protocol. Patients will undergo 1-2 cycles of standard of care therapy during the period of vaccine preparation. Patients for whom vaccine production is successful will undergo vaccination with DC/MM fusions on day 1 of cycle 1, 2, and 3. Subsequent cycles (following cycle 3) will consist of Nivolumab alone on Days 1 and 15 for a total of 6 cycles.

5.1 Evaluations Prior to Enrollment

The following evaluations must be performed within 2 weeks prior enrollment

1. History, physical examination, height and weight
2. ECOG Performance Status
3. Baseline AE Evaluation
4. CBC with differential
5. Liver Functions and blood chemistries: Na, K, Cl, CO2, Ca, Mg, PO4, Creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, LDH
6. Beta-2 Microglobulin, CRP
7. TSH, Free T4, Free T3
8. Evaluation of creatinine clearance
9. Pregnancy test in FOCBP
10. Laboratory Disease Evaluation:
    - Quantitative serum immunoglobulin levels.
    - Serum protein electrophoresis (SPEP).
    - 24-hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP).
    - Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    - Serum free light chain ratios (FLC)
11. Bone marrow to assess plasma cell involvement in the marrow as per eligibility criteria. Unilateral bone marrow biopsy and aspirate are required. If performed within 30 days it does not need to be repeated.
12. Skeletal bone survey to include cranium, axial skeleton and proximal long bones or alternative imaging to capture areas of bone disease
13. EKG
14. Vital signs (including ambulatory O2 sat)

5.2 Tumor Collection

Following registration, patients will undergo collection of multiple myeloma cells through bone marrow aspirate collection. Bone marrow aspirates will be obtained (20-30cc) under local anesthesia. If there is an insufficient yield of tumor cells a second collection will be permitted.

At the time of tumor collection, 50ml of plasma in sodium heparin tubes will be collected from the peripheral blood. This will be repeated if a second collection is indicated. Standard infectious serologies will be drawn as per BIDMC practice for storage of cellular products (drawn in 2 red top tubes and 3 pink top tubes and sent to the Stem Cell Lab at BIDMC).

5.3 Dendritic Cell Collection

Patients may receive up to 1 cycle of bridging therapy prior to undergoing leukapheresis. Leukapheresis will be performed when after recovery of blood counts (an ANC >1000 K/uL and PLT >50 K/uL). When possible, leukapheresis will be performed via peripheral access. If peripheral access is inadequate, patients will undergo placement of a temporary central venous catheter. Standard infectious serologies will be drawn within 8 days of isolation dendritic cells as per BIDMC practice for storage of cellular products (drawn in 2 red top tubes and 3 pink top tubes and sent to the Stem Cell Lab at BIDMC).

5.4 SOC Anti-Myeloma Bridging Therapy During Period of Vaccine Preparation

Patients may receive up to 2 cycles of standard of care therapy following leukapheresis. Bridging therapy is at the discretion of the physician, however the use of IMiDs (ie. Lenalidomide or pomalidomide) is prohibited.

5.5 Evaluation Prior to Initiation of Immunotherapy

Patients will be evaluated within 14 days prior to initiation of immunotherapy. The following tests will be performed

at that time:

1. History, physical examination, height and weight
2. ECOG Performance Status
3. AE Assessment
4. Medications
5. CBC with differential, platelet count
6. Liver Functions and blood chemistries: Na, K, Cl, CO2, Ca, Mg, PO4, Creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, LDH
7. Beta-2 Microglobulin, CRP
8. TSH, Free T4, Free T3
9. Evaluation of creatinine clearance
10. Pregnancy test in females of child bearing potential
11. Laboratory Disease Evaluation:
    - Quantitative serum immunoglobulin levels.
    - Serum protein electrophoresis (SPEP).
    - 24-hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP).
    - Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    - Serum free light chain ratios (FLC)
12. Bone marrow biopsy and aspirate for re-staging, Note, if marrow was done within prior 6 weeks then this does not need to be repeated.
13. EKG
14. Skeletal bone survey or alternative imaging to include cranium, axial skeleton and proximal long bones or alternative imaging to capture areas of bone disease, if clinically indicated
15. Evaluation of Pre-Treatment Eligibility Criteria and registration to second time point on study.

5.6 Day 1 of Cycles 1-3 (+/- 3 days)

1. History, physical examination, height and weight
2. ECOG Performance Status
3. AE Assessment
4. Medications
5. CBC with differential, platelet count
6. Liver Functions and blood chemistries: Na, K, Cl, CO2, Ca, Mg, PO4, Creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, LDH
7. Beta-2 Microglobulin, CRP
8. TSH, Free T4, Free T3
9. Evaluation of creatinine clearance
10. Pregnancy test in FOCBP
11. Laboratory Disease Evaluation:
    - Quantitative serum immunoglobulin levels.
    - Serum protein electrophoresis (SPEP).
    - 24-hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP).
    - Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    - Serum free light chain ratios (FLC)
12. EKG
13. Nivolumab infusion (Per Section 5.12.1)
14. Vaccine administration (Per Section 5.12.2)
15. Vital Signs (including ambulatory O2 sat) per Section 11
16. Study tubes as per Section 10 will be drawn at the pre-immunotherapy visit. They will not be repeated at the start of C1, but will be drawn on day 1 of C2 and C3.

5.7 Day 15 of Cycles 1-3 (+/- 3 days)

1. History, physical examination, height and weight
2. ECOG Performance Status
3. AE Assessment
4. Medications
5. CBC with differential, platelet count
6. Liver Functions and blood chemistries: Na, K, Cl, CO2, Ca, Mg, PO4, Creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, LDH
7. EKG
8. Nivolumab infusion (Per Section 5.12.1)
9. Vital Signs (including ambulatory O2 sat) per Section 11

5.8 Day 1 of Cycle 4 (+/- 3 days)

1. Bone marrow and aspirate to assess disease response.
2. Bone marrow aspirate for research samples

5.9 Day 1 of Cycles 4-6 (+/- 3 days)

1. History, physical examination, height and weight
2. ECOG Performance Status
3. AE Assessment
4. Medications
5. CBC with differential, platelet count
6. Liver Functions and blood chemistries: Na, K, Cl, CO2, Ca, Mg, PO4, Creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, LDH
7. Beta-2 Microglobulin, CRP
8. TSH, Free T4, Free T3
9. Evaluation of creatinine clearance
10. Pregnancy test in FOCBP
11. Laboratory Disease Evaluation:
    - Quantitative serum immunoglobulin levels.
    - Serum protein electrophoresis (SPEP).
    - 24-hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP).
    - Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    - Serum free light chain ratios (FLC)
12. EKG
13. Nivolumab infusion (Per Section 5.12.1)
14. Vital Signs (including ambulatory O2 sat) per Section 11
15. Study tubes as per Section 10

5.10 Day 15 of Cycles 4-6 (+/- 3 days)

1. History, physical examination, height and weight
2. ECOG Performance Status
3. AE Assessment
4. Medications
5. CBC with differential, platelet count

6. Liver Functions and blood chemistries: Na, K, Cl, CO2, Ca, Mg, PO4, Creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, LDH
7. EKG
8. Nivolumab infusion (Per Section 5.12.1)
9. Vital Signs (including ambulatory O2 sat) per Section 11

5.11 Follow Up

Participants will be followed monthly for the first 6 months following their last dose of treatment. Participants who complete treatment per protocol will be followed as outlined in section 5.11.1 and then followed for Progression Free Survival as outlined in section 5.11.2.

