MC038C

Mayo Clinic Cancer Center

Phase I/II Trial of Systemic Administration of Edmonston Strain of Measles Virus, Genetically Engineered to Express NIS, with or without Cyclophosphamide, in Patients with Recurrent or Refractory Multiple Myeloma

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Document History	(Effective Date)	Document History	(Effective Date)
Activation	January 15, 2007	MCCC Addendum 12	May 9, 2013
MCCC Addendum 1	March 21, 2007	MCCC Addendum 13	August 5, 2013
MCCC Addendum 2	March 21, 2007	MCCC Addendum 14	December 26, 2013
MCCC Addendum 3	August 21, 2007	MCCC Addendum 15	January 31, 2014
MCCC Addendum 4	December 18, 2007	MCCC Addendum 16	August 13, 2014
MCCC Addendum 5	February 4, 2008	MCCC Addendum 17	September 2, 2014
MCCC Addendum 6	September 22, 2008	MCCC Addendum 18	September 30, 2014
MCCC Addendum 7	December 7, 2009	MCCC Addendum 19	November 10, 2014
MCCC Addendum 8	April 20, 2010	MCCC Addendum 20	February 5, 2015
MCCC Addendum 9	July 27, 2010	MCCC Addendum 21	June 4, 2015
MCCC Addendum 10	October 13, 2011	MCCC Addendum 22	February 4, 2016
MCCC Addendum 11	October 2, 2012	MCCC Amendment 23	January 20, 2017

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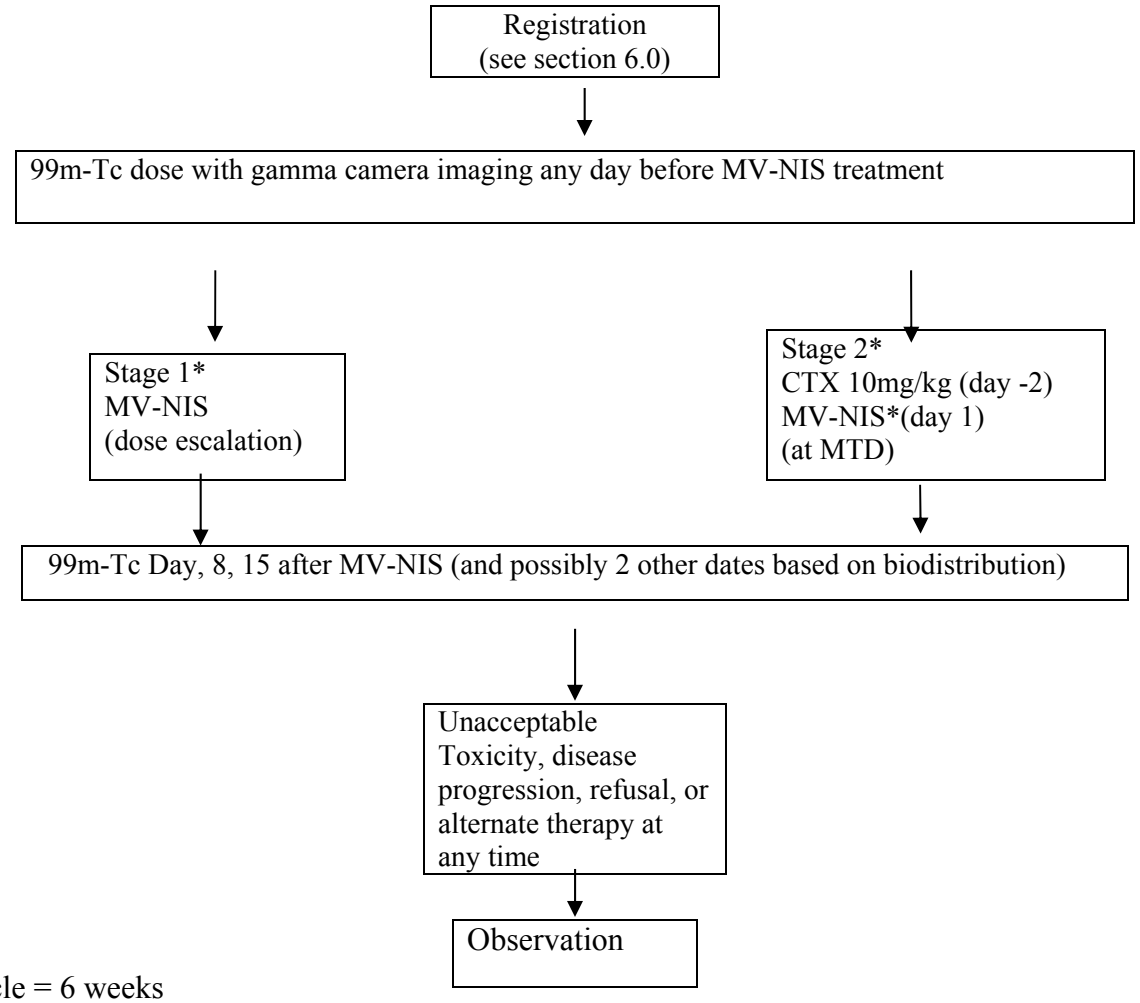
Phase I Schema

