A Randomized, Double-blind, Placebo-Controlled Phase II Trial of an Allogeneic Myeloma GM-CSF Vaccine With Lenalidomide in Multiple Myeloma Patients in Complete or Near Complete Remission

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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_____ _____

Signature of Investigator Date

Syed Abbas Ali, M.D.

Printed Name of Investigator

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations

STUDY PERSONNEL

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1. PROTOCOL SYNOPSIS

PROTOCOL TITLE: A Randomized, Double-blind, Placebo-Controlled Phase II Trial of an Allogeneic Myeloma GM-CSF Vaccine With Lenalidomide in Multiple Myeloma Patients in Complete or Near Complete Remission	
PROTOCOL NUMBER:	JHU Protocol #: J16118 Celgene Tracking #: RV-CL-MM-PI-005749
DATE PROTOCOL FINAL:	June 16, 2020
STUDY DRUG:	Allogeneic myeloma GM-CSF vaccine, Revlimid ® (lenalidomide)
INDICATION:	Augmenting clinical response with vaccine plus lenalidomide
STUDY PHASE:	Randomized Phase II
BACKGROUND AND RATIONALE: This study seeks to determine whether addition of an allogeneic myeloma vaccine can augment clinical responses to lenalidomide in patients with near complete remission (nCR), complete remission (CR) leading to a significant improvement in progression-free survival.	

STUDY OBJECTIVES AND ENDPOINTS:

Primary:

- To compare the 2-year progression free survival of patients with multiple myeloma in a complete remission (CR), or near complete remission (nCR), treated with lenalidomide plus an allogeneic myeloma vaccine in combination with lenalidomide (with or without Prevnar vaccine) or versus placebo in combination with lenalidomide (control arm).

Secondary:

- To compare the 2-year progression free survival for those treated with or without Prevnar in addition to an allogeneic myeloma vaccine and lenalidomide
- To determine the rate of conversion from near CR (immunofixation positive) to true CR (immunofixation negative)
- To determine the rate of conversion from MRD (Minimal Residual Disease) positive status to MRD negative status by NGS (next generation sequencing).
- Determine time to response
- Determine progression free survival at 3 and 5 years
- Determine the toxicity of the allogeneic myeloma vaccine in combination with lenalidomide
- Measure tumor specific immunity and correlate with systemic immunity

STUDY DESIGN:

This is a single institution, three- arm, randomized controlled, Phase II study examining the clinical efficacy of an allogeneic GM-CSF secreting myeloma vaccine in combination with lenalidomide (with or without Prevnar) compared to lenalidomide and placebo (control arm). Patients enrolled in the study must have two disease measurements (including the last one) consistent with a near complete remission (M-spike negative with persistence of immunofixation), or complete remission (M-spike negative, negative immunofixation, and <5% clonal plasma cells on bone marrow) per criteria for response in a 3 month period. All patients must be minimal residual disease (MRD) positive at 10^{-4} by NGS sequencing at enrollment. Prior to enrollment, patients will have been treated with a lenalidomide containing regimen for a minimum of 6 cycles. All patients will continue on a standard dose of lenalidomide as a single agent until progression, or treatment limiting toxicity, following enrollment. Patients will be randomized to receive either an allogeneic myeloma vaccine and Prevnar vaccine in combination with lenalidomide, or allogeneic myeloma vaccine without Prevnar vaccine in combination with lenalidomide, or lenalidomide in combination with placebo. Patients will receive allogeneic myeloma vaccine or placebo injections on day 14 (+/-3 days) of cycles 1, 2, 3 and 6 from enrollment, and then annually thereafter for up to 3 years. If assigned to allogeneic myeloma vaccine plus Prevnar vaccine arm, Prevnar-13 will be administered with each allogeneic myeloma vaccine. If assigned to either of the two arms that do not include Prevnar, then patients will receive a placebo in lieu of Prevnar on the same schedule. All patients will be followed for a minimum of 3 years.

STUDY DURATION: 3-5 years	**TOTAL SAMPLE SIZE:** 54 (18 per arm)

DOSING REGIMEN(S):	**STUDY DRUG SUPPLIES:**
Lenalidomide: Patients will continue on a stable dose of lenalidomide on days 1 – 21 of a 28 day cycle until progression Allogeneic myeloma vaccine consisting of 3 cell lines: H929 $5x10^7$ cells/ vaccine U266 $5x10^7$ cells/ vaccine K562/GM-CSF $5x10^6$ cells/ vaccine Prevnar-13 administered with each myeloma vaccine	Allogeneic myeloma vaccine consisting of 3 cell lines to be manufactured by Aduro Biotech, and dispensed by the Cell Therapy Lab (CTL) at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC). Myeloma vaccine placebo injections will be prepared by the CTL at Johns Hopkins SKCCC. Prevnar, and Prevnar placebo, will be prepared by the Pharmacy and Investigational Drug Service (IDS) at the Johns Hopkins Hospital. All placebo will be made with saline. For study participants, lenalidomide will be administered as a commercial drug.

2. SCHEDULE OF STUDY ASSESSMENTS*

Procedure	Screen/Baseline[9] (Cycel 1 D 1 (28 days before)	Cycle 1 D 14 (+/- 3 days)	Cycle 2 D 14(+/- 3 days)	Cycle 3 D 14(+/- 3 days)	Cycle 6 D 14(+/-3 days)	1 year (+/-7 days)/Off-Study	18 months (+/-7 days)/Off-Study	2 years (+/-7 days)/Off-	30 months (+/-7 days)/Off-Study	3 years (+/-7 days)/Off-Study
Informed Consent	X									
Eligibility	X									
Complete medical history	X									
Interval history and review of patient vaccine reaction diary[1]		X	X	X	X	X	X	X	X	X
Review of systems[1]	X	X	X	X	X	X	X	X	X	X
Confirm diagnosis and stage	X									
Performance Status (ECOG)[1]	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy[1]	X	X	X	X	X	X	X	X	X	X
Myeloma Vaccine or placebo[2]		**X**	**X**	**X**	**X**	**X**		**X**		**X**
Prevnar Vaccine or placebo[3]		X	X	X	X	X		X		X
Research Blood[4]	X				X	X		X		X
Bone Marrow Aspiration & Biopsy[5]	**X**				**X**	**X**		**X**		**X**
Safety Assessments:										
Adverse event query	-	X	X	X	X	X	X	X	X	X
Physical Examination, vital signs, weight	X	X	X	X	X	X	X	X	X	X
CBC with differential	X	X	X	X	X	X	X	X	X	X
Comprehensive panel	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing[6,7]	X[6]	X	X	X	X	X	X	X	X	X
Disease Measurements:										
Minimal Residual Disease (MRD) testing[8]	X[10]				**X**	**X**		**X**		**X**
Protein electrophoresis (serum and 24 hr urine) or M-spike quantification (serum and 24hr urine)	X	X	X	X	X	X	X	X	X	X
Free light chain assay	X	X	X	X	X	X	X	X	X	X
Quantitative Immunoglobulins	X	X	X	X	X	X	X	X	X	X
Immunofixation studies (serum and 24 hour urine)	X	X	X	X	X	X	X	X	X	X
Beta-2 microglobulin	X									
Assessment of response[1]	X	X	X	X	X	X	X	X	X	X

In addition to the regularly scheduled study visits, an unscheduled visit can occur at any time during the study. Investigators may also assess participants via telemedicine at any point the investigator, local health or government authorities and/or other Hopkins authorities deem it appropriate. In these cases, an assessment may not include a physical exam or samples collection. All efforts should be made to perform in person visits if possible. Source documents must be maintained for these remote visits and unscheduled

visits. The date for the visit and any data generated must be recorded on the appropriate CRF.

If physical examination, vital signs, weight and ECOG performance status were done within 7 days of Day 1, they do not need to be repeated at Study Day 1.

* A variation of +/- 3 days of a scheduled visit is permitted.
[1] Needs to be documented with the cycle in which patients are getting the vaccine. Can also occur on day 1 of each cycle.
[2] Myeloma Vaccine consists of 3 cell lines admixed, irradiated and administered over 3 limbs.Placebo administration will occur along the same schedule in the same limbs in the placebo arm
[3] Prevnar-13 Vaccine or placebo will be administered together with the myeloma vaccine. It will be injected intramuscularly in one arm.
[4] 100ml of blood in heparinized syringes and 10cc tiger top tube and 2 green top tubes will be collected.
[5] Collect 20 ml of bone marrow in a heparinized 20 ml syringe. Includes cytogenetic and FISH analysis.
[6] Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at anytime in the preceding 24 consecutive months).
[7] Pregnancy tests must occur within 10 – 14 days prior to prescribing lenalidomide, and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). A FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix 5: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods)
[8] MRD testing by NGS. Patients who are MRD negative will not proceed with the clinical trial
[9]Screening and baseline assessments can be completed within 28 days from consent and prior to C1D1
[10]MRD assessments resulted within 60 days prior to consent are acceptable for screening at PI's discretion
Patients may continue treatment with lenalidomide provided there is evidence of clinical efficacy.

3. GLOSSARY OF ABBREVIATIONS

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
BiRD	Biaxin, Revlimid and dexamethasone
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTC	Common toxicity criteria
DSMB	Data Safety Monitoring Board
DTIC	Dacarbazine
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for Evaluation of Medicinal Products
FDA	Food and Drug Administration
FCBP	Females of child bearing potential
G-CSF	Granulocyte colony stimulating factor, filgrastim (Neupogen)
GM-CSF	Granulocyte/macrophage colony stimulating factor
GCP	Good clinical practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDS	Investigational Drug Service
IFN	Interferon
IL-2	Interleukin-2
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat

IVRS	Interactive Voice Response System
KRd	Carfilzomib, Revlimid and dexamethasone

LD	Longest diameter

LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activity
MRD	Minimal Residual Disease
NGS	Next Generaion Sequencing
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OS	Overall survival
PCV	Pneumococcal Conjugate Vaccine
PD	Progressive disease
PFS	Progression Free Survival
PR	Partial response
RBC	Red blood cell
RD	Revlimid and dexamethasone
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
SMC	Safety Monitoring Committee
TPP	Therapeutics Product Program
TTP	Time to progression
VRD	Velcade, Revlimid and dexamethasone
WBC	White blood cell
WHO	World Health Organization

4 BACKGROUND AND RATIONALE

4.1 Multiple Myeloma:

Multiple myeloma (MM) is the second most frequent malignancy of the blood in the USA after non-Hodgkin lymphoma [1]. It accounts for about 1% of neoplastic diseases and 13% of hematological malignancies [2]. Multiple myeloma is most often diagnosed in middle aged and elderly individuals with a median age at diagnosis of about 69 years [3]. Only about 2% of patients are younger than 40 years [4]. The annual incidence is a little over 6 per 100,000, and a little over 26,000 new cases are estimated to occur in the USA in 2015 [3]. Multiple myeloma is a neoplasm arising from clonal expansion of malignant plasma cells, and is characterized by renal insufficiency, hypercalcemia, and destructive lytic bone lesions [5]. Malignant plasma cells can produce large amounts of monoclonal immunoglobulins, most commonly IgG (50-60%) and IgA (20-25%) and occasionally IgD, IgM and IgE.[6] Patients often suffer from bone pain and skeletal fragility.[7]

The etiology remains unknown, but risk factors are thought to include chronic immune stimulation, autoimmune disorders, exposure to ionizing radiation, occupational exposure to pesticides or herbicides, occupational exposure to dioxin, and perhaps prolonged use of certain hair coloring products.[8,9]

The diagnosis is made using several criteria including results of radiographic skeletal survey or magnetic resonance imaging (MRI), bone marrow examination, measurement of serum and/or urine monoclonal protein (M-protein), and free light chain assay. [10,11] Disease stage and extent of tumor burden is determined by one of two staging systems, the International Staging System (ISS), or the Durie-Salmon Staging system (both stage I, II, and III). The ISS incorporates data from levels of β-2 microglobulin and serum albumin, while Durie-Salmon Staging system includes subjective measures such as tumor cell density in the bone marrow, as well as measures of end-organ damage such as hemoglobin, serum calcium,renal insufficiency, immunoglobulin burden and status of lytic bone lesions. [12,13] The lack of subjectivity and the simplicity of the ISS have led to its becoming the preferred staging system.