Participants taken off treatment due to toxicity will be followed as outlined in section 5.11.1 and will continue to be followed for Progression Free Survival as outlined in section 5.11.2.

Participants taken off treatment due to disease progression or to start alternative anti-myeloma therapy per MD discretion will be required to do a toxicity assessment visit 30 days after the last dose of study treatment. Participants then will continue to be followed for Survival for 5 years. Requirements for the toxicity assessment visit are outlined in section 5.11.3.

5.11.1 Active Follow Up (+/- 7 days)

Participants will be followed monthly for 6 months following the last dose of treatment on study.

1. History, physical examination, height and weight
2. ECOG Performance Status
3. AE Assessment
4. Medications
5. CBC with differential, platelet count
6. Liver Functions and blood chemistries: Na, K, Cl, CO2, Ca, Mg, PO4, Creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, LDH
7. Beta-2 Microglobulin, CRP
8. TSH, Free T4, Free T3
9. Evaluation of creatinine clearance
10. Laboratory Disease Evaluation:
    - Quantitative serum immunoglobulin levels.
    - Serum protein electrophoresis (SPEP).
    - 24-hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP) required for participants with +UPEP at baseline. Otherwise, random UPEP is permitted. If the random UPEP is positive, a 24-hour urine collection is required.
    - Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
11. Vital Signs (including ambulatory O2 sat) per Section 11
12. Bone marrow and aspirate as per Section 11
13. Skeletal bone survey to include cranium, axial skeleton and proximal long bones or alternative imaging to capture areas of bone disease at months 1 and 6
14. Study tubes as per Section 10

5.11.2 Progression Free Survival (+/- 14 days)

Participants will be followed every 3 months for 5 years. Participants will be followed until time of disease progression, at which time they will be followed for survival as outlined 5.11.4. At the time of disease progression

patients will have disease assessments and study bloods/aspirate as outlined in section 10.

1. Laboratory Disease Evaluation:
    - Quantitative serum immunoglobulin levels.
    - Serum protein electrophoresis (SPEP).
    - 24-hour urine collection to determine creatinine clearance and protein excretion, urine electrophoresis (UPEP) required for participants with +UPEP at baseline. Otherwise, random UPEP is permitted. If the random UPEP is positive, a 24-hour urine collection is required.
    - Immunofixation of urine and serum protein regardless of SPEP and UPEP results.

5.11.3 **Toxicity Assessment Visit (+/- 7 days)**

Participants taken off treatment due to disease progression or to start alternative anti-myeloma therapy at MD discretion will be required to do a toxicity assessment visit 30 days after the last dose of study treatment.

1. History, physical examination, height and weight
2. ECOG Performance Status
3. AE Assessment If patients have ongoing related AEs at the toxicity assessment visit, this should continue to be followed at least monthly, or as clinically indicated, until resolution.)
4. Medications
5. CBC with differential, platelet count
6. Liver Functions and blood chemistries: Na, K, Cl, CO2, Ca, Mg, PO4, Creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, LDH
7. TSH, Free T4, Free T3
8. Evaluation of creatinine clearance
9. Vital Signs (including ambulatory O2 sat) per Section 11

5.11.4 **Survival Follow-Up**

Participants will be followed in clinic or by phone every 6 months for 5 years from the last dose of treatment.

5.12 Agent Administration

5.12.1 Nivolumab

Patients will be treated with Nivolumab 240 mg on days 1 and 15 of a 28-day cycle. Nivolumab will be given every two weeks (±3 days). Patients may be dosed no less than 12 days from the previous dose of drug.

Nivolumab is to be administered as a 60-minute IV infusion (+/- 10 minutes), using a volumetric pump with a 0.2/1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 1.0 mg/mL. It is not to be administered as an IV push or bolus injection.

Vital signs (BP, HR, Temp, RR, O2 sat) will be taken within 15 minutes prior to start of nivolumab infusion and within 15 minutes following completion of the infusion.

5.12.2 DC/MM Fusion Vaccine

Patients will receive the DC/myeloma fusion vaccine/GM-CSF (vaccine) on day 1 of cycles 1, 2, and 3. Vaccine will be administered by subcutaneous injection with 100 ug GM-CSF given subcutaneously at the vaccine site on day of vaccination and daily for a total of 4 days of each cycle. The vaccine will be administered at least 1 hour following

Nivolumab infusion. On the first day of GM-CSF administration, 100 ug of GM-CSF subcutaneously will be administered subcutaneously. The patient will be trained to inject the remaining three GM-CSF injections (100ug dose once a day at the vaccination site) for self-administration subcutaneously at home.

5.13 General Concomitant Medication and Supportive Care Guidelines

Patients started on systemic anti-neoplastic chemotherapy or immune suppression while on treatment will be taken off the study drug. The administration of live vaccinations while on treatment is prohibited. Short courses of corticosteroids for adverse events may be permitted after discussion with the Study Chair, Jacalyn Rosenblatt, MD.

5.14 Criteria for Taking a Participant Off Treatment

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for up to 6 cycles of nivolumab or until one of the following criteria applies:

- Disease progression by IMWG criteria, after the administration of study treatment
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.15 Criteria for Taking a Participant Off Study

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

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Disease progression by IMWG criteria, prior to the administration of study treatment

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following sections. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the

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

6.1 Dose Delays

To initiate cycle 1 of therapy with vaccine and nivolumab, participants must meet the eligibility criteria outlined in section 3.3.

Patients experiencing any of the following toxicities judged to be possibly or definitely related to study treatment will not receive further therapy.

- Grade 3 or higher non-hematologic toxicities that do not resolve within 14 days of onset;
    - Please note the following exceptions indicated in Appendix B that necessitate immediate discontinuation of therapy:
        - Grade 4 creatinine elevation
        - Grade 3 or higher pulmonary toxicity
        - ALT/AST or total bilirubin grade 3 or higher elevation
        - Grade 3 or higher adrenal insufficiency
        - Grade 3 or higher neurological adverse event
        - Grade 3 or higher myocarditis
- Grade 4 or higher non-hematologic toxicities;
- Grade 4 or higher hematologic toxicities that do not resolved within 7 days of onset;
    - Please note that this excludes lymphopenia, as mentioned in section 5.9.3;
- Grade 4 or higher nivolumab infusion reactions.
- Laboratory abnormalities that are not thought to be clinically significant (i.e. lymphopenia) will not be included in criteria for holding of therapy

Patients experiencing grade 3 non-hematologic toxicity, grade 2 immune associated toxicity as outlined in Appendix B, and grade 4 hematologic toxicity will have therapy held.

Patients not meeting these criteria may have therapy held for clinical reasons with the approval of the study PI or designee.

Patients who experience grade 4 hematologic toxicity that resolves to grade 1 or baseline within 7 days OR grade 3 non-hematologic toxicity that resolves to grade 0-1 within 14 days OR grade 2 immune associated toxicity requiring hold of therapy as outlined in Appendix B that resolves to grade 0-1 within 14 days may have therapy restarted UNLESS otherwise specified in Appendix B.

Therapy is restarted at the point of dose interruption so that all intended doses of vaccine and nivolumab are administered.

Patients experiencing recurrence grade 3 non-hematologic toxicity, grade 2 immune associated toxicity as outlined in Appendix B, and grade 4 hematologic toxicity will have therapy discontinued UNLESS otherwise specified in Appendix B.