<u>Prior to discussing protocol entry with the patient</u>, call the Mayo Clinic Cancer Center Registration Office (507-284-2753) to confirm study status and insure that a place on the protocol is currently available to the patient.



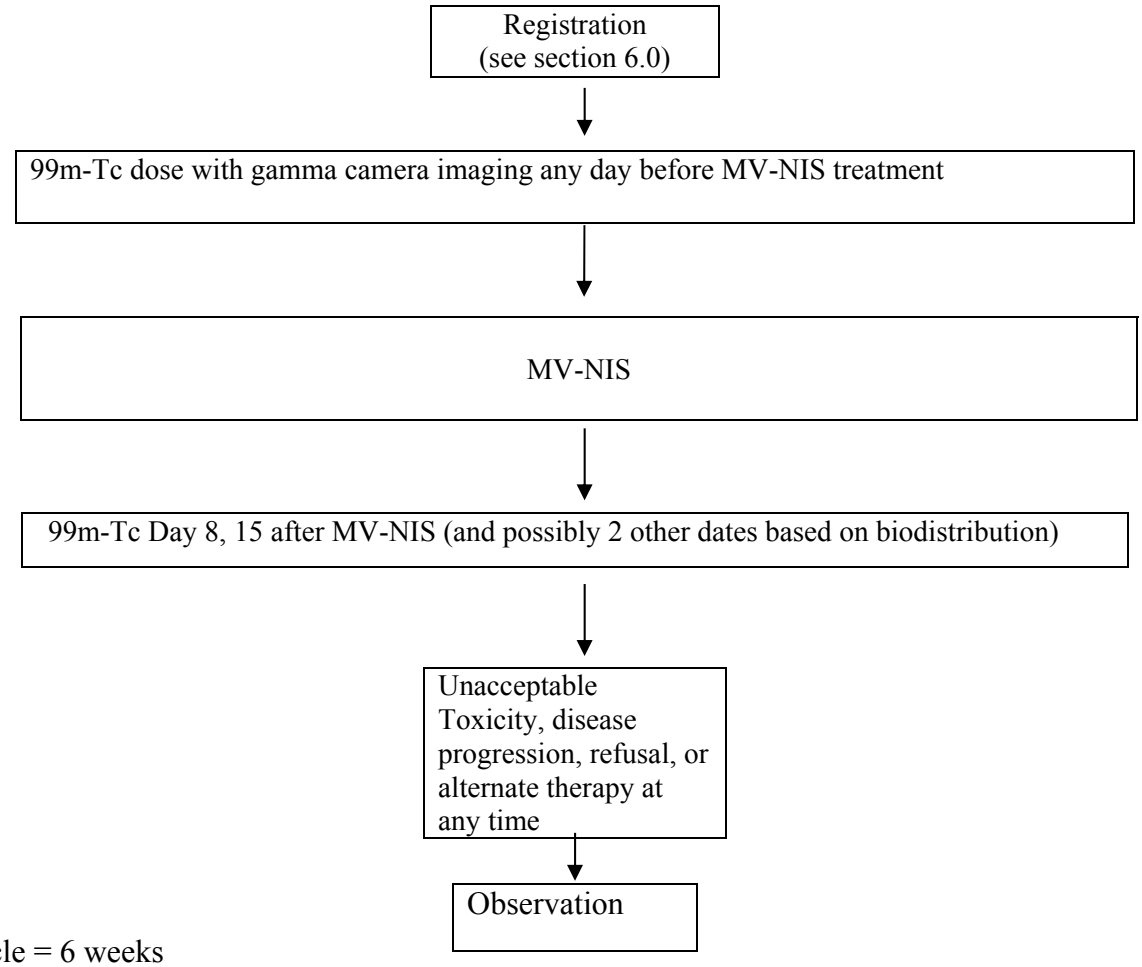
Cycle = 6 weeks

* Stage 1 (MV-NIS alone) will be evaluated first; once MTD of stage 1 is determined, subsequent patients will be accrued to Stage 2 (cyclophosphamide + MV-NIS); see Section 7.0.**-STAGE 1 CLOSED TO ACCRUAL ON DECEMBER 17, 2009. STAGE 2 TEMPORARILY CLOSED ON October 13, 2011, AND STAGE 1 RE-OPENED FOR 2 MORE DOSE LEVELS and Phase II expansion**