The therapy of patients with newly diagnosed multiple myeloma (NDMM) is based on a combination of features including cytogenetic risk stratification, age and eligibility for autologous stem cell transplantation (ASCT). Several recent randomized trials have evaluated the addition of a novel agent to oral melphalan and prednisone in older patients, while novel agents have been incorporated before, during and after ASCT, in younger individuals. Newer investigational approaches that are not age-dependent include continuous myeloma suppression with dexamethasone plus an immunomodulatory derivative, or the use of multiple cycles of combination regimens followed by a treatment break or maintenance therapy. Survival prospects in MM have improved during the last decade with the introduction of new drug regimens, including immunomodulatory drugs (IMiDs; such as lenalidomide, thalidomide), and pomalidomide and proteasome inhibitors (such as bortezomib and carfilzomib). [14] However, despite the use of novel agents and immunotherapies, Multiple Myeloma largely remains an incurable disease in the vast

majority of patients with a median survival of 4 to 6 years.[15] Most patients relapse with few experiencing long-term disease-free survival with current therapeutic approaches.[14] There is an urgent need for more effective therapies to treat this challenging disease.

Long-term responses have been demonstrated in the allogeneic transplant setting. However, this treatment is associated with severe graft versus hostdisease (GVHD) and substantial mortality, which has limited its use.[16] A major goal of newer studies has been to increase the overall clinical efficacy without added toxicity. Clearly, the ability to impart a myeloma-specific immune response without the toxicity seen with allogeneic transplants offers significant appeal. Recent studies attempting to utilize vaccine approaches alone or in combination with adoptive immunotherapy have shed significant light into the potential efficacy of these approaches. More importantly, these studies underscore the profound limitations of the current interventions and enabled the development of novel strategies with greater anti-tumor specificity.

4.2 Clinical responses to Lenalidomide and Dexamethasone

In patients with relapsed refractory myeloma, responses to lenalidomide and dexamethasone were compared to that of dexamethasone and placebo in a large randomized North American study.[17] Patients were enrolled from February 27th, 2003, to April 14th, 2004. Results were presented for response and time to progression were based on data before unblinding, and the results for safety were based on data obtained prior to December 31st, 2005. Median follow-up was 17.6 months. Complete, near-complete, or partial responses occurred in 108 patients (61.0%) in the lenalidomide and dexamethasone group and in 35 patients (19.9%) in the control group treated with dexamethasone alone (P<0.001); complete responses occurred in 14.1% and 0.6%, respectively (P<0.001). The median time to progression was 11.1 months in the lenalidomide group and 4.7 months in the control group (P<0.001). Median overall survival times in the two groups were 29.6 months and 20.2 months, respectively (P<0.001). Grade 3 or 4 adverse events were reported in 85.3% of the lenalidomide group and in 73.1% of the control group; these events resulted in study discontinuation in 19.8% and 10.2%, respectively. Grade 3 or 4 neutropenia and venous thromboembolism were more common in the lenalidomide group than in the control group (41.2% vs. 4.6% and 14.7% vs. 3.4%, respectively; P<0.001 for bothcomparisons).

In newly diagnosed patients, the combination of lenalidomide and dexamethasone was tested in 34 patients at the Mayo Clinic.[18] Overall, thirty-one patients achieved an objective response, defined as a partial response or better (91%; 95% confidence interval, 79%-98%), with a complete response plus very good partial response rate of 56%. The complete response plus very good partial response among the 21 patients who received Rev-Dex without SCT was 67%. The 2-year progression-free survival rates for patients proceeding to SCT and patients remaining on Rev-Dex were 83% and 59%, respectively; the OS rates were 92% and 90% at 2 years and 92% and 85% at 3 years, respectively. An IFM/DFCI 2009 study with two arms, Velcade-Revlimid-dexamethasone (VRd) plus transplant vs VRd with no transplant, followed by Revlimid maintenance (without steroids) in the post transplant setting, demonstrated a 3-year OS rate for the whole cohort in both

arms of 88%, and showed significant improvement in the sCR/CR rate.[19] In Phase III multicenter randomized trial lenalidomide maintenance (without steroids) was compared to no maintenance after melphalan, prednisone, lenalidomide (MPR). Lenalidomide maintenance improved clinical responses and progression free survival when compared to no maintenance.[20] In a CALGB study, lenalidomide maintenance (without steroids) was compared to placebo after autologous stem cell transplant. A 58% decreased risk in disease progression was noted in the patients who were on maintenance lenalidomide.[21] A recent meta-analysis of three major trials presented at the annual ASCO meeting in June 2016 concluded that lenalidomide maintenance significantly prolonged OS in the post-autologous stem cell transplant (ASCT) setting. There was an estimated 2.5 year improvement in OS (HR = 0.74, 95% CI: 0.62-0.89, p = 0.001). The benefit gained outweighed the risk of secondary primary malignancies, and thus lenalidiomide maintenance following ASCT can be considered standard of care.

4.3 Lenalidomide augments responses to Prevnar vaccination

In preclinical models lenalidomide has been shown to augment immune responses in vitro while the in vivo immunomodulatory properties of this drug are unknown. We previously conducted a clinical trial in relapsed myeloma patients examining the ability of lenalidomide to augment both endogenous, as well as vaccine-specific cellular and humoral immune responses to the pneumococcal vaccine, Prevnar [22]. Prevnar was given either before or during administration of lenalidomide in two cohorts of patients. Cohort A received their first vaccination prior to administration of Lenalidomide, and the second vaccine on cycle 2, day 15 of Lenalidomide. Cohort B received both vaccines after initiation of Lenalidomide: cycle 2, day 15 and cycle 4, day 15. Pneumococcal serotype titres as well as CRM-197 T cell responses quantified the B and T cell responses, respectively, to Prevnar vaccination and were correlated with lenalidomide administration. Systemic immune responsiveness was determined by DTH responses to candida and by flow cytometric analysis of immune cell subsets. 24 patients were enrolled. 17 patients were evaluable with 10 in Cohort A and 7 in Cohort B.

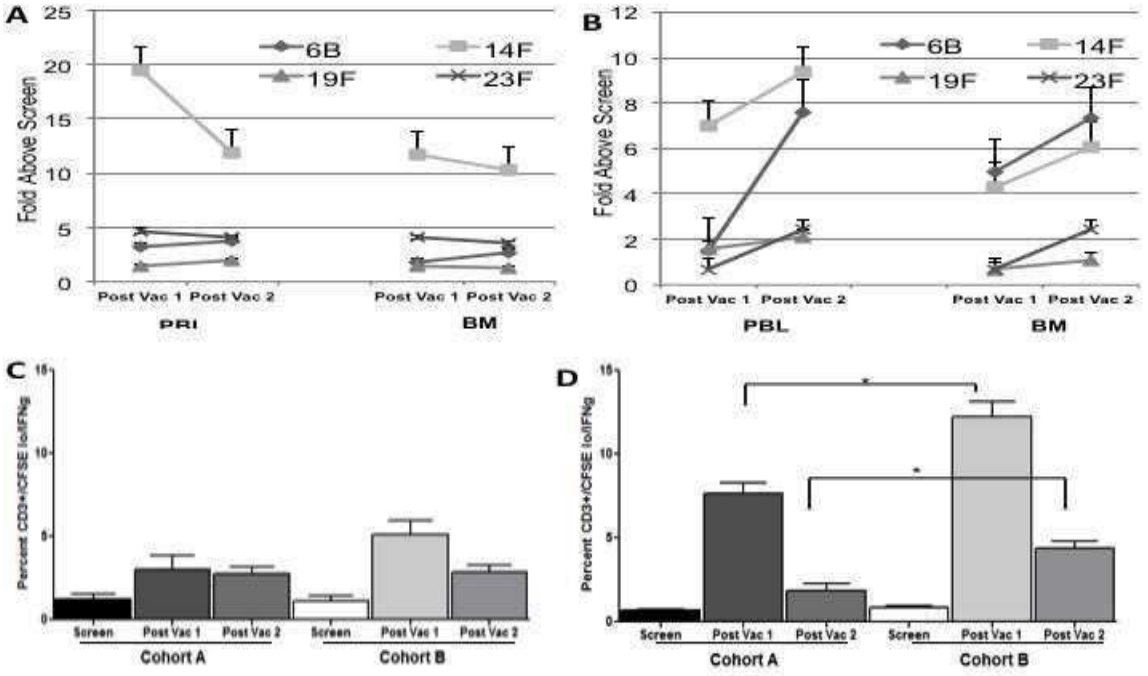


Fig 1:

Lenalidomide augments Prevnar-specific Vaccine responses: Cohort A received Prevnar prior and on day 14, cycle 2 whereas Cohort B received Prevnar on day 14 of Cycles 2 and 4. Antibody responses to Prevnar were increased in Cohort B compared to Cohort A (Fig B vs. A). T cell responses to CRM-197 were also greater in Cohort B when measured in both blood (Fig C) as well as bone marrow (Fig D).

7 patients with progressive disease while on study were not evaluable. All patients had measurable T cell and antibody responses to Prevnar. T cell responses to CRM-197 demonstrated significantly higher responses in Cohort B with a peak 5.8 fold-increase above baseline compared to 1.5 in Cohort A in the blood. The bone marrow T cells showed a greater response which persisted longer in Cohort B (15.5 fold to 4.5 at 6 months) vs. A (12.5 fold to 1.8 at 6 months). A tendency owards better T cell responses were observed in patients with better clinical responses to lenalidomide. Vaccination primed serotype responses in both groups. While the second Prevnar vaccine in Cohort B further augmented antibody titres, no subsequent increase was observed in Cohort A. As a measure of systemic immunity, DTH responses to Candida were examined. Cohort B demonstrated up to a 78-fold increase in induration compared to no change in Cohort A. Flow cytometric analyses showed increased NK (1.2 fold) and CD8 (2.5 fold) in Cohort B. Furthermore, T cell subset analyses revealed an increase of activation markers as well as an increase in the central memory and effector memory phenotypes in both peripheral blood and bone marrow. Interestingly, greater myeloma clinical responses were observed in Cohort B (57% ORR) vs Cohort A (10% ORR).