To initiate cycles 2-6 of therapy, subjects must not have any evidence of TLT as outlined above or in section 7. In the event that the toxicity is clearly related to nivolumab alone (such as infusion reactions) and meets criteria for discontinuation, patients may continue to receive vaccine alone per protocol. Patients experiencing immune-related adverse events may be treated with corticosteroids (up to prednisone of 1 mg/kg or equivalent). Patients who improve to grade 1 or less in this context as outlined above AND who can be tapered to prednisone of 10 mg or equivalent or less may continue on therapy. There will be no dose modifications.

Treatment may be held for up to 14 days for unrelated adverse events, or as clinically indicated, at the discretion of the treating physician.

6.2 Management of Nivolumab-Related Infusion Reactions

Infusion reactions to Nivolumab may consist of fever, chills, rigors, headache, rash, urticaria, angioedema, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to NCI CTCAE version 4.0 guidelines.

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated) Infusion rate may be slowed or interrupted and restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [*e.g.*, antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours), and no further nivolumab will be administered at that visit.

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate.
If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and (acetaminophen) (or paracetamol) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction):

Grade 3 symptoms: prolonged [*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [*e.g.*, renal impairment, pulmonary infiltrates]).

Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated). Nivolumab will be permanently discontinued:

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and bronchodilators, epinephrine 0.2 to 1 mg of a 1: 1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1: 10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur.
- In the event of anaphylaxis, follow institutional guidelines.
- In the case of late-occurring hypersensitivity symptoms (*e.g.*, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine, or corticosteroids). Additional treatment prior to next dose as per guidelines above.
- Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

6.3 Management of Other Nivolumab-Related AEs

Please refer to Appendix B: Dose Modifications for Nivolumab-related AEs.

6.4 Management of DC/MM Vaccine Site Reaction

If a patient experiences a grade 2 or higher (graded according to CTCAE v4.0) injection site reaction during the days when GM-SCF is administered, subsequent doses of GM-CSF may be held until the injection site reaction improves to grade 1 or less at the discretion of the treating investigator. On the day of subsequent vaccine administrations, patients will receive pre-medication with diphenhydramine (Benadryl) 25-50 mg and/or acetaminophen (Tylenol) 650-1000 mg to minimize potential allergic-related symptoms.

7. IDENTIFICATION OF TREATMENT LIMITING TOXICITIES

Treatment limiting toxicities (TLT) will be defined as toxicity judged to be possibly or definitely related to the study treatment and meeting the following criteria:

- Grade 3 or higher non-hematologic toxicities that do not resolve within 14 days of onset;
    - Please note the following exceptions that necessitate immediate discontinuation of therapy:
        - Grade 4 creatinine elevation
        - Grade 3 or higher pulmonary toxicity
        - Grade 3 or higher ALT, AST or total bilirubin elevation
        - Grade 3 or higher adrenal insufficiency
        - Grade 3 or higher neurological adverse event
        - Grade 3 or higher myocarditis
- Grade 4 or higher clinically significant non-hematologic toxicities;
- Grade 4 or higher hematologic toxicities that do not resolve to grade 1 or baseline within 7 days of onset;
    - Please note that this excludes lymphopenia, as mentioned in section 5.9.3;
- Grade 4 or higher nivolumab infusion reactions.

Patients experiencing TLT will not receive further therapy

If 3 or more patients experience a TLT within the first 28 days of initiating therapy among the first 10 patients enrolled, then accrual will be suspended. TLTs will be defined per the above criteria with grades determined by CTCAE version 4.0 that are possibly, probably or definitely related to the study treatment. Patients will be monitored for the occurrence of TLTs during the first 28 days of treatment.

Once the 10th participant is enrolled, accrual will be paused until the 10th participant completes a full cycle of treatment (28 days) without experiencing any TLTs.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

8.1 Expected Toxicities

8.1.1 Adverse Events Lists

8.1.1.1 Adverse Event List(s) for Nivolumab

Events that are listed as very common (experienced in ≥10% of patients) according to the current IB (Version 16 dated June 23, 2017) include the following: fatigue and diarrhea

Events that are listed as common (experienced in ≥1% to <10% of patients) include: hypothyroidism, hyperthyroidism, hyperglycemia, nausea, vomiting, chills, colitis, stomatitis, asthenia, gastritis,

abdominal pain, constipation, dry mouth, pyrexia, edema peripheral, infusion related reactions, increased lipase, increased amylase, increased aspartate aminotransferase, increase alanine aminotransferase, increased creatinine, increased thyroid stimulating hormone, hyponatremia, decreased appetite, back pain, myalgia, arthralgias, pain in extremity, headache, pruritis, dizziness, pneumonitis, dyspnea, cough, rash, vitiligo, dry skin, erythema, maculopapular rash
Events that are listed as uncommon ≥0.001% of patients to < 1% include the following: musculoskeletal pain, arthritis, neck pain, musculoskeletal chest pain, bone pain, polyarthritis, peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, vasculitis, lung infiltration, tubulointerstitial nephritis, renal failure, acute kidney injury, hypertension, hypotension, alopecia, dermatitis acneiform, macular rash, urticaria, dermatitis, erythematous rash, generalized rash, papular rash, psoriasis, pustular rash, drug eruption, bronchitis, hypersensitivity, upper respiratory infections, edema, facial edema, peripheral swelling, localized edema, nephritis, autoimmune hepatitis, hepatitis, pancreatitis, uveitis, diabetes mellitus, thyroiditis, autoimmune hypophysitis, increased blood bilirubin, hypopituitarism, adrenal insufficiency, tachycardia, autoimmune colitis, atrial fibrillation, vertigo, dry eye, vision blurred, mucosal inflammation, generalized edema, respiratory failure, lung infiltration

Events that are listed as rare risk (experienced by ≥0.00001% to <0.001% of patients) include arrhythmias, Stevens Johnson Syndrome, dermatitis exfoliative, allergic dermatitis, rosacea, erythema multiforme, diabetic ketoacidosis, autoimmune hypothyroidism, iridocyclitis, periorbital edema, mouth ulceration, acute pancreatitis, acute hepatitis, sarcoidosis, anaphylactic reaction, myositis, musculoskeletal discomfort, osteoarthritis, pain in jaw, polymyalgia rheumatica, polymyositis, rhabdomyolysis, polyneuropathy, burning sensation, encephalitis, Guillain-Barre syndrome, myasthenia gravis, demyelination, autoimmune nephritis, organizing pneumonia, acute respiratory distress syndrome, vasculitis

Events that are listed as very rare (experienced by < 0.0001%) include ventricular arrhythmias, mucosal ulceration, demyelinating polyneuropathy, myasthenic syndrome, and toxic epidermal necrolysis

8.1.1.2 Adverse Event List(s) for DC/MM Fusion Vaccines

Toxicities related to the vaccine are:

- Hematologic: Leukopenia
- Neurologic: Headache
- Gastrointestinal: Diarrhea, decrease appetite.
- Constitutional: Weakness chills and fever.
- Musculoskeletal: arthralgia and myalgia.
- Dermatologic: rash, itching, periorbital edema and local reaction in the site of infusion (swelling, pain, erythema and pruritus).
- Endocrine: elevated TSH.
- Other: ANA positivity

8.1.1.3 Adverse Event List(s) for GM-CSF

Potential side effects of GM-CSF treatment include fever, chills, nausea, vomiting, diarrhea, fatigue, weakness, headache, decreased appetite, facial flushing, bone and muscle pain, local reaction at the site of injections, rashes, low blood pressure, shortness of breath and low blood counts. Rarely patients may develop blood clots, rapid or irregular heartbeats, feeling of faintness, kidney and liver problems, allergic reactions or fluid retention, including potential fluid retention in lungs or around the heart, and keratitis (inflammation of the cornea).