Mayo Drug Names/Abbreviations

Generic name: MV-NIS (recombinant Edmonston measles virus carrying the human NIS gene) Mayo abbreviation: MV-NIS	Generic:Cyclophosphamide Brand name(s) Cytoxan® Mayo abbreviation: CTX	Generic Technetium 99m Mayo Abbreviation: 99m-Tc

Phase II Schema



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1.0 Background

1.1 Introduction

MV-NIS is an attenuated measles virus, engineered to express the human thyroidal sodium-iodide symporter (NIS). The virus is selectively oncolytic, targeting and destroying tumor cells through CD46, a membrane regulator of complement activation that is known to be overexpressed on many human malignancies. CD46 is the cellular receptor for MV-NIS, mediating both virus entry and subsequent cell killing through cell-cell fusion. The cytopathic effect of MV-NIS increases exponentially as the density of CD46 receptors on target cells increases and is therefore dramatic at high CD46 receptor densities (tumor) but minimal at low densities (normal tissues). NIS expression in MV-NIS infected cells permits noninvasive monitoring of virus spread by serial gamma camera imaging of radioiodine uptake. In addition, the anti-neoplastic activity of the virus can be amplified by administering I-131, a potently ionizing beta emitting isotope of radioiodine. Multiple myeloma is an incurable malignancy of terminally differentiated plasma cells that is widely disseminated at diagnosis. Myeloma plasma cells over-express CD46 and are therefore highly susceptible to MV-NIS. Also, systemic virus administration is feasible in advanced myeloma since these patients have greatly reduced circulating titers of anti-measles antibodies. MV-NIS demonstrated considerable oncolytic potency when administered intravenously to rodents bearing human myeloma xenografts. Also, intratumoral spread of the virus could be monitored non-invasively by radioiodine imaging and the anti-neoplastic potency of the virus was significantly boosted by I-131. We therefore propose to conduct a phase I clinical trial to evaluate the safety of MV-NIS administered intravenously to patients with advanced treatment-refractory multiple myeloma, to determine the maximum tolerated dose by this route, to perform pharmacokinetic studies to determine the location of virus-infected cells, the time course of viral gene expression, the evolution of the immune response and its impact on the virus, and to obtain preliminary evidence for anti-myeloma activity in human subjects. Our overall hypothesis is that *MV-NIS administered intravenously to patients with advanced multiple myeloma will selectively propagate in myeloma deposits throughout the body, leading to tumor cell killing and reduction of tumor burden*. This hypothesis will be tested by serial gamma camera imaging of radioiodine uptake after MV-NIS therapy to monitor the changing number and location of virus-infected cells.

1.2 MV-NIS: Description

MV-NIS is a live tissue culture adapted measles virus engineered to express the human thyroidal sodium iodide symporter (NIS). The virus propagates selectively in human cancer cells, leading directly to tumor cell killing. MV-NIS-infected tumor cells express NIS, a membrane ion channel that actively transports iodide ions into the cell. Radioiodine uptake by cells expressing NIS provides a basis for *in vivo* radioiodine imaging studies to reveal the profile of MV-NIS gene expression and the location of MV-NIS-infected cells during virus spread and elimination. MV-NIS was constructed by inserting the NIS gene into a full-length infectious molecular clone of an attenuated Edmonston lineage measles virus (MV-tag) and propagates on Vero cells with kinetics equivalent to the parental strain.

1.21 MV-NIS: Mechanism of tumor targeting

MV-NIS is selectively oncolytic, targeting and destroying tumor cells through CD46, a membrane regulator of complement activation, that is typically over-expressed on human malignancies [1-3]. CD46 is the major cellular receptor for MV-NIS, mediating virus attachment entry and subsequent cell killing through cell-cell fusion [4]. The CD46 tropism of attenuated Edmonston lineage measles viruses was acquired during tissue culture adaptation [5] and distinguishes them from wild-type measles viruses, which enter cells primarily through an alternative receptor, SLAM, expressed on activated T cells, B cells and monocytes [6]. MV-NIS has dual tropism for both SLAM and CD46.