This is the first *in vivo* demonstration of the immunomodulatory properties of lenalidomide, and lenalidomide-mediated augmentation of both cellular and humoral responses in myeloma patients. These data suggest a synergy between the immunomodulatory effects of lenalidomide and vaccines. Surprisingly, the increased anti-tumor effect observed in Cohort B suggests the possibility of lenalidomide-induced vaccine-mediated epitope spreading.

This pilot study established the scientific rationale for utilizing lenalidomide as an immune adjuvant with vaccines. Implications of the use of lenalidomide as a vaccine adjuvant apply to both cancer vaccines as well as infectious diseasevaccines.

4.4 Allogeneic Myeloma GVAX with Lenalidomide in Near Complete Remission Enhances Progression Free Survival

As the depth of response to therapy in MM correlates with improved progression free survival, we extended the above research to examine whether vaccinating patients on lenalidomide in a near complete remission (nCR) (negative M-spike, IFE positive), could further deepen the clinical response and generate measurable myeloma specific immunity.[23]

Patients on a Len-containing regimen (VRD, Rd, BiRD or R) that achieved and maintained a nCR for 4-6 months were eligible for the study. Patients continued only on single agent Len and received 4 GVAX vaccinations consisting of two allogeneic MM lines: H929, U266 admixed with K562 transduced to express GM-CSF as well as PCV. Patients received 3 monthly vaccines and a boost at 6 months. Immune monitoring was performed on BM samples obtained at baseline, 6 months and 1 year.

To date 32 patients have been screened. 17 patients initially in a nCR were ineligible for vaccination: 3 (18%) had disease progression, 7 (42%) entered into an IFE negative CR, and 7 (42%) maintained a nCR during the observation period but opted not to enroll. 15 patients have been enrolled and completed their vaccinations. Patient characteristics are shown in the Table. Of note, none possessed high-risk features by ISS or FISH. Median follow-up for the study is 34.0 months. Median progression free survival (PFS) of the cohort of vaccinated patients has not been reached whereas the PFS in the observation arm that remained on the multidrug Len-containing therapy was 17.9 months ($p<0.001$) (figure 2). Vaccination in the setting of a rising M-spike was less likely to induce a durable remission with a median PFS of 14.3 months ($p<0.003$) (figure 3). Laboratory analysis showed that the patients achieving a CR had greater expression of PD-1 on CD4 and CD8 cells at baseline in the BM. Furthermore, durable responses were associated with the development and persistence of MM-specificimmunity.

Patient charateristics:

	Vaccination (n=15)	**Observation (n=16)**
Age	69 (55-81)	66 (40-83)

FISH (high risk)	0%	0%
ISS Stage III	2 (13%)	3 (19%)
IFE negative	0 (0%)	7 (42%)
Prior Therapies	1.8 (1-4)	1.8 (1-3)

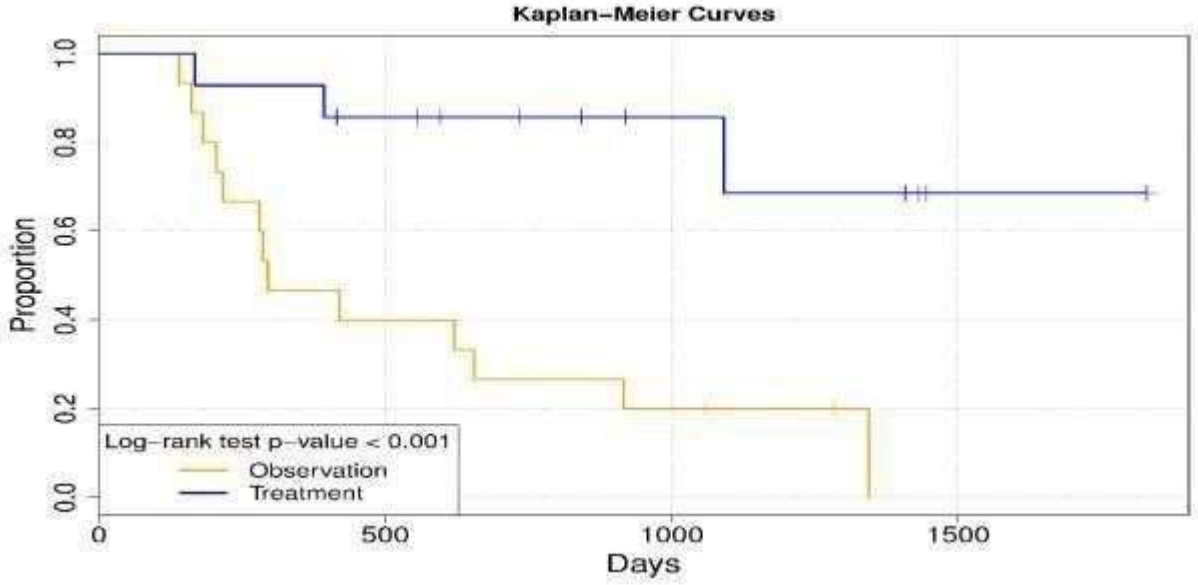


Figure 2. GVAX significantly prolong PFS in patients in a nCR

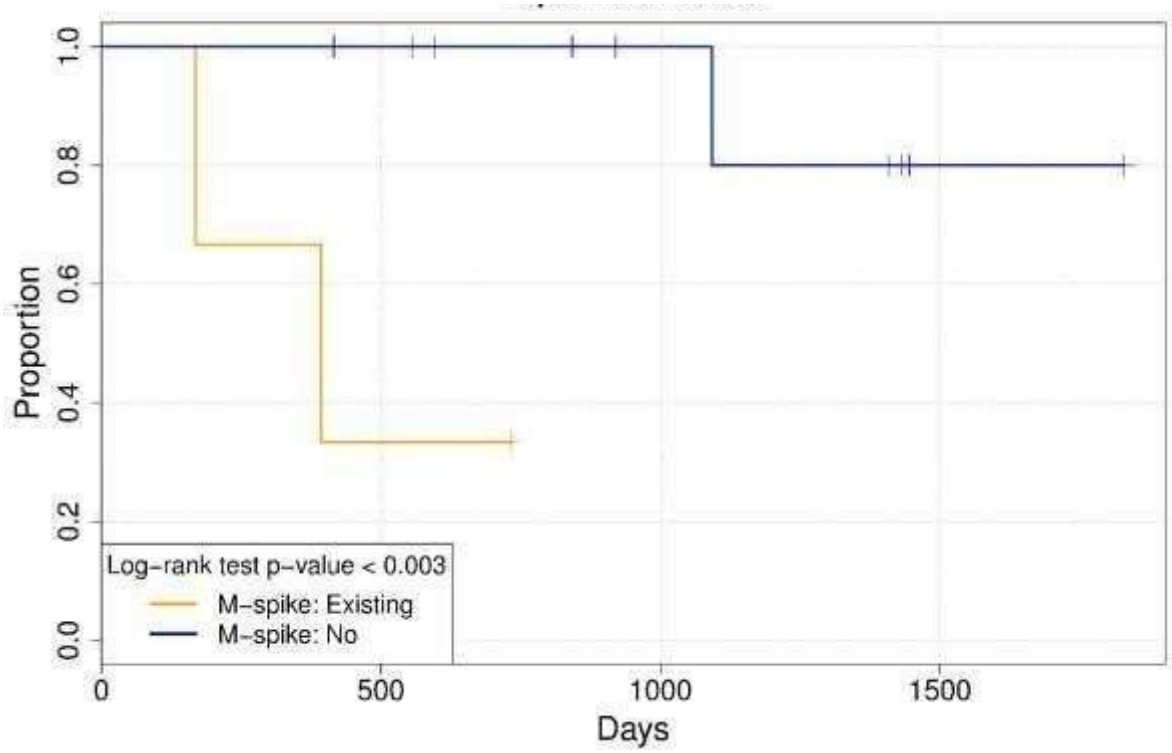


Figure 3. Presence of Disease Reduces Vaccine Efficacy

Vaccination with a poly-antigenic approach such as GVAX in combination with lenalidomide induced immunomodulation in patients with minimal residual disease generates potent MM-specific immunity, and appears to significantly extend the PFS. The promising early clinical activity has led us to design a randomized phase II trial to further explore this approach as a means to maintaining durable clinical remissions.

4.5 K562/GMCSF vaccine:

Tumor cell-based vaccine strategies seek to enhance the immunogenicity of tumor cells by modifying them in vitro to express immunomodulatory cytokines.[24-27] Our group and many others have demonstrated the generation of T-cell mediated systemic anti-tumor immunity capable of eradicating a small, pre-established tumor burden in certain murine models following vaccination. The vaccination site has been shown to contain an influx of eosinophils, activated macrophages, [26] and dendritic cells (DCs),[28] with complete destruction of the vaccinating tumor cells within three to five days.[29] GM-CSF producing tumor vaccines act by recruiting and activating professional antigen presenting cells (APCs) which process antigens liberated from the irradiated tumor cells at the vaccine site and migrate to the draining lymph nodes.[30] Here, processed antigen is presented to tumor-specific T-cells leading to their activation.

APCs are critical in the priming phase of this response. This is underscored by demonstration that tumor-specific CD8+ cytotoxic T- lymphocytes (CTL) are actually primed by bone marrow derived APCs that have processed exogenous tumor antigen in response to vaccination ("cross-priming"), rather than by tumor presentation of endogenous antigen.[31] Significantly, this provides a rationale for the use of allogeneic tumor cells as a source of antigen in clinical settings where collection of autologous tumor is not feasible. Many tumor-associated antigens identified to date are not patient specific, but rather are common to the type of tumor. Since host APCs initiate the T-cell response to such vaccines, it is not necessary to "match" the HLA of the allogeneic tumor cell with that of the patient; instead antigens are liberated from the irradiated cell lines, captured, processed, and presented by host APCs in an autologous HLA-restricted fashion to host T-cells.

The efficacy of GM-CSF transduced tumor vaccines has been demonstrated in multiple animal models of melanoma, lung cancer, colon cancer, renal cell cancer,[26] as well as prostate cancer, acute leukemia, and B-cell lymphoma.[32-34] In addition, early clinical trials with GM-CSF expressing vaccines have tested patients with renal cell carcinoma, prostate cancer, melanoma, non-small cell lung cancer and pancreatic cancer.[35-38] The clinical data available to date reveal minimal toxicities (local swelling and tenderness at the vaccine site) at doses as high as $5x10^8$ cells per injection, with tumor cells secreting up to 1000 ng GM-CSF/10^6 cells/24 hours (i.e. up to 500 micrograms of GM-CSF/day), with serum GM-CSF levels peaking 3 days post vaccine and becoming undetectable by

7 days. In vitro assays have demonstrated the induction of tumor-specific cytotoxic lymphocyte activity,[37] and the appearance of high titer antibody to the vaccinating cell population.[36]

4.6 K562/GM-CSF as a universal GM-CSF producing Bystander Cell:

K562, a cell line, derived from a CML patient in blast crisis was transfected with a plasmid vector encoding human GM-CSF. K562/GM-CSF grows well in serum-free media, stably expresses > 1000 ng of GM-CSF / 10^6 cells/ 24 hours, and is easily expanded to large numbers for vaccine production.