8.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

8.3 Adverse Event Reporting

8.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

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

8.3.3 DF/HCC Adverse Event Reporting Guidelines

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

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

8.3.4 Protocol-Specific Adverse Event Reporting Exclusions

AEs that occur prior to initiation of vaccine will not be captured or reported with the exception of AEs and SAEs that are related to tumor cell harvest and dendritic cell collection. Events that are thought to be related to tumor cell harvest or dendritic cell collection will be captured and reported as an SAE should it meet the DF/HCC as per DF/HCC guidelines.

AEs and SAEs will be captured and reported after initiation of vaccine will be captured and reported as per DF/HCC guidelines.
Laboratory abnormalities that are not clinically significant and are not related to study treatment will not be captured or reported.

8.4 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

8.5 Reporting to the Institutional Biosafety Committee (IBC)

Participating investigators will register and report on research protocols involving biohazards (i.e., recombinant DNA or infectious agents) according to the reporting requirements set by their respective IBC.

8.6 Reporting to Hospital Risk Management

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

8.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

9. PHARMACEUTICAL INFORMATION

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

9.1 Nivolumab

9.1.1 Description

Nivolumab is a fully human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cell surface membrane receptor. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon- gamma (IFN-γ) release in vitro.

9.1.2 Form

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, nonpyrogenic, single-use, isotonic

aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80, pH 6.0 and includes a 0.7 mL overfill to account for vial, needle, and syringe (VNS) holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

9.1.3 Storage and Stability

The product does not contain a preservative. Vials of nivolumab injection must be stored at 2-8°C (36°-46°F) and protected from light, freezing, and shaking.
After preparation, store the nivolumab infusion either: At room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation. Do not freeze. If a temperature excursion is noted, sites should follow institutional policies for notifying Bristol-Myers Squibb and assessing if the drug is still able to be used.

9.1.4 Compatibility

Do not co-administer other drugs through the same intravenous line. Flush the intravenous line at end of infusion. No incompatibilities between nivolumab and polyvinyl chloride (PVC), non-PVC/non DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

9.1.5 Handling

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

9.1.6 Availability

Nivolumab for injection will be supplied free of charge by BMS.

9.1.7 Preparation

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.
Withdraw the required volume of nivolumab and transfer into an intravenous container.
Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration greater than or equal to 0.35mg/ml .. Mix diluted solution by gentle inversion. Do not shake.

9.1.8 Administration

Administer the infusion over 60 minutes (+/- 10 minutes) through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

9.1.9 Ordering

Each institution will order nivolumab directly from the supplier Bristol Myers Squibb Pharmaceuticals (BMS). A study specific order form will be supplied by the lead site.

9.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9.1.11 Destruction and Return

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances. BMS will be notified of all Nivolumab drug destructions.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification (ID) of the person disposing the containers. The method of disposal, (e.g., incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.

9.2 DC/MM Fusion Vaccine

9.2.1 Isolation of Tumor Cells

Patients will undergo aspiration of 30 mL of bone marrow from which myeloma cell preparations will be generated. Bone marrow will be aspirated into sterile heparinized syringes with approximately 5-8 mL aspirated per syringe to avoid significant hemodilution of bone marrow mononuclear cells. Bone marrow aspirate samples will be transferred in sterile syringes to the cell manipulation facility, and mononuclear cells will be isolated by ficoll density gradient centrifugation. Autologous plasma will be obtained by harvesting supernatant following centrifugation of 50 mL of peripheral blood. Bone marrow mononuclear cells will be cultured in media with 10% autologous plasma. An aliquot of the tumor cells will undergo immunohistochemical staining as detailed below. Tumor lysate will be prepared by freeze/thawing or sonication of an aliquot of tumor cells for immunological analysis. Myeloma cells may be frozen in 10% DMSO/90% autologous plasma stored in liquid nitrogen for potential subsequent vaccine generation.

9.2.2 DC Generation

Patients will undergo leukapharesis for DC and vaccine generation. The leukapheresis product will be transferred in a sterile container to the cell manipulation facility, and PBMC will be isolated from the leukapheresis product and cultured in the presence of autologous plasma for 1- 2 hours and then cultured for 5-7 days with GM-CSF and IL-4. Cultures are re-fed with cytokines after 3 days. Twenty-five ng/mL of TNFα will be then be added for 48-72 hours to induce DC maturation. An aliquot of the DC preparation will undergo immunocytochemical staining for immunophenotypic analysis.

9.2.3 DC/MM Fusion Vaccine Preparation

Tumor cells will be thawed (when relevant). Tumor cells and DC preparations will be co-cultured at ratio of 1:3 and washed in serum-free medium. After low-speed centrifugation, the cell pellet will be re-suspended in 50% solution of polyethylene glycol (PEG) and will be progressively diluted by the slow addition of serum-free medium. An aliquot of the DC, tumor, and fusion cell preparations will undergo immunocytochemical analysis for vaccine characterization. Dependent on cell yields, 3 doses of 1-5 x 10^6 fusion cells will be prepared. The fusion cells will then be separated into appropriate aliquots of fusion cells, radiated at 30 Gy, and frozen in 10% DMSO/90% autologous plasma in liquid nitrogen. A minimum of 2 doses will be required to proceed with treatment. An aliquot

of the vaccine product will be sent for microbiological assessment consisting of endotoxin, mycoplasma and sterility testing as detailed in the CMC section. Release criteria for vaccine administration are:

1) > 50% of DC prep express CD86
2) Viability of DC prep > 70%
3) Fusion efficiency > 15%
4) Fusion viability > 50%
5) Sterility, mycoplasma, and endotoxin assays are negative

9.2.4 Administration

Patients will be vaccinated with 1-5x10^6 fusion cells in the upper thigh region. The site will be alternated for each vaccine administration (right and left extremity). Vaccination will be administered subcutaneously using a 25-gauge 5/8-inch needle. Tumor vaccine will be administered first, followed by GM-CSF injection.

9.2.5 Ordering

Vaccine will be ordered from the Stem Cell Lab at BIDMC on the day of treatment. The lab should be notified of all scheduled treatment days at least 1 week in advance.

9.3 GM-CSF

GM-CSF is commercially available and will be purchased in bulk from commercial supply by the research pharmacy and billed to grant. On the day of vaccination, the clinical research nurse/physician assistant will administer 100 ug of GM-CSF subcutaneously at the site of the vaccine. Research pharmacy will reconstitute the drug with bacteriostatic water at the appropriate dose for the patient. The patient will be trained to inject the remaining three GM-CSF injections (100ug dose once a day) for self-administration subcutaneously at home. Tumor vaccine will be administered first, followed by GM-CSF injection.

10. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

10.1 Correlative Studies

10.1.1 Myeloma-reactive T cells in the peripheral blood

- 10 mLs of peripheral blood will be collected in a green top tube at the pre-immunotherapy visit, prior to cycles 2-6, at each active monthly follow up visit, and at time of progression.
- Specimens will be delivered to the Avigan lab at BIDMC.
- Samples will be processed in the Avigan lab. Ficoll centrifugation of the peripheral blood sample will be performed to isolate peripheral blood mononuclear cells (PBMCs). PMBCs will be co-cultured with autologous tumor lysate prepared from the enrollment bone marrow aspirate. Surface antibody staining for CD4 and CD8 positive lymphocytes in addition to intracellular staining for IFN gamma will be performed on this co-culture to quantify IFN gamma producing T cells.

10.1.2 Myeloma-reactive T cells in the bone marrow

- 5 mLs of bone marrow aspirate will be collected in a green top tube at the pre-immunotherapy visit, prior to cycle 4, at one, three, and six month active follow up visits and at time of progression.
- Specimens will be delivered to the Avigan lab at BIDMC.
- Samples will be processed in the Avigan lab. Ficoll centrifugation of the aspirate sample will be performed to isolate bone marrow mononuclear cells (BMMCs). BMMCs will be co-cultured with autologous tumor lysate prepared from the enrollment bone marrow aspirate. Surface antibody staining for CD4 and CD8 lymphocytes in addition to intracellular staining for IFN gamma will be performed on this co-culture to quantify IFN gamma producing T cells.

10.1.3 Effect of treatment on circulating T cells binding the MUC1, NY-ESO, Survivin, PRAME, and WT1 tetramers in HLA-A2.1 patients

- 10 mLs of peripheral blood in a green top tube at the pre-immunotherapy visit, prior to cycles 2-6, at each active monthly follow up visit, and at time of progression.
- Specimens will be delivered to the Avigan lab at BIDMC.
- Samples will be processed in the Avigan lab using a tetramer assay to isolate tetramer-specific T cells. Functional characteristics of the pentamer positive cells will be determined by quantifying expression of IFNγ, granzyme B, IL-4, and IL-10 expression by intracellular FACS staining.

10.1.4 T cell subsets , T cell checkpoint receptors, and MDSCs

- 10 mLs of peripheral blood in a green top tube at the pre-immunotherapy visit, prior to cycles 2-6, at each active monthly follow up visit, and at time of progression.
- 5 mLs of bone marrow aspirate will be collected in a green top tube prior to cycle 4, at one, three, and six month active follow up visits and at time of progression.
- Specimens will be delivered to the Avigan lab at BIDMC.
- Samples will be processed in the Avigan lab. The PB and BM aspirate samples will undergo ficoll centrifugation to obtain PBMCs/BMMCs. From the PBMCs/BMMCs, T cell subsets and MDSCs will be isolated by antibody staining and quantified by flow cytometric analysis.

10.1.5 Optional vaccine site biopsy

- Patients will be referred to dermatology clinic for a punch biopsy of vaccine site reaction.
- The biopsy specimen will be delivered to the Avigan lab at BIDMC.
- Specimens will be stained using immunohistochemistry for T cell, DC, and myeloma markers to assess for immune cell infiltrate and possible tumor infiltrate.

10.1.6 Optional samples for future research studies

- 10 mLs of PB in a green top tube at the pre-immunotherapy visit, prior to cycles 2-6, at each active monthly follow up visit, and at time of progression.
- 5 mLs of bone marrow aspirate will be collected in a green top tube prior to cycle 4, at one, three, and six month active follow up visits and at time of progression.
- These specimens will be delivered to the Avigan lab at BIDMC.
- The specimens will be cryopreserved in the Avigan lab for possible future research studies.

10.2 Sample Collection time points

Sample Collection for Stem Cell Lab	
Required[1]	**At enrollment (at the time of tumor collection)**
Bone marrow aspirate for tumor collection (30 mL)	X

Plasma for Vaccine Production (50 mL)	X
Infectious Serologies	X

1. Total tubes: 3 of the 10mL Na-Hep green top tubes aspirate, 5 of the 10mL Na-Hep green top tubes, 2 of the 6mL red top tubes and 3 of the 6mL pink top tubes peripheral blood

Sample Collection for Avigan Lab				
Required	**At the pre-immunotherapy visit[1]**	**Prior to each cycle[1, 3]**	**Months 1-6 Active Follow-up[2]**	**Disease Progression[1]**
Bone Marrow Aspirate for Myeloma Reactive T Cells (5 mL)	X	X (cycle 4 only)	X (months 1, 3 and 6 only)	X
Bone marrow aspirate for tetramer reactivity (5 mL)	X	X (cycle 4 only)		X
Bone marrow aspirate for T cell subsets, T cell checkpoint receptors, MDSCs (5 mL)		X (cycle 4 only)	X (months 1, 3 and 6 only)	X
Peripheral Blood for Myeloma Reactive T Cells (10 mL)	X	X	X	X
Peripheral blood for tetramer analysis (10 mL)	X	X	X	X
Peripheral blood for T cell subsets, T cell checkpoint receptors, MDSCs (10 mL)	X	X	X	X

1. Total tubes: 3 of the 10mL Na-Hep green top tubes peripheral blood and 2 of the 10mL Na-Hep green top Aspirate
2. Total tubes: 3 of the 10mL Na-Hep green top tubes peripheral blood
3. These samples do not need to be collection at cycle 1, as they were collected at the pre-immunotherapy visit.

Optional Sample Collection for Avigan Lab				
Required	**At enrollment (at the time of tumor collection)[1]**	**Prior to each cycle[1]**	**Months 1-6 Active Follow-up[2]**	**Disease Progression[1]**
Optional Peripheral Blood Samples for Future Research (10 mL)	X	X	X	X
Optional Bone Marrow Aspirate Samples for Future Research (5 mL)		X (cycle 4 only)	X (months 1, 3 and 6 only)	X

1. Total tubes: 1 of the 10mL Na-Hep green top tube peripheral blood; 1 of the 10mL Na-Hep green top tube aspirate
2. Total tubes: 1 of the 10mL Na-Hep green top tube peripheral blood

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to registration.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Cycles 1-3

Study Assessments	Pre-Enrollment	At Enrollment (at the time of tumor collection)	Pre-Immunotherapy	Day 1	Day 15	Day 21
History, physical exam, weight and height	X		X	X	X	
Vital Signs[1]	X		X	X		
Ambulatory O2 sat[2]	X		X	X	X	
CBC, differential, platelet count, and blood chemistries	X		X	X	X	
TSH, Free T4, Free T3	X		X	X		
Evaluation of Creatinine Clearance	X		X	X	X	
Pregnancy test	X		X	X		
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		
B2M, CRP	X		X	X		
Skeletal Survey or alternative imaging	X					
Bone marrow aspirate and biopsy	X		X[6]			
EKG	X		X	X	X	
Toxicity Assessment	X		X	X	X	
Con Meds	X		X	X	X	
DC/MM Fusion Vaccine and GM-CSF Administration[3]				X		
Nivolumab Infusion				X	X	
Study Tubes[4]			X	X		

1. Vitals (BP, HR, Temp, RR, O2 sat) to be taken within 15 minutes prior to start of nivolumab infusion and within 15 minutes following completion.
2. Pulse oximetry should be obtained prior to each dose of nivolumab and at any time a subject has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the patient's status changes the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the patient should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 2 of the IB. Not all results are required to be collected by BMS.
3. GM-CSF will be administered at home by the patient on days 2-4 and recorded on the GM-CSF body chart.
4. Please refer to section 10
5. Skeletal survey/alternative imaging is only needed at the pre-immunotherapy visit if the patient received bridging therapy and this is needed for re-staging.
6. If marrow was done within prior 6 weeks then this does not need to be repeated.