The cytopathic effect of MV-NIS increases exponentially as the density of CD46 receptors on target cells increases. Killing is therefore minimal at the lower CD46 receptor densities that typify normal tissues whereas it is dramatic at higher CD46 receptor densities associated with the neoplastic phenotype. CD46 regulates complement activation by acting as a co-factor for factor I-mediated cleavage of C3b and thereby protects the cells on which it is expressed from complement-mediated lysis [1, 2]. Numerous studies have demonstrated that CD46 is expressed at higher levels on human tumors of many different lineages than on their non-transformed counterparts [1, 3]. Thus, MV-NIS is a new class of antineoplastic agent that targets a widely expressed tumor phenotype; namely, a high membrane expression of CD46.

1.22 MV-NIS: Radioiodine uptake

NIS is an intrinsic membrane protein of 643 amino acids that spans the plasma membrane 13 times with three potential sites for N-linked glycosylation. NIS is a symporter that imports two sodium ions with every iodide ion transported into the cell. NIS expression in thyroid follicular cells has been exploited for more than 50 years in clinical practice for thyroid imaging (with ^{123}I or Tc99m) or ablation (with ^{131}I) and for systemic therapy of well-differentiated thyroid malignancies [7, 8]. It has recently been shown that radioiodine is efficiently trapped by experimental tumors transduced with a NIS gene [9-15]. Non-invasive assessment of NIS gene expression can then be achieved through γ-camera imaging of ^{123}I uptake, and tumor ablation can be achieved by administration of ^{131}I as a source of ionizing radiation. The local bystander killing potential of NIS gene therapy is considerable because the average tissue path-length of the β particles emitted by ^{131}I is approximately 6 cell diameters [16]. Tumor cell lines and primary tumor cells infected with MV-NIS show efficient uptake of radioiodine that can be inhibited by perchlorate, a specific inhibitor of NIS. Moreover, *in vivo* uptake of radioiodine by MV-NIS-infected tumor xenografts is readily detected by ^{123}I γ-camera imaging.

1.3 Multiple myeloma: Need for alternative therapies

Multiple myeloma is a disseminated malignancy of antibody-secreting plasma cells [17]. The neoplastic cells preside predominantly in bone and bone marrow where they secrete a monoclonal immunoglobulin and proliferate to form discrete, well-vascularized tumors (myelomas) that strongly stimulate osteoclastic bone resorption. The monoclonal immunoglobulin provides a convenient serum or urine marker for disease monitoring, but can also cause significant clinical pathology including renal failure, hyperviscosity and tissue amyloid deposition. Other classic disease manifestations are bone pain,

hypercalcemia, pathological fractures, anemia and recurrent infections due to profound suppression of humoral immunity.

Multiple myeloma is not curable with current therapy and was expected to cause 10,800 deaths in the USA in 2002 [18]. Median survival is approximately four years and new approaches to therapy are urgently required. The disease responds initially to alkylating agents (melphalan, cyclophosphamide) and corticosteroids (prednisolone, dexamethasone), but eventually becomes refractory. High dose (myeloablative) melphalan therapy following by autologous stem cell transplantation leads to better remissions but does not greatly prolong survival [19-21]. Thalidomide and the proteosome inhibitor, PS341, have activity against myeloma but have not yet been shown to impact survival [22, 23]. Supportive therapy includes analgesia for pain, regular blood transfusions or erythropoietin therapy for anemia, bisphosphonates to inhibit osteoclastic bone resorption and antibiotics or intravenous immunoglobulins for infections.

1.4 Safety of measles vaccine in myeloma patients despite suppression of humoral immunity

Multiple myeloma is unique amongst human malignancies in that because of the associated suppression of humoral immunity, systemic administration of a therapeutic virus is feasible, even if previous virus exposure has occurred. Successful deployment of oncolytic viruses for the treatment of disseminated malignancy requires efficient delivery to tumor sites via the bloodstream, which can be inhibited by antiviral antibodies [24]. Oncolytic virotherapy is therefore less likely to be effective when there is preexisting antiviral immunity. Multiple myeloma is characterized by profound suppression of humoral immune responses with hypogammaglobulinemia, typically affecting IgG, IgA and IgM fractions [25-27]. Antibody titers against common vaccine antigens (e.g., measles, mumps, rubella, diphtheria and tetanus) are greatly reduced [28, 29], and immune responses following vaccination are considerably impaired [27, 30]. We tested stored serum samples from patients with heavily pretreated myeloma and age-matched controls for anti-measles virus antibody titer and found, in keeping with published observations, that sera obtained from myeloma patients often contained very low levels of anti-measles antibody.