Clinical trials performed at Johns Hopkins initially used the K562/GM-CSF vaccine as a "bystander" cell together with irradiated autologous tumor in patients with multiple myeloma and acute myeloid leukemia. In those studies, analysis of vaccine biopsy sites, serum GM-CSF levels, and serial white blood cell counts indicate that GM-CSF production is sustained for at least 3-5 days post vaccination.

4.7 Allogeneic myeloma vaccine preparation:

We have developed an allogeneic myeloma vaccine which consists of 3 cell lines:
1. H929 – is an unaltered myeloma cell line grown in serum-free medium. This is an IgA cell line isolated from the pleural effusion of a patient with end-stage myeloma. The cell line possesses the t(4; 14) as well as the N-13 ras mutation. It also expresses MAGE-A2 and NY-ESO-1.

2. U266 – is an unaltered myeloma cell line isolated from a patient with plasma cell leukemia. The line contains the t(11;14), overexpression of cyclin D1 and amplification of bcl-2. It also expresses NY-ESO-1 and GAGE-3.

3. K562/GM-CSF – is a CML cell line modified to express stable, high levels of GM-CSF to be used as the GM-CSF-producing bystander. This cell line was chosen in that it lacks surface HLA expression. The cell line produces approximately 1500ng/10^6 cells/24hrs of GM-CSF.

4.8 Rationale for Allogeneic Myeloma Vaccine

In multiple myeloma, donor lymphocyte infusions (DLI) have been able to induce prolonged remissions in patients who relapsed after allogeneic transplantation.[39] This approach demonstrates the efficacy of immune mediated anti-tumor effect in myeloma. We have been able to measure tumor specific T cell responses in a recent trial using an autologous vaccine in the setting of a stem cell transplant. However, significant barriers still exist that prevent us from maximizing vaccine-mediated anti-tumor efficacy. Results from both pre-clinical and clinical studies have demonstrated that tumor vaccines work

best in the setting of minimal residual disease. A possible explanation for these findings is the immunosuppressive effects of advanced tumors in tumor-bearing hosts. Specifically, the increase in VEGF levels that result in impaired dendritic cell function, changes in ζ-chain signaling on the T cell receptor resulting in global immunosuppression, the induction of myeloid suppressor cells exerting an inhibitory immune effect via nitric oxide and arginase-dependent pathways and the development of antigen-specific tolerance induction resulting in a skewing from a positive Th1 CD4 response to an inhibitory Th2 response.

These findings have enabled us to identify putative targets to improve the underlying immune responsiveness of the host in an effort to augment the efficacy of tumor-specific vaccine strategies in an immune responsive host, and to impart an immune-mediated anti-tumor effect on chemo-resistant tumors, that underscore the ability of active immunotherapy to exert its anti-tumor effect through non-cross-reactive mechanisms. Taken together, these findings provide a strong rationale for studies that integrate tumor vaccines into a setting in which prior therapy achieved its maximal anti-tumor benefit.

We have tested the immunomodulatory role of lenalidomide on pneumococcal vaccine (Prevnar) responses in arecently conducted clinical trial (described above) in patients with relapsed myeloma [22]. Ultimately the data demonstrated that lenalidomide augments *in vivo* immune responses in patients with advanced/relapsed multiple myeloma, which provides the rationale for utilizing this drug in combination with cancer vaccines to augment anti-tumor efficacy.

Most patients achieving a CR still go on to relapse[14]. However, the depth and duration of CR may play an important role in disease prognosis, and higher CR has been shown to correspond with improved survival. The potential benefit of tumor vaccine may be best seen in the setting of minimal residual disease (MRD), where tumor induced tolerogenic mechanisms may be less relevant, and may be an effective mechanism of achieving a deeper remission such as stringent CR when not already in stringent CR, or molecular CR.

We will study the effect of the tumor vaccine in patients achieving at least a near complete remission (nCR), as well as a complete remission (CR) with a lenalidomide based regimen. The goal of the study will be to improve the clinical responses in patients with near complete remission (nCR) or complete remission who are also minimal residual disease positive (MRD+), and to determine whether the allogeneic myeloma vaccine confers a PFS advantage upon patients treated with allogeneic myeloma vaccine in combination with lenalidomide (with or without Prevnar vaccine) as compared to a non-vaccine control arm with patients on lenalidomide alone. The effect of adding Prevnar to the allogeneic myeloma vaccine and lenalidomide combination will also beexplored.

Since administration of corticosteroids can dampen immune responses, patients will discontinue dexamethasone or other steroids at least one month prior to receiving the first vaccine, and must not show evidence of progressive disease as defined by the International Uniform Response criteria [47], prior to being started on the trial. The adverse

effects and significant morbidity from long term use of corticosteroids are well described, and this trial will give us an excellent opportunity to explore novel treatment strategies in a 'steroid free' regimen with a goal to improve the depth of response and have a low toxicity profile.

The incorporation of the Prevnar vaccination in our earlier study had a dual purpose. We were able to measure the efficacy of the vaccine by examining both the humoral, as well as cellular responses to Prevnar; and we uncovered a potential therapeutic effect of Prevnar vaccine in our earlier study. Specifically, the ability of Prevnar to prime T cell responses targeting HB-EGF (heparin binding epidermal growth factor), a cell adhesion molecule expressed on a significant percentage of myeloma cells. [22, 23]

We believe that the data support the efficacy of lenalidomide in augmenting *in vivo* immune responses in patients with multiple myeloma, and thus warrant the investigation of lenalidomide in combination with the allogeneic myeloma vaccine without the potentially confounding effect of Prevnar. However, to confirm that clinical benefits are primarily due to the effect of allogeneic myeloma vaccine alone, there is an additional comparison arm consisting of allogeneic myeloma vaccine along with Prevnar, in combination with lenalidomide which was the composition of the vaccine in our Phase I trial.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study objectives:

Primary:

- To compare the 2-year progression free survival of patients with multiple myeloma in a near complete remission (nCR) or complete remission (CR) who are also minimal residual disease positive (MRD+), treated with an allogeneic myeloma vaccine in combination with lenalidomide (with or without Prevnar vaccine) versus placebo in combination with lenalidomide.

Secondary:

- To compare the 2-year progression free survival for those treated with or without Prevnar in addition to an allogeneic myeloma vaccine and lenaliodmide
- Determine rate of conversion of nCR to true CR
- Determine rate of conversion of MRD positivity to MRD negativity
- Determine time to response
- Determine the progression free survival at 3 and 5 years
- Evaluate toxicity of the allogeneic myeloma vaccine
- Measure tumor specific immunity and correlate with systemic immunity

6 INVESTIGATIONAL PLAN

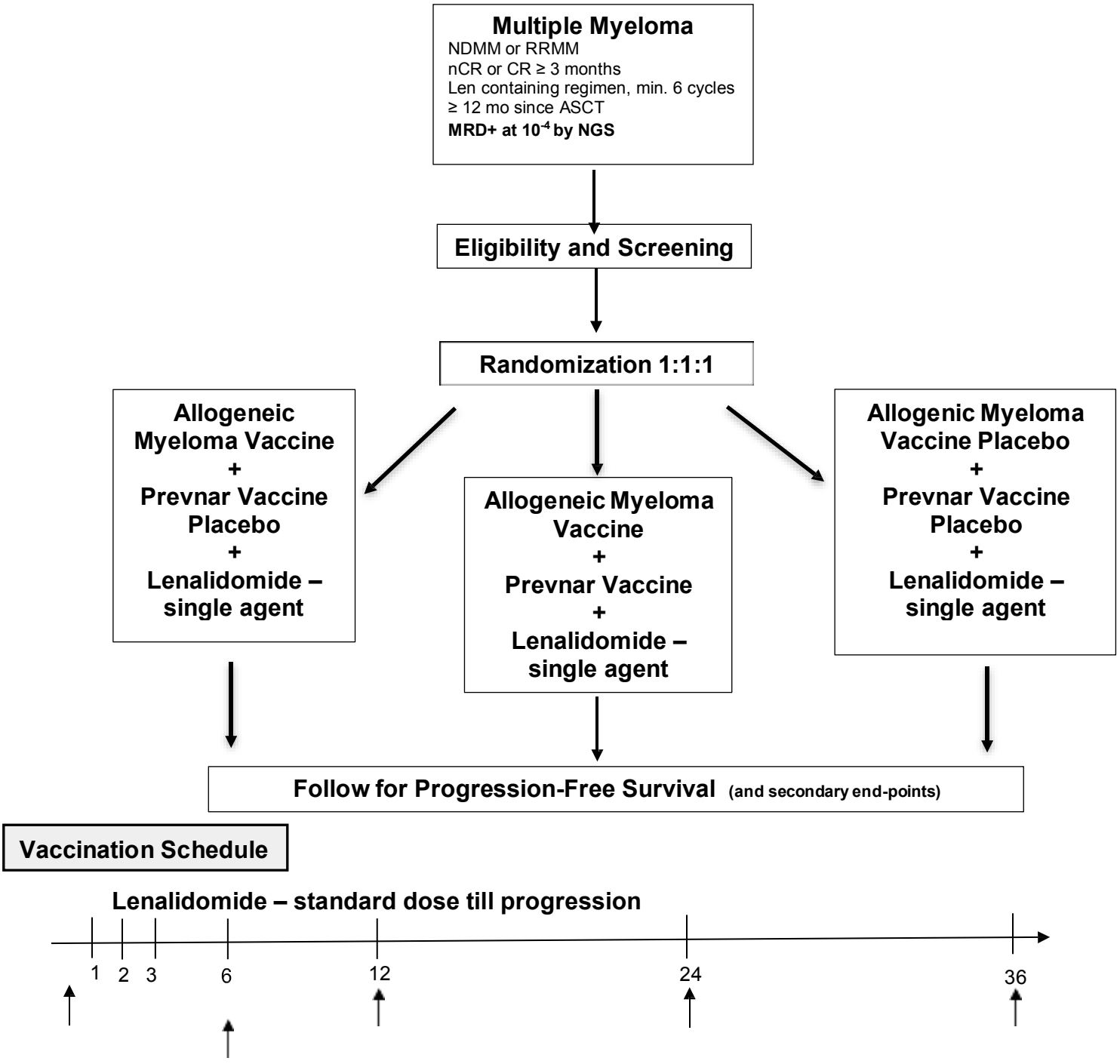
6.1 Overall design:

Patients with newly diagnosed or relapsed/refractory multiple myeloma (NDMM or RMM) in CR or nCR who meet appropriate criteria will be eligible for enrollment. Specifically:

- Patients with NDMM who have completed 6 cycles of treatment with any lenalidomide containing regimen (e.g. KRD, VRD, Rd, BiRD or R alone) and who have been in CR or nCR for ≥ 3 months.
- Patients with MM who have undergone ASCT will only become eligible ≥ 12 months following date of cell infusion, will have been on lenalidomide maintenance for ≥ 6 cycles prior to enrollment, and continue to meet criteria for CR or nCR for ≥ 3 months.
- Patients with RMM will need to have completed at least 6 cycles of current therapy with a lenalidomide containing regimen, and be in CR or nCR for ≥ 3 months.
- All patients must be MRD positive at 10^{-4} by NGS sequencing at enrollment