Cycles 4 - 6

Study Assessments	Day 1	Day 15
History, physical exam, weight and height	X	X
Vital Signs[1]	X	X
Ambulatory O2 sat[2]	X	X
ECOG performance score	X	
CBC, differential, platelet count, and blood chemistries	X	X
TSH, Free T4, Free T3	X	
Evaluation of Creatinine Clearance	X	X
Pregnancy test	X	
Quantitative serum immunoglobulins	X	
SPEP and immunofixation	X	
24 Hour Urine for UPEP, protein excretion and immunofixation	X	
Serum free light chain ratio	X	
B2M, CRP	X	
Skeletal Survey or alternative imaging		
Bone marrow aspirate and biopsy[4]	X	
EKG	X	X
Toxicity Assessment	X	X
Con Meds	X	X
Nivolumab Infusion	X	X
Study tubes[3]	X	

1. Vitals (BP, HR, Temp, RR, O2 sat) to be taken within 15 minutes prior to start of nivolumab infusion and within 15 minutes following completion.
2. Pulse oximetry should be obtained prior to each dose of nivolumab and at any time a subject has any new

or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the patient's status changes the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the patient should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 2 of the IB. Not all results are required to be collected by BMS.

3. Please refer to section 10
4. Bone marrow aspirate and biopsy only required on day 1 of cycle 4.

Follow Up

Study Assessments	**Toxicity Assessment Visit (+/- 7 days)[0]**	**Months 1-6 (+/- 7 days)**	**Progression Free Survival[1] (+/- 14 days)**	**Survival Follow-Up** (every 6 months for 5 years)
History, physical exam, weight and height	X	X		
Vital Signs[2]	X	X		
Ambulatory O2 sat[3]	X	X		
ECOG performance score	X	X		
CBC, differential, platelet count, and blood chemistries	X	X		
TSH, Free T4, Free T3	X	X		
Evaluation of Creatinine Clearance	X	X		
Quantitative serum immunoglobulins		X	X	
SPEP and immunofixation		X	X	
24 Hour Urine for UPEP, protein excretion and immunofixation		X	X[4]	
Bone Marrow Biopsy and Aspirate	X	X[5]	X[5]	
Serum free light chain ratio		X	X	
B2M, CRP		X		
Toxicity Assessment	X	X		
Skeletal Survey or alternative imaging		X[6]		
Con Meds	X	X		
Survival status	X			X
Study tubes		X[7]		

0. Only required for patients who are removed from treatment due to progressive disease or to start alternative anti-myeloma therapy per MD discretion
1. Every 3 months after 6 month follow up visit for 5 years
2. Vitals (BP, HR, Temp, RR, O2 sat) to be taken within 15 minutes prior to start of nivolumab infusion and within 15 minutes following completion.
3. A O2 saturation reading at rest and on exertion should be obtained during each study visit.

4. Only required for participants with +UPEP at baseline, otherwise random UPEP is permitted. If the random UPEP is positive, a 24-hour urine collection is required.
5. At Months 1, 3 and 6 follow up and at time of progression.
6. Months 1 and 6 only
7. Please refer to section 10

At Time of Disease Progression

Study Assessments	At Time of Disease Progression
Quantitative serum immunoglobulins	X
SPEP and immunofixation	X
24 Hour Urine for UPEP, protein excretion and immunofixation[1]	X
Bone Marrow Biopsy and Aspirate	X
Serum free light chain ratio	X
Study tubes[2]	X

1. Only required for participants with +UPEP at baseline, otherwise random UPEP is permitted. If the random UPEP is positive, a 24-hour urine collection is required.
2. Please refer to section 10

12. MEASUREMENT OF EFFECT

12.1 Definition of Disease Status

Patients' disease status at each data collection period will be evaluated based on the International Uniform Response Criteria. Until disease progression, all disease classifications are relative to the patient's disease status prior to autologous transplant (i.e. study entry). At time of disease progression, disease classifications are relative to the patient's best response since time of study entry.

12.2 Response Categories

12.2.1 Stringent Complete Response (sCR):

sCR requires, in addition to CR (defined below), *all* of the following:

- Normal free light chain ratio (FLC).
- Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.

12.2.2 Complete Response (CR):

CR requires *all* of the following:

• Absence of the original monoclonal paraprotein in serum and urine by routine electrophoresis and by immunofixation. The presence of new monoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
• Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed.

• No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture does not exclude CR)*.
• Disappearance of soft tissue plasmacytomas.
**If not clinically indicated, radiographs are not required to document CR.*

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as partial responses (see below), providing the remaining criteria satisfy the requirements for partial response. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

12.2.3 **Very Good Partial Remission (VGPR):**

VGPR requires, in addition to PR (defined below), all of the following:

• Serum or urine paraprotein detectable by immunofixation but not on electrophoresis. OR
• Greater than or equal to 90% reduction in serum paraprotein plus urine paraprotein <100 mg/24hrs.
• For free light chain only disease, VGPR requires a 90% reduction of involved light chain

12.2.4 **Partial Response (PR)**

PR requires one of the following:

• Greater than or equal to 50% reduction in the level of the serum monoclonal paraprotein and reduction in 24 hour urinary monoclonal paraprotein either by greater than or equal to 90% or to <200 mg/24 hours in light chain disease.
• If the only measurable non-bone marrow parameter is FLC, greater than or equal to 50% reduction in the difference between involved and uninvolved FLC levels or a 50% decrease in level of involved FLC with 50% decrease in ratio,
• If the bone marrow is the only measurable parameter, greater than or equal to 50% reduction in bone marrow plasma cells given that the baseline count was greater or equal to 30%,
• Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas if present at baseline (by radiography or clinical examination).

12.2.5 **Stable Disease (SD)**

• Patients who do not meet criteria for sCR, CR, VGPR, partial response or progressive disease (section 3.1.1.2) are considered to have stable disease (SD).

12.2.6 **Disease Progression (PD)**

Progression from CR or sCR requires one or more of the following:

- A reappearance of serum monoclonal paraprotein, with a level of at least 0.5 g/dL.
- 24-hour urine protein electrophoresis with at least 200 mg paraprotein/24 hours.
- Abnormal FLC levels of >10 mg/dl, only in patients without measurable paraprotein in the serum and urine.
- At least 10% plasma cells in a bone marrow aspirate or on trephine biopsy.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.

12.2.7 **Progressive Disease (PD)**

For patients not in CR or sCR, progressive disease requires one or more of the following measured from the time of randomization:

- >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL.

- >25% increase in 24-hour urine protein electrophoresis, which must also be an absolute increase of at least 200 mg/24 hours.
- Absolute increase in the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl), only in patients without measurable paraprotein in the serum and urine.
- >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of a compression fracture does not exclude continued response and may not indicate progression.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.