The measles-mumps-rubella (MMR II) vaccine (Merck) delivers 10^3 to 10^4 infectious units of live attenuated measles virus to each human recipient. Patients who undergo autologous or allogeneic stem cell transplantation lose immune memory for past exposure to infectious agents and vaccines and therefore require a re-vaccination strategy which typically includes live-attenuated measles-mumps-rubella vaccine at 24 months post-transplant. We retrospectively studied multiple myeloma (MM) patients who received both their transplant and routine 2 year post-auto SCT vaccination with MMR II at Mayo Clinic. Thirty-six patients (M:F – 23:13) who received an autologous stem cell transplantation (auto SCT) and also received routine 2 year post-SCT MMR II vaccination at Mayo Clinic were identified. MMR II re-vaccination was delivered an average of 799 days (range: 539 - 1209) days after SCT. Follow-up time after re-vaccination averaged 755 days (range: 56 - 2345). Thirty-three of the 36 patients studied, remain alive. Most of these patients have experienced disease relapse requiring treatment. Eleven patients continue under observation without treatment since their original SCT. Overall, there was no significant change after re-vaccination in the patients' absolute lymphocyte counts or immunoglobulin levels, nor was there significant change in the monoclonal protein levels. No specific toxicities were documented following MMR administration. While 5 patients did have a small decrease in monoclonal protein level,

averaging only 0.42g/dL (range: 0.1- 1.2) after re-vaccination, only 2 of the 5 patients were remote from the influence of treatment effect for relapsed disease at the time. One of these 5 patients continues to live relapse free without treatment and with a stable monoclonal protein. These data strongly suggests that conventional doses of MMR vaccine administered by intramuscular injection are safe, but inadequate for expression of oncolytic activity in patients with multiple myeloma.

Although MV-NIS has not previously been administered to humans, there is a vast knowledge base concerning the toxic effects of closely related viruses in the human population. Thus wild-type MV causes a well-described illness characterized by fever, rash, upper respiratory tract symptoms and transient immunosuppression [32]. The case fatality rate in the United States of America is 0.1 to 0.2 %, but is higher in underdeveloped countries where opportunistic infections secondary to MV immunosuppression are a more significant problem. At the other end of the spectrum, live attenuated MV vaccines have been used extensively. In the USA alone, more than 550 million doses of MV vaccine have been distributed to date. Several different members of the Edmonston virus lineage have been used for vaccination, and all of them are capable of causing a mild measles-like illness in some variable percentage of vaccinees [33-34, 39] It is therefore anticipated that some MV-NIS-treated patients may develop a measles-like illness. However, in the entire history of measles vaccination, no case of reversion of vaccine strain to wild-type measles has been documented, and only 6 deaths have been reported due to uncontrolled spread of the vaccine strain virus in severely immunocompromised individuals. In contrast to their effects in non-immune subjects, neither wild-type nor attenuated measles viruses cause a measles-like illness in patients previously exposed to the virus [41].

1.5 Multiple myeloma: Susceptibility to MV-NIS

Neoplastic plasma cells from multiple myeloma patients express high levels of CD46 and are fully susceptible to infection by MV-NIS. Myeloma cells over-express CD46 compared to normal marrow elements and unstimulated peripheral blood lymphocytes. CD138+ myeloma cells from 5 patient bone marrow aspirates were infected with MV-NIS, and radioiodine uptake was measured 48 hours later. In addition to the classical measles virus cytopathic effect of cell-cell fusion, the infected cells were shown to efficiently concentrate radioiodine achieving intracellular concentrations 50-fold higher than that of the incubation medium.

Multiple myeloma cells are selectively infected and killed by attenuated measles viruses of the Edmonston vaccine lineage. A recombinant measles virus expressing a fluorescent GFP marker protein could efficiently fuse and kill multiple myeloma cells but not non-transformed cells [31].

Intravenous MV-NIS (or MV-Edm) is a potent oncolytic agent in multiple myeloma xenograft models. Multiple myeloma cells (ARH77, RPMI8226, KAS 6/1, MM1) were implanted subcutaneously into the flanks of athymic or SCID mice and the mice were treated intravenously with MV-NIS or MV-Edm (identical sequence to MV-NIS but lacking the NIS gene). Intravenous administration of MV-