Eligible patients who go on to enroll will be randomized in a 1:1:1 fashion to one of three arms. All patients will continue on a standard dose of lenalidomide (15mg daily, to be adjusted as clinically necessary), given on days 1 – 21 of a 28 day cycle. Patients on the myeloma vaccine arm will receive injections with an allogeneic myeloma vaccine administered intradermally on day 14 of cycles 1, 2, 3, 6 and annually for a minimum of 36 months in addition to lenalidomide unless otherwise clinically indicated, or until progression. Patients on myeloma plus Prevnar vaccine arm will receive injections of both allogenic myeloma vaccine, intradermally, and Prevnar vaccine, intramuscularly, on day 14 of cycles 1, 2, 3, 6, and annually for a minimum of 36 months in addition to lenalidomide unless otherwise clinically indicated, or until progression. Patients on the myeloma vaccine placebo arm will receive myeloma vaccine placebo on the same schedule as allogeneic myeloma vaccine. If assigned to either of the two arms that do not include Prevnar, then patients will receive placebo in lieu of Prevnar on the same schedule. The placebo will be saline. The study schema is shown below:

SCHEMA



Allogeneic Myeloma Vaccine or placebo administration – in months: 1, 2, 3, 6, 12, 24, and 36
Prevnar or Prevnar placebo administration – concurrent with myeloma vaccine administration
MRD testing – enrollment, 6 mo, 12 mo, annually for the duration of study

6789

6.1.1 Registration on Study and Randomization

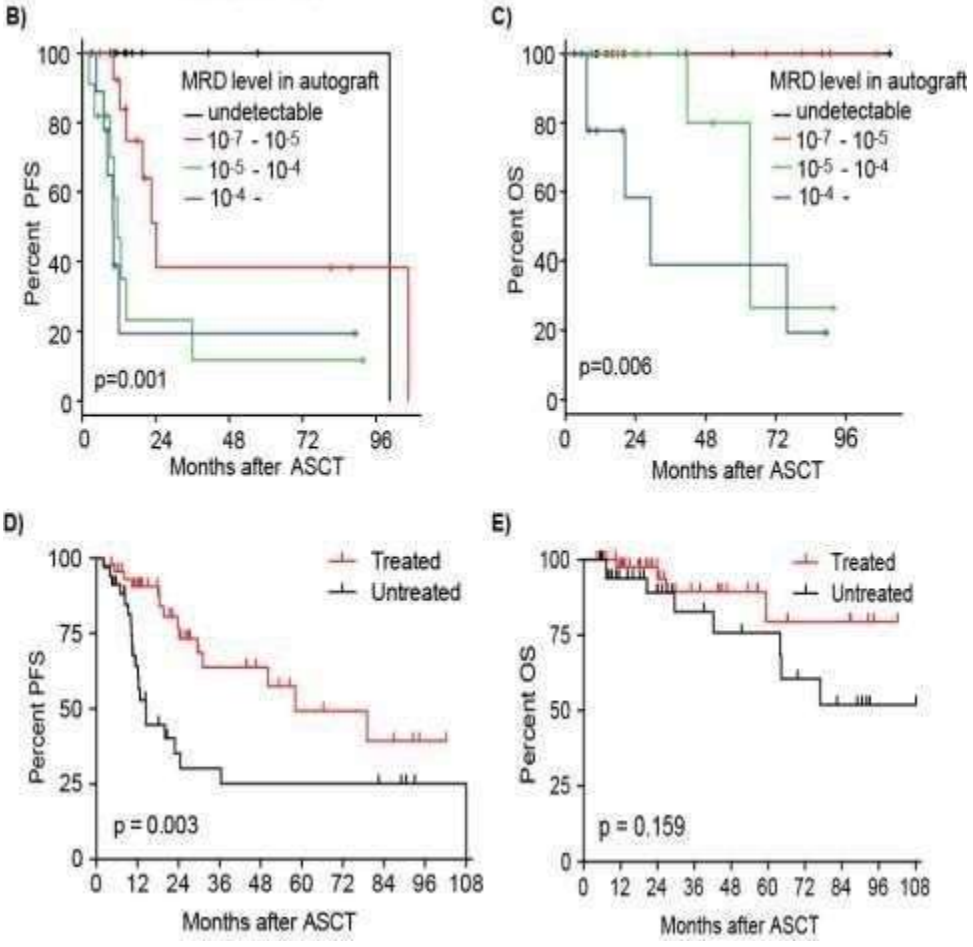
At registration, patients will have the baseline evaluations listed in Sections 2 and 7. Once eligibility requirements are met, the patients will proceed to bone marrow biopsy with cytogenetics and FISH analysis, and/or GEP assessment via myPRS, if this information is not already available at diagnosis, or on recent testing. Randomization in a 1:1:1 fashion will occur after screening and eligibility requirements have been met, and bone marrow biopsy obtained if needed. The primary criteria for stratification will be:

- Near Complete Remission vs Complete Remission (nCR v CR)
- Prior autologous stem cell transplant vs no prior autologous stem cell transplant

6.1.2 Minimal Residual Disease Testing

Outcomes for patients with MM have improved significantly over the past decade, with improvements in both progression-free survival and overall survival.[44] Many patients are now achieving a complete response to treatment, and consequently highly sensitive assays are needed for detection of minimal residual disease (MRD) in patients with MM.[44] Results of multicolour flow cytometry and deep-sequencing studies suggest that among patients achieving a complete response, MRD-negative status is associated with substantial improvements in progression-free, and overall survival.[44] MRD status seems, therefore, to be an important prognostic factor in patients with MM. The prognostic value of sequencing based MRD testing was demonstrated in a publication by Hiroyuki Takamatsu et al at the 57th Annual ASH Meeting, 2015.[45] One hundred and twenty-three Japanese patients with newly diagnosed MM who received various induction regimens prior to ASCT were retrospectively analyzed. All patients received ASCT and were followed between June 15, 2004 and April 25, 2015. All patients had achieved a partial response (PR) or better after ASCT. Analyzed samples included: (1) BM slides from 96 MM patients at diagnosis, (2) fresh/frozen BM cells from 27 MM patients at diagnosis, (3) autografts and/or (4) post-ASCT BM cells obtained at the time of best response based on serum and urine tests. IGH-based ASO-PCR was performed as described previously [46]. NGS-based (Next Generation Sequencing-based) MRD assessment was performed using the immunosequencing platform (Adaptive Biotechnologies, South San Francisco, CA) [47]. Patients whose autografts were negative by NGS-based MRD assessment (N=19) had 100% PFS and OS at 5 years post ASCT irrespective of whether or not they received post ASCT treatment. Conversely, post ASCT treatment had a significant effect on the outcome of patients whose autografts

were MRD positive by NGS. Specifically, the NGS-based MRD positive patients who received post ASCT treatment (N=45) had a significantly better PFS.



To be able to study the interaction between allogeneic vaccine and MRD negativity on outcomes in our study, we plan to incorporate NGS-based MRD testing for all patients at enrollment, six months, one year and annually thereafter.

6.2 Administration of Allogeneic Myeloma Vaccine or Placebo

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for allogeneic myeloma/K562/GM-CSF vaccine and lenalidomide, as well as appropriate dose modifications for lenalidomide, are described below. No dose modification exists for the allogeneic myeloma K562/GM-CSF vaccine. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

6.2.1 Administration Parameters

At time of enrollment all patients will be on a stable, standard dose of lenalidomide given on days 1 – 21 of a 28 day cycle.

The following parameters must be present for each dose of the vaccine to be administered:

- No systemic infections requiring treatment
- Hemoglobin $>$ 8g/dL
- Platelets > 20,000
- ALT/AST $<$ 3X upper limit of normal
- Patient must be receiving lenalidomide on the day of thevaccine
- Missed vaccine doses can be made up within 2 weeks of the missed dose, with a delay by an equal number of days for the next dose (and the remaining doses), for the first 4 vaccine doses (there wil be a minimum of one month between doses).
- Vaccine doses that are missed beyond the 4th dose of vaccine, can be made up within 1 month of the original date of administration.Subsequent doses do not need to be delayed.

6.2.2 Vaccine Formulation

The cell lines used for the vaccine preparation were manufactured and released by the Cell Processing and Gene Therapy Facility, a cGMP compliant facility, at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.. The vaccine cells are irradiated prior to cryopreservation and stored frozen in the vapor phase of liquid nitrogen until the day of use. The details of production, irradiation, freezing, and preparation for administration have been discussed in detail in the Investigational New Drug (IND) submission. Equal numbers (5×10^7 each) of the myeloma cell lines H929 and U266 cells will be combined with the bystander cell line K562/GM-CSF (5×10^6) to prepare the vaccine. Vaccine cells frozen in an injectable formulation Pentaspan® (10% Pentastarch in 0.9% sodium chloride with 2% human serum albumin and 5% DMSO) will be thawed on the day of vaccination in a 37ºC water bath, mixed, and then taken up into three labeled syringes prior to administration. .The cells are kept at 2-8ºC with gel packs until administration Injections should be started within 60 minutes of the thaw. Myeloma vaccine placebo injections will be saline solutions and will be prepared by the CTL at Johns Hopkins SKCCC in accordance with standard policies in order to maintain blinding.

6.2.3 Vaccine Administration

Each vaccination will consist of three total intra-dermal injections, one each in the right and left anterior upper thighs, and one in the non-dominant upper arm (unless

contraindicated). In the event that the specified limb is contraindicated, the dominant arm may be used. Vaccine injections sites shall be at least 5 cm at needle entry from the nearest neighbor. The approximate volume of each vaccination injection is approximately 0.7 – 0.8 mL

Application of a lidocaine based topical anesthetic (may include but is not limited to EMLA or ELA-MAX) cream at each injection site approximately 1-2 hours prior to vaccination will be recommended to diminish the discomfort associated with the intra-dermal injections. The topical anesthetic is optional and participants are allowed to decline its use. Self-application of the topical anesthetic is allowed after the research participant receives instruction. If the research participant is does not comply with application instructions, the topical anesthetic may be applied by the research nurse. If the subject is allergic to lidocaine, the topical anesthetic will not be used. All research participants will be seen in the oncology outpatient center for vaccine administration and monitoring for at least 30 minutes after vaccination is completed. Those administrating the vaccine will record:
a. Clinical lot number. Record of this will be kept by CTL in order to maintain blinding
b. Date of vaccine administration
c. Number of syringes dispensed
d. Total vaccine dose. Record of this will be kept by CTL in order to maintain blinding
e. Vaccination sites

Vaccinations will occur on Day 14 (±3 days) of cycles 1, 2, 3 and 6 and then annually from enrollment thereafter through 36 months.

Treatment will be discontinued if any of the following occur:

a. Intercurrent illness that prevents further administration of treatment,
b. Unacceptable adverse events(s),
c. The patient decides to withdraw from the study, or
d. General or specific changes in a patient's condition render further treatment inappropriate in the clinical judgment of the investigator.