12.2.8 **Minimal residual disease assessment**

Absence of evidence of clonal myeloma population based on multichannel flow cytometry with discrimination of $1{:}1x10^4 – 1x10^5$

13. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

13.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

13.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

13.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; TLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

The study is designed as a Phase II open label study of vaccination with DC/myeloma fusions/GM-CSF plus nivolumab therapy as part of treatment for patients with relapsed multiple myeloma. Patients meeting initial eligibility will undergo harvesting tumor cells and undergo vaccine production. During this period patients will receive an initial cycle of nivolumab and will then undergo a series of vaccinations on day 1 of cycles 1-3. 25 evaluable patients will be enrolled. Therapy with nivolumab will continue for three additional cycles. Based on a prior phase II study of vaccination of myeloma patients with the DC/MM fusion vaccine approximately 50% patients demonstrated a >10-fold increase in IFNγ expression to the baseline. Therefore, the combination of vaccination and nivolumab will be considered promising if the study shows evidence of at least 75% patients with >10-fold increase in IFNγ expression, and would not be considered promising if >10-fold increase is observed in 50% or less patients. With total n=25 patients, the combination will be considered promising for further study if 17 or more patients demonstrate significant immune response. This decision rule has a 0.1 (significance level) probability of accepting the combination for further study if the true underlying significant immune response is 50% and a 0.85 (power) probability of accepting the combination if the true underlying immune response is 75%. For the absolute increase in IFNγ expression, with n=25 patients, we will have at least 90% power to detect an effect size of 0.66 (one-sided Wilcoxson rank sum test, significant level of 0.05), which corresponds to a 0.36 difference in log10 IFNγ fold increase assuming a standard deviation of 0.54 or a 2.3 difference in IFNγ expression fold increase assuming a standard deviation of 3.5. We estimate the median fold increase in IFNγ expression of vaccination alone be 14 (DFCI trial 04098). Therefore, the fold-change that can be detected in the combination is at least 16.1.

As a secondary clinical endpoint, response will be assessed according to IMWG response criteria. In a prior phase I trial of DC/MM vaccination in patients with relapsed MM, 69% (11/16) patients had disease stabilization. No patients demonstrated disease response (PR, VGPR, or CR). In the present phase II trial, overall response rate per IMWG criteria will be assessed. An exact binomial test with a 10% one-sided significance level will have 82% power to detect the difference between the ORR proportion of 0.15 (null hypothesis) and the alternative ORR proportion of 0.35 when the sample size is 25. An ORR of 35% is considered worthy of further study in a larger trial.

If 3 or more patients experience a TLT, accrual will be suspended.

	True but Unknown Rate of DLT				
	0.10	0.20	0.25	0.30	0.40
Probability of continuation of enrollment (≤ 2 TLT in 10 pts)	0.930	0.678	0.526	0.383	0.167

If the true rate of TLT is 25%, the probability of observing 2 or fewer TLTs within a cohort of 10 patients is 0.526.

14.1.1 Primary Immunologic Endpoint

Myeloma reactive T-cells： Log transformations will be used to induce normality in quantitative measurements, and if still non-normal, then nonparametric tests will be used. The primary endpoint of log 10 peak change in tumor reactive T cells from baseline will be quantified. A secondary analysis of peak change in tumor reactive T cells will be done by comparing the proportions of patients who experience >10-fold increase in IFNγ expression, using a chi-squared test. Peak immune response will be correlated with clinical response in an exploratory fashion to assess the relationship between immune response and clinical response.

14.1.2 Secondary Immunologic Endpoints

Additional exploratory analyses will be conducted in a similar fashion to examine a number of secondary immunologic endpoints, including: myeloma specific T cells in the bone marrow, antigen specific reactivity by tetramer analysis, and quantification of T-cell subsets and PD-1 expressing lymphocytes by flow cytometry. In each case, log transformations will be considered to induce normality, and if still non-normal then nonparametric tests will be used. Profiles of these secondary immunologic endpoints will be described at each time point. The

correlation between the immune environment measures and the myeloma specific T-cell response will be assessed and reported using Spearman rank correlation at each time point.

14.1.3 Duration of follow-up

Patients will be followed monthly for the first 6 months following the end of treatment and then every 3 months for 5 years to assess disease status.

15. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B: DOSE MODIFICATIONS FOR NIVOLUMAB-RELATED AES

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

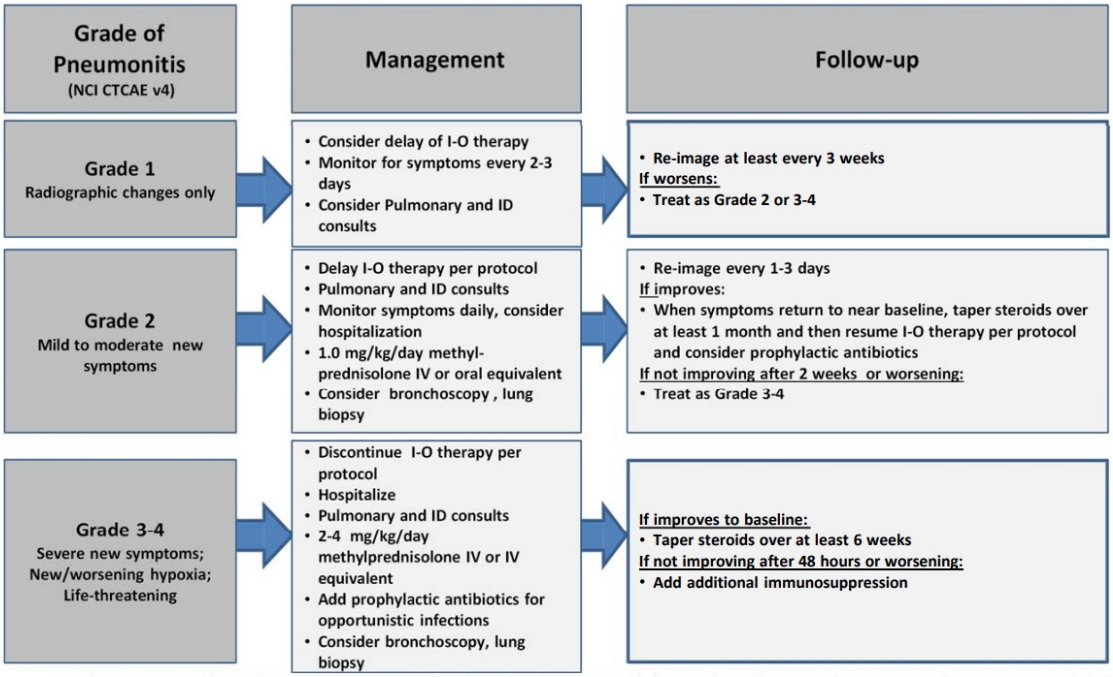
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

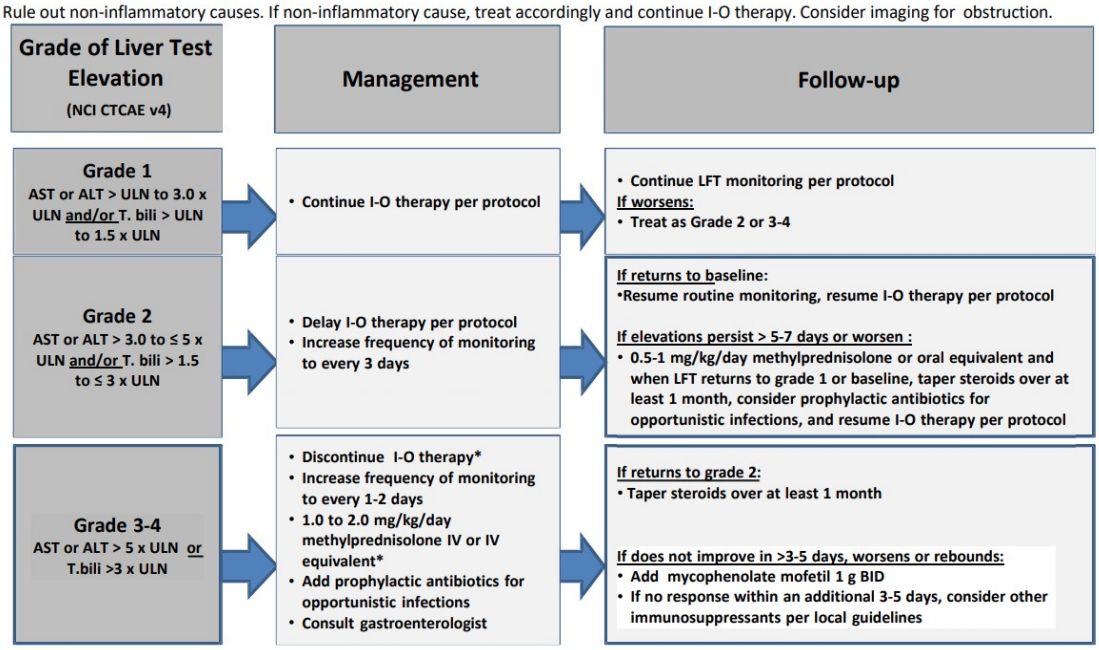
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

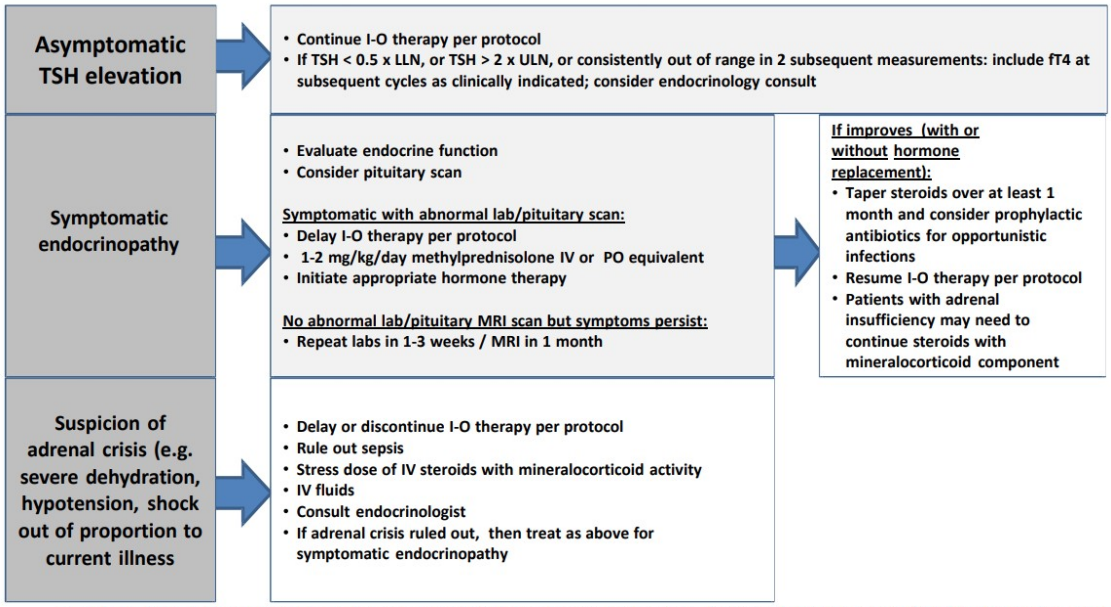


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

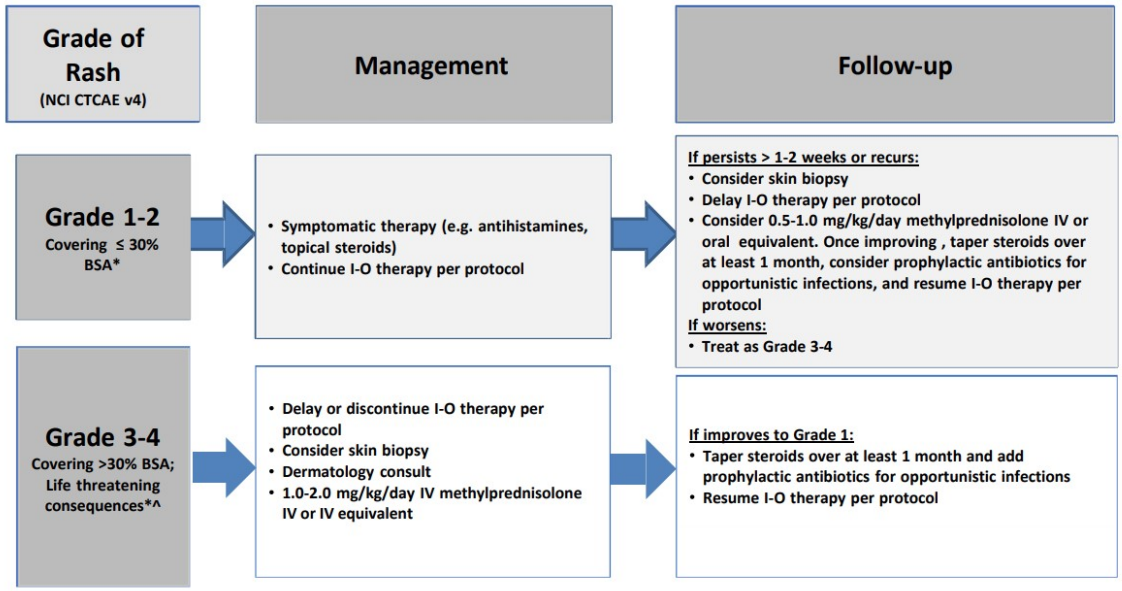
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. **If worsens:** • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	**If improves to baseline:** •Resume I-O therapy per protocol when improved to baseline **If worsens:** • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	**If improves to Grade 2:** • Taper steroids over at least 1 month **If worsens or atypical presentation:** • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Myocarditis Adverse Event Management Algorithm

Grade of Myocarditis (NCI CTCAE v4)	Management	Follow-up

Grade 2
Symptoms with mild to moderate activity or exertion
	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  o Troponin and BNP
	  o ECG ± continuous cardiac monitoring
	  o Echocardiogram
	  o Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac monitoring
	• Cardiac evaluation to include:
	  – Troponin and BNP monitoring
	  – ECG ± continuous cardiac monitoring
	  – Echocardiogram
	  – Cardiac MRI
	  – Myocardial biopsy if feasible
	• Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	Additionally, for Grade 4:
	• Hospitalize/transfer to institution with expertise in intensive cardiac monitoring
	• Consider ATG as second agent given its immediate effect
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessments and cardiology follow-up

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

Adverse Reaction	Severity	Dose Delays
Other – excluding hematologic toxicities	Other Grade 3 adverse reaction: First occurrence	Withhold dose and resume when AE returns to Grade 0 or 1
	Recurrence of same grade 3 adverse reaction[1]	Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

1. Laboratory abnormalities determined to be not clinically significant are not subject to this criteria, hematologic in nature or otherwise.