6.2.4 Potential Vaccine Toxicities

Toxicities associated with the intravenous administration of Pentaspan® include circulatory overload, abnormalities of coagulation (prolonged prothrombin, partial thromboplastin and clotting times), and hypersensitivity reactions characterized by wheezing, urticaria, hypotension, and anaphylactic/anaphylactoid reactions. Additionally, patients who are allergic to corn can also develop hypersensitivity to Pentaspan®.

The experience with K562/GM-CSF to date has shown it to be safe and well tolerated [48]. Elevated levels of GM-CSF can be detected in the serum for 3-5 days post vaccination, and this is accompanied by a transient rise in the white blood cell, neutrophil, and absolute

eosinophil counts. Toxicity is generally limited to myalgias and grade 1-2 injection site erythema, induration, tenderness, and localized pruritus. Most patients experience local vaccine site reactions that last for approximately 1 week; induration has ranged from 0.5 cm to as great as 20 cm. In other trials of GM-CSF producing vaccines, systemic reactions have included fever, headache, rash, generalized pruritus, andmalaise.

As with any vaccine, there is a possibility of a serious allergic reaction although to date this has not been observed with any of the GM-CSF based vaccines administered here at Johns Hopkins. As with any investigational drug, other adverse reactions may develop that have not yet been described.

There is a theoretical risk of autoimmune disease reactivation or development with GM-CSF producing vaccines. In a previous multiple myeloma vaccine trial, induction of immune responses to autologous tumor cells has been demonstrated in vitro. Importantly, all multiple myeloma patients who had undergone autologous stem-cell transplant followed by vaccination have had normal kinetics of engraftment. There has been no serological or clinical evidence of autoimmune disease to date arising in recipients of the K562/GM-CSF vaccine in the previous AML, CML and myelomatrials.

6.2.5 Availibility

The vaccine is derived from the three master banks for K562/GM-CSF, H929 and U266. The master cell banks are the source material for all working clinical lots.The clinical grade allogeneic myeloma K562/GM-CSF vaccine will be manufactured by the GMP facilities operated by Aduro Biotech, and shipped to Johns Hopkins.

6.3 PREVNAR-13®

Other names: Pneumococcal 13-Valent Conjugate Vaccine

Classification: Infectious vaccine

Supplier: Prevnar-13 will be purchased from Wyeth Pharmaceuticals.

Dosage:

Prevnar-13 will be administered at 0.5ml dose by intramuscular injection. This dose will thus contain serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F and approximately 20µg of CRM_{197} carrier protein; and 0.125mg of aluminum phosphate.

Since the product is a suspension containing an adjuvant, shake vigorously immediately prior to use to obtain a uniform suspension in the vaccine container. The vaccine should not be used if it cannot be resuspended or if particulate matter or discoloration is found.

Storage:

Vaccine is to be stored refrigerated at 2^{O}C to 8^{O}C (36^{O}F to 46^{O}F). It should not be frozen.

Contraindications:

Hypersensitivity to any component of the vaccine, including diphtheria toxoid, is a contraindication to use of this vaccine.

Warnings:

Healthcare professionals should prescribe and/or administer this product with caution to patients with a possible history of latex sensitivity since the packaging contains dry natural rubber.

Precautions:

Prevnar® is for intramuscular use only. Prevnar SHOULD UNDER NO CIIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY. The safety and immunogenicity for other routes of administration (e.g., subcutaneous) have not been evaluated.

6.4 LENALIDOMIDE:

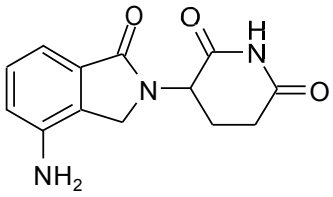
6.4.1 Other names: Revlimid ®

6.4.2 Classification: Immunomodulatory drug

6.4.3 Description:

Revlimid® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide:



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon

atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

6.4.4 Mode of action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells [49] (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 invitro.

Lenalidomide is a proprietary IMiD™ compound of Celgene Corporation. IMiD™ compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. [50] Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF. In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production. Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis. In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin anddexamethasone.

6.4.5 Adverse effects:

The most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication, include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulites, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental

status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, all cause death and fractures. Complete and updated adverse events are available in the FDA label.

6.4.6 Storage:

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

6.4.7 Prescribing Lenalidomide:

Lenalidomide (Revlimid®) will be supplied commercially to research subjects for the duration of their participation in this trial by their insurance providers. Lenalidomide will be provided in accordance with Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS®program. Prescriptions must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient during each cycle.

Further information about the Revlimid REMS® program is available at **www.celgeneriskmanagement.com.**

6.4.8 Pharmacokinetics and Drug Metabolism:

6.4.8.1 Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations (Cmax) occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption [51], but does reduce the Cmax by 36%. The pharmacokinetic disposition of lenalidomide is linear, i.e. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). No plasma accumulation was observed with multiple daily dosing. Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg.[51] Exposure in multiple myeloma patients is 57% higher than in healthy male volunteers.

6.4.8.2 Pharmacokinetic Parameters:

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

6.4.9 Supplier(s)

Celgene Corporation will supply Revlimid® (lenalidomide) commercially to study participants.

6.4.10 Packaging

Lenalidomide will be shipped directly to patients. Each bottle will contain a sufficient number of capsules for one cycle of dosing**.**

6.4.11 Dosage forms:

5, 10, 15 and 25 mg capsules.

6.4.12 Dosing regimen and dose reductions:

Patients will need to be on a maintenance dose of lenalidomide upon being enrolled in the study. Doses of lenalidomide for investigation can vary from 5-25 mg/day, orally on days 1 - 21 followed by 7 days rest (28 day cycle). Patients may be kept on whichever regimen of Revlimid they were taking at the time of enrollment, or changed to an adjusted dose at the PI's discretion.

Prescriptions must be filled within 7 days.

If a patient is on a 10mg dose of lenalidomide upon enrollment into the study, they can be dose reduced to 5mg and remain on study. If a patient requires a dose reduction to less that 5mg, further continuation on study must be approved by the principal investigator.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

6.4.13 Dose adjustments/modifications can be made if needed based on toxicity:

Table 1: LENALIDOMIDE Dose Reduction Steps

Starting Dose	Dose Reduction
15 mg daily on Days 1-21 every 28 days	*10 mg daily on Days 1-21 every 28 days*
10 mg daily on Days 1-21 every 28 days	*5 mg daily on Days 1-21 every 28 days*

Overdose

Overdose, as defined for this protocol, refers to Revlimid® dosing only.

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

PO any amount over the protocol-specified dose

IV 10% over the protocol-specified dose

SC 10% over the protocol-specified dose

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

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

6.4.14 Concomitant therapy:

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate. Considering that all patients will be on lenalidomide for several cycles prior to enrolling on the study, they will be kept on whichever regimen they were taking at the time of enrollment.

6.4.15 Prohibited Concomitant Therapy

Concomitant use of other anti-cancer therapies, corticosteroids, G-CSF, including radiation, thalidomide, or other investigational agents is not permitted while subjects are receiving protocol therapy during the treatment phase of the study. Topical, ophthalmic and inhaled corticosteroids are excluded.

6.4.16 Anticoagulation Considerations

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis particularly when combined with steroids (e.g. dexamthasone, prednisone), or other anticancer drugs known to cause thrombosis (e.g. anthracyclines [Doxil, Adriamycin] and erythropoietin).

Consideration should be given to use of aspirin (81 or 325 mg) or some other form of prophylactic antipcoagulant as deemed appropriate. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR. If prophylaxis is used, it should be held when platelet counts < 50,000, and then restarted when platelet counts are above this level.

6.4.17 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of lenalidomide with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

The allogeneic myeloma K562/GM-CSF vaccine is an immune based treatment. As such, immunosuppressants in the form of steroids, cyclosporine, imuran, cellcept, sirolimus, tacrolimus and others should not be administered during this clinical trial. For questions, address the Primary Investigator.

6.5 Duration of Follow-up

Patients will be followed for a minimum of 36 months after enrollment in the study or until relapse or death, whichever occurs first. Patients removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.6 Dose delay/Dose modifications

There are no dose modifications for the vaccine. Lenalidomide dose adjustments as noted in section **6.4.13.**

NCI CTC Toxicity Grade (CTC AE 4.0)	Dose Modification Instructions
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2, restart lenalidomide at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • **NOTE**: Consider criteria (perhaps based on platelet count) for holding and then resuming prophylactic anti-coagulation, if applicable. • If thrombocytopenia resolves to ≤ grade 2, restart lenalidomide at next lower dose level and continue through scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at start of next cycle. Omitted doses are not made up.
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1, restart lenalidomide at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.
Neuropathy **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level). • Omit lenalidomide for remainder of cycle. See Anticoagulation Consideration (Section 5.6.1.2)
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21, restart lenalidomide and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

7 SCREENING AND ELIGIBILITY

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

7.1 Inclusion Criteria:

- Myeloma eligibility criteria are the following:
  - Near complete remission (nCR) for ≥ 3 months defined as no measurable M-spike, and a positive serum immunofixation
    - For patients with a light chain only myeloma, they will be in deemed to be in a CR if they meet criteria for CR by International Myeloma Working Group (IMWG) consensus criteria 2016.
    - For patients with a light chain only myeloma that meet criteria for Very Good Partial Response (VGPR) by IMWG consensus criteria 2016 and are IFE –ve (negative serum immunofixation), they will be considered to be in a near complete remission (nCR).
  - Or complete remission (CR) (no measurable M-spike, immunofixation negative and bone marrow clonal plasma cells <5%)
  - NDMM or RMM in nCR or CR having completed a minimum of 6 cycles of a lenalidomide based regimen for a minimum of ≥ 3 months
  - NDMM or RMM a patients who have been off corticosteroids for ≥ 4 weeks
  - Patients with NDMM or RMM who have had autologous stem cell transplant are eligible, but must be ≥ 12 months from transplant
  - All patients must be MRD positive at 10^{-4} or greater by NGS sequencing at enrollment
- All patients must be currently taking Revlimid at screening.
- Age >18 years
- ECOG performance scores 0-2
- History of measurable serum or urine M protein or free light chains
- Life expectancy greater than 12 months
- Corrected serum calcium < 11 mg/dL, and no evidence of symptomatic hypercalcemia
- Serum creatinine< 2 mg/dl
- ANC >1000/µL
- Platelet >100,000/µL
- Total bilirubin ≤ 1.5 x ULN
- AST (SGOT) and ALT (SGPT) ≤ 3 x ULN.
- Ability to comprehend and have signed the informed consent.
- Have previously agreed to continue on maintenance therapy with lenalidomide concurrent with vaccine administration until disease progression, or clinical indication to cease therapy.
- All patients must be willing and able to comply with the requirements of the REMS® program as directed by their providers.
- All study participants will have been registered into the mandatory Revlimid REMS® program as per standard of care, prior to enrollment.
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

- Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to starting lenalidomide with each cycle (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before taking lenalidomide, as per standard of care. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See **Appendix 5**: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
- Able to take prophylactic anticoagulation (aspirin 81 or 325 mg/daily or, for patients intolerant to ASA, warfarin or low molecular weight heparin).

† A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

7.2 Exclusion Criteria:

- Disease progression after stopping corticosteroids as defined as the appearance of a detectable serum or urine M-spike, or an absolute increase of >10 mg/dl between involved and uninvolved light chains, in the absence of measurable serum or urine M-protein.
- Patients who are MRD negative by NGS at screening.
- Patients with a known diagnosis of POEMS syndrome, plasma cell leukemia, CNS involvement, non-secretory myeloma and amyloidosis
- High-risk myeloma defined by presence of at least one of the following defining features on initial diagnostic, or most recent bone marrow biopsy:
    - High risk chromosomal translocations by FISH: t(4;14), t(14;16), t(14;20),
    - del(17p), del(1p), amplification 1q.;
    - MyPRS GEP-70 or SkylineDx high risk signature either from diagnosis or at time of registration for the study;
    - LDH > 300 U/L at diagnosis;
    - Relapse from prior therapy within 12 months.
- HIV disease, active infection requiring treatment with antibiotics, anti-fungal or anti-viral agents within 2 weeks of enrollment would be excluded from the study.
- History of a pre-existing malignancy other than myeloma within the last 5 years with exception of treated basal cell or squamous cell carcinoma of the skin, or carcinoma “in situ” of the uterus, cervix or breast.
- Patients who have participated in any clinical trial, within the last four weeks, which involved an investigational drug.
- Autoimmune disease requiring active treatment.
- Known contra-indication to any component of allogeneic myeloma vaccine
- History of an allogeneic transplant

7.3 Visit Schedule And Assessments

Screening assessments and procedures to be performed on study scheduled visits are outlined in Section 2 Table of Study Assessments. All screening assessments should be completed within 28 days from consent and prior to Cycle 1 Day 1. The day 14 visit can occur ± 3 days.

An unscheduled visit can occur at any time during the study. For all unscheduled visits, source documents must be maintained and the date for the visit and any data generated must be recorded on the appropriate CRF.

Investigators may also assess participants via telemedicine at any point the investigator, local health or government authorities and/or other Hopkins authorities deem it appropriate. In these cases, an assessment may not include a physical exam or samples collection. All efforts should be made to perform in person visits if possible.

7.4 Follow-Up

Subjects who discontinue study treatment for any reason will undergo a safety assessment approximately 30 days post the last dose of study drug.

7.5 Serious Adverse Event (SAE) Definition

A serious adverse event (SAE) is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Pregnancy

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

7.6 Adverse Drug Reaction Reporting

Toxicity will be scored using CTC Version 4.0 for toxicity and adverse event reporting. A

copy of the CTC Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC Version 4.0. All adverse events (AEs), whether observed by the investigator or

reported by the patient, must be recorded with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The principal investigator is responsible for evaluating all adverse events, obtaining supporting documents, and determining that documentation of the event is adequate. The principal investigator is responsible for determining the severity and relationship of the adverse event to the investigational drug. The principal investigator may delegate these duties to sub-investigators and must assure that these sub-investigators are qualified to perform these duties under the supervision of the principal investigator.

All adverse events will be recorded in the subject's Case Report Form and in the study data base. The detailed description of the event will include appropriately graded severity of the adverse event and its relationship to the studydrug.

Severity of adverse events will be categorized by toxicity grade according to the NCI Common Terminology Criteria for Adverse Events version 5.0 available at http://ctep.cancer.gov/reporting/ctc.html

7.6.1 Adverse events not listed in the NCI Common Terminology Criteria

Adverse events not listed in the NCI Common Terminology Criteria for Adverse Events will be evaluated using the following criteria:

Grade 1, Mild: Awareness of symptom, but easily tolerated; usually transient requiring no special treatment; does not interfere with usual status oractivities

Grade 2, Moderate: May be ameliorated by simple therapeutic measures; may interfere with usual activities

Grade 3, Severe: Incapacitating, inability to perform usual activities

Grade 4, Life-threatening/Disabling: Subject was at risk of death or significant disability at the time of the event

Grade 5, Death related to AE

7.6.2 Relationship of the Adverse Event to the Investigational Drug

Relationship of the adverse event to the investigational drug will be determined by the principal investigator, and will be categorized as:

Not Related: The adverse event is clearly related to other factors such as the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.

Possible: The adverse event follows a reasonable temporal sequence from administration of the study drug, and/or follows a known response pattern to the study drug, but could readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.

Probable: The adverse event follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug, and cannot readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.

The investigator must appraise all abnormal clinical laboratory results for their clinical significance. In accordance with FDA requirements and guidelines, we shall report the most frequent and most serious adverse events (SAEs) suffered by subjects on the clinical trial.

If any abnormal laboratory result is considered clinically significant and possibly drug related, the investigator must provide details about the action taken with respect to the study drug and about the patient's outcome.

7.7 Expedited Reporting By Investigator To Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number **(RV-CL-MM-PI-005749)** and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE form, and retained with the patient records.

7.8 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP

is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

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

IF THE OUTCOME OF THE PREGNANCY WAS ABNORMAL (E.G., SPONTANEOUS OR THERAPEUTIC ABORTION), THE INVESTIGATOR SHOULD REPORT THE ABNORMAL OUTCOME AS AN AE. IF THE ABNORMAL OUTCOME MEETS ANY OF THE SERIOUS CRITERIA, IT MUST BE REPORTED AS AN SAE TO CELGENE DRUG SAFETY IMMEDIATELY BY FACSIMILE, OR OTHERAPPROPRIATE METHOD, WITHIN 24 HOURS OF THE INVESTIGATOR'S KNOWLEDGE OF THE EVENT USING THE SAE REPORT FORM, OR APPROVED EQUIVALENT FORM.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

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

7.9 Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: **drugsafety@celgene.com**

7.10 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33

provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows:

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive, Suite 700
Berkeley Heights, NJ 07922
Tel: (908) 673-9000

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

7.11 Report Of Adverse Events To The Institutional Review Board

The Principal Investigator is required to notify the Institutional Review Board (IRB) by facsimile using the serious adverse experiences CRF within 7 calendar days of observing or learning of a serious and unexpected adverse event. A mailed hard copy to the IRB (with a copy to the study monitor) must be submitted within 15 calendar days of observing or learning of the event. The written report should identify all safety reports previously filed with the IND concerning a similar adverse reaction and should analyze the significance of the adverse reaction in light of the previous, similar reports.

7.12 Investigator Reporting To The FDA

Adverse drug reactions that are **Serious, Unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators Brochure, or reference safety information documents should be reported promptly to the Food and Drug Administration (FDA) in writing by the Primary Investigator (PI) engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The PI must notify the FDA by telephone or fax of any unexpected, fatal or life threatening experience associated with the use of the drug as soon as possible but no later than 7 days of the sponsors initial receipt of the information.

7.13 Adverse Event Updates/Ind Safety Reports

Celgene shall notify the Primary Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Primary Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Primary Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file.

8 RESPONSE CRITERIA

Baseline tumor assessments must occur within ≤ 28 days of initiation of the study as indicated in Section 2, Schedule of Study Assessments.

Measurements of anti-myeloma efficacy will occur prior to the initiation of each cycle of lenalidomide. Myeloma response assessments will be based on the International Uniform Criteria. [52]

Patients with confirmed progressive disease will be eligible to cross over on to the vaccine arm based on clinical judgement, available response data, and the PI's discretion, or be removed from study treatment.

Research blood and marrow will be used to assess responses during the trial. This will likely include but are not limited to:

1. Tumor specific immunity
2. Assessment of myeloid derived suppressor cell (MDSC) numbers and function by flow cytometry and T cell proliferation assays.
3. Activation markers on T cells by flow cytometry
4. Clonogenic myeloma precursors by flow cytometry.
5. Minimal Residual Disease (MRD) testing

The major purpose of this study is to determine whether the addition of an allogeneic myeloma vaccine can augment clinical responses to Lenalidomide.

9 PROTOCOL AMENDMENTS/DEVIATIONS

9.1 Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Celgene. Amendments should only be submitted to IRB/EC after consideration of Celgene review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

9.2 Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be reported only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study treatment. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

10 DATA MANAGEMENT

10.1 Analyses and Reporting

Patients will be considered evaluable for safety and efficacy once they have initiated any study treatment (lenalidomide, vaccine and/or Prevnar vaccine).

Safety will be monitored continuously throughout the trial. Efficacy will be analyzed upon trial completion. No interim efficacy analyses are planned.

10.2 Study monitoring and Auditing

The protocol will be monitored internally by the Principal Investigator and externally via the SKCCC Compliance Monitoring Program which provides external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The Institution's Safety Monitoring Committee (SMC) Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

10.2.1 Investigator Responsibilities

The Primary Investigator's responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Study data will be entered onto a dedicated GVAX database. The Primary Investigator will permit study-related monitoring visits and audits by Celgene or its representatives, IRB/IEC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Primary Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, to resolve any queries and to allow direct

access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each monitoring visit and be made available to the Celgene representative so that the accuracy and completeness may be checked.

10.2.2 Data Safety Monitoring Board (DSMB)

The role of the DSMB will be to monitor the study for safety and toxicity issues regarding the combination of Lenalidomide with a cellular myeloma vaccine. Interim analysis of toxicity, outcome, and ongoing scientific investigations will be performed at least annually by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB Recommendation letter will state the timeline for the next required review. The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate.

11 BIOSTASTICAL ANALYSIS

11.1 Sample Size Considerations

The primary endpoint of this phase II study is progression free survival (PFS). The primary analysis will compare the control arm (lenalidomide plus placebo) versus the pooled allogenic myeloma vaccine arms (with and without Prevnar) In a prior study, the median PFS for patients on Len containing therapy was 17.9 months. Patients will be accrued over the course of 2 years with a minimum follow-up of 3 years (i.e. all patients will have 3-5 years of follow-up). A sample size of 54 patients (18 placebo vs 36 allogenic myeloma) would provide 80% power to detect an increase in the median PFS from 18 months in the control arm to 42.8 months in the pooled vaccine arm (HR = 0.4199) based upon a log-rank test assuming a two-sided type I error rate of 10% and a loss to follow- up rate of 1% per year (5% overall). The accrual rate is expected to be 2.3 per month. Due to the small sample size, no interim efficacy analysis is planned at this time.

Our principal secondary endpoints will be conversion from "near CR" (M-spike at or below 0 but IFE positive), to "true CR" (IFE negative), and conversion from MRD positive status to MRD negative status. The trial will accrue patients for a total n=18 per arm at single center for a period two years, while trial duration for every patient enrolled will be 3 years. The analysis will be performed on the intention to treat population.

11.2 Statistical Analyses

The efficacy and safety analysis populations will include all patients that received at least one dose of their assigned treatment. The primary analyses will compare the control arm with the pooled vaccine arm. Secondary analyses will compare the two vaccine arms to one another and to the control arm.

Demographic and disease characteristics will be summarized overall and within each treatment group using medians and ranges for continuous variables and counts and proportions for categorical variables.

The primary outcome (PFS) is defined as the time from randomization until progression or death. Individuals who do not have an event will be censored at the date of last assessment. Kaplan-Meier estimates of the survival function will be used to compare the two treatment groups graphically as well as to provide estimates of the median PFS and the proportion who have progressed at key time points (e.g. 1-, 2-, and 3-years) with 90% confidence intervals. Log-rank tests will be used to compare the treatment groups and Cox proportional hazards models will be used to examine the effects of specific risk factors of interest and their interaction with treatment (e.g. vaccine by MRD status interactions). If the proportional hazards assumption is violated, the piecewise proportional hazards models or other semi-nonparametric approaches will be used. Key secondary endpoints include conversion from “near CR” (M-spike at or below 0 but IFE positive), to “true CR” (IFE negative), and conversion from MRD positive status to MRD negative status. These and other time to event outcomes including will be analyzed in a similar manner to the primary outcome as well as with competing risk models to account for death or progression.

Tumor immunology assessments will be made at baseline and on day 14 of cycles 3, 6, and 12 (the 1-year assessment). At each time point, graphical (e.g. boxplots over time, spaghetti plots) and numeric (e.g. median, range, proportion) summaries will be used to explore the continuous (e.g. T cell populations) and binary (e.g. tumor specific immunity) outcomes. If appropriate, transformations (e.g. log) will be used to address skewness in the data. Cross-sectional comparisons will be made using t-tests, Kruskal-Wallis tests, or linear regression and Chi-squared tests, Fisher’s exact test, or logistic regression for continuous and categorical outcomes, respectively. Generalized estimating equations and mixed effects models will be used to formally model the behavior over time and compare treatment groups and/or risk factors while adjusting for repeated measurements within each individual. The association between baseline tumor measuarement as well as changes in tumor measurements over time and clinical outcomes will be assessed using Cox proportional hazards models.

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse events. All toxicities will be summarized overall, by treatment group, and within subgroups of interest (e.g. true CR status, MM type). The number of toxicities and number of affected patients will be tabulated by type, grade, and relatedness to study treatment (overall and for each treatment). In addition to counts and proportions, the toxicity rates will be modeled and compared between treatment groups and subgroups of interest using Poisson regression or Negative Binomial regression, as appropriate.

11.3 Toxicity Stopping Guidelines:

The proportion of unacceptable toxicities will be continuously monitored in each arm separately. Unacceptable toxicities include hematologic toxicities of lenalidomide: low neutrophils (ANC <1000) and low platelets (<50K), for which we would hold the vaccine administration, as well as vaccine related toxicities which include: grade 3/4 local reactions (erythema, swelling, pain) and systemic symptoms (fevers, rash) (Refer to **7.6.1** and **7.6.2** for guidelines on attribution of toxicities).

Unacceptable toxicities as scored using **NCI CTCAE V5.0** include:

- Any laboratory or clinical organ dysfunction ≥ Grade 3
- Abnormalities of coagulation (prolonged prothrombin, partial thromboplastin and clotting times ≥ Grade 3
- Autoimmune disease reactivation or development ≥ Grade 2
- Immune system disorders including myalgias or headaches ≥ Grade 3
- Immune system disorders including allergic or hypersensitivity reactions such as rash, or fever ≥ Grade 3
- Immune system disorders including anaphylaxis or anaphylactoid reactions (eg. Wheezing, urticarial, hypotension) ≥ Grade 3
- General disorders and administration site conditions including injection site reactions such as tenderness with or without associated symptoms (e.g., warmth, erythema, itching, and malaise) ≥ Grade 3
- Any other undefined or unanticipate adverse event ≥ Grade 3
- Any death on study

If the levels of uacceptable toxicitiy is too high (i.e. a high probability that they exceed the maximum threshold of 30%), then enrollment will be suspended pending review by the PI, DSMB, and Celgene. Any death on study within 30 days of GVAX administration will lead to suspension of enrollment pending review by the PI, DSMB, and Celgene.

A Bayesian stopping guideline will be used to assess the level of unacceptable toxicity. We expect the rate of unacceptable toxicities to be 25%. Hence a Beta(1, 3) prior was used. After the first three patients are recruited, toxicity will be monitored continuously. Accrual will be suspended if the probability that the unacceptable toxicity rate exceeds 30% is 0.70 or higher. Table 11.1 shows the number of toxicities needed to halt accrual.

Table 11.1. The number of toxicities needed to trigger stopping guidelines throughout the course of the study.

Number of Subjects Per Treatment Arm	Number of toxicities needed to trigger re-evaluation
3-4	3
5-7	4
8-10	5
11-13	6
14-16	7
17-18	8

The operating characteristics of these stopping guidelines were generated based upon 5000 simulations (Table 11.1).

Table 11.2. Probability of triggering stopping guidelines based upon range of underlying toxicity rates.

True Toxicity (DLT) Risk	Prob. Declare Treatment Too Toxic	Avg. Sample Size
0.05	<0.1%	18.0
0.10	0.4%	18.0
0.15	2.7%	17.7
0.20	7.6%	17.2
0.25	15.2%	16.5
0.30	27.7%	15.4
0.35	44.0%	13.8
0.40	59.5%	12.3
0.45	74.2%	10.7

12 REGULATORY CONSIDERATIONS

121 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional ReviewBoards.

The Primary Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

122 Informed consent

The Primary Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

123 Subject confidentiality

The Primary Investigator and Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Primary Investigator to permit Celgene's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Primary Investigator to obtain such permission in writing from the appropriate individual.

124 Study records requirements

The Primary Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug be retained for as long as needed to comply with national, international and site specific regulations (generally 2 years after discontinuing clinical development or last marketing approval. This applies to copies of CRFs and source documents including but not limited to hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; and original signed informed consents. The Investigator agrees to adhere to the document/records retention procedures by signing theprotocol.

125 Premature discontinuation of study

The Primary Investigator as well as Celgene have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.

- Falsification of records.
- Failure to adhere to the study protocol.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

13 RESPONSIBILITIES

13.1 Primary Investigator

The Primary Investgator is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Taking responsibility for the overall conduct of the study, andand for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)

14 PATIENTS WITH PROGRESSIVE DISEASE ON THE CONTROL ARM

Patients on the placebo control arm without GVAX vaccine with evidence of progressive disease by criteria defined in this protocol, who were in CR (defined as no measurable M-spike, immunofixation negative and bone marrow plasma cells <5%) but no longer meet the criteria for CR, or patients who were in nCR (no measurable M-spike, and a positive serum immunofixation) who develop measurable M-protein or free light chains in the serum or urine, or patients who were MRD negative who subsequently become MRD positive, can be evaluated, and potentially considered for roll over to the vaccine arm, provided they meet criteria for enrollment, and at the clinical discretion of the PI.

APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS SCALE

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

For list of Treatment Assignment Stratification prognostic indicators, see Appendix IV.

APPENDIX 2: TUMOR CLASSIFICATION

Diagnostic Criteria for Multiple Myeloma

Major Criteria

1. Plasmacytomas on tissue biopsy
2. Bone marrow plasmacytosis (> 30% plasma cells)
3. Monoclonal immunoglobulin spike on serum electrophoresis IgG > 3.5 g/dL or IgA> 2.0 g/dL; kappa or lambda light chain excretion > 1 g/day on 24 hour urine protein electrophoresis.

Minor criteria:

1. Bone marrow plasmacytosis (10 to 30% plasma cells)
2. Monoclonal immunoglobulin present but of lesser magnitude than given under major criteria
3. Lytic bone lesions
4. Normal IgM<50 mg/dL, IgA<100 mg/dL or IgG<600 mg/dL

Any of the following sets of criteria will confirm the diagnosis of multiple myeloma:

- Any two of the major criteria
- Major criterion 1 plus minor criterion b, c, or d

- Major criterion 3 plus minor criterion a or c
- Minor criterion a, b and c or a, b and d

International Staging System for Multiple Myeloma
Stage I
- Albumin ≥3.5 g/dl AND
- Beta-2-microglobulin <3.5 mg/L

Stage II
Neither stage I nor stage III

Stage III
- Beta-2-microglobulin >5.5 mg/L

Durie-Salmon Staging of Multiple Myeloma
Stage I
All of the following must be present:
- Hemoglobin > 10.5 g/dL or hematocrit>32%
- Serum calcium level normal
- Low serum myeloma protein production rates as evidenced by all of the following:
  - IgG peak < 5g/dL
  - IgA peak < 3g/dL
  - Bence Jones protein < 4g/24 h
- No bone lesions

Stage II
All patients who do not meet criteria for Stage I or III are considered Stage II.

Stage III
One of the following abnormalities must be present:
- Hemoglobin < 8.5 g/dL, hematocrit< 25%
- Serum calcium >12 mg/dL
- Very high serum or urine myeloma protein production rates as evidenced byone or more of the following:
  - IgG peak > 7g/dL
  - IgA peak > 5g/dL
  - Bence Jones protein > 12g/24 h
  - > 3 lytic bone lesion on bone survey (bone scan not acceptable)

Subclassification
A: Serum creatinine< 2.0 mg/dL
B: Serum creatinine>2.0 mg/dL

APPENDIX 3: CRITERIA FOR DISEASE EVALUATION

The serum and urine M-protein levels obtained at baseline will be used as the reference baseline for calculation of increases or decreases in the M-protein level. The M-protein levels from the time of diagnosis will also be obtained, and response calculations using that value as baseline will also be performed in secondary analyses.

Definitions of Response

Responses will be defined as per the modified International Uniform Response Criteria for myeloma.[52]

Response sub category	Response criteria[a]
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow[b]
nCR	Serum and urine M-protein undetectable. Immunofixation positive.
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 h.
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200mg per 24 h. If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, X50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
SD[e]	Not meeting criteria for CR, VGPR, PR or progressive disease
PD	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: • Serum M-protein (absolute increase must be ≥0.5 g/dL) • Serum M-protein increase ≥1 g/dL, if the lowest Mcomponent was ≥5 g/dL • Urine M-protein (absolute increase must be ≥200 mg/24h)

	• In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%) • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease
Relapse from CR	Any of the following criteria: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the bone marrow Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)
Relapse from MRD-negative CR	Any one or more of the following criteria: • Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma) • Reappearance of serum or urine M-protein by immuno xation or electrophoresis Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response; PD, progressive disease; MRD, minimal residual disease.

a. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
b. Confirmation with repeat bone marrow biopsy not needed.
c. Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 44:1 or 1:2.
d. Refer to “Practical details of response evaluation” for definitions of measurable disease.
e. SD is not recommended for use as an indicator of disease.

Practical details of response evaluation

Definitions of measurable disease

Response criteria for all categories and subcategories of response except CR are applicable only to patients who have 'measurable' disease defined by at least one of the following three measurements:

1. Serum M-protein ≥1 g/dl (≥10 gm/l)[10 g/l]
2. Urine M-protein ≥200 mg/24 h
3. Serum FLC assay: Involved FLC level ≥10 mg/dl (≥100 mg/l) provided serum FLC ratio is abnormal

APPENDIX 4: NCI CTC VERSION 4.03

Toxicity will be scored using NCI CTC Version 4.03 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.03 can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4.0.

APPENDIX 5: RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from

heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.

- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give lenalidomide to anotherperson.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation oflenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.

APPENDIX 6: SKCCC DATA SAFETY MONITORING PLAN

https://oassrv3.onc.jhmi.edu/cro/pageData/SKCCC%20Data%20and%20Safety%20Monitoring%20Plan.Posted%202019.03.25.pdf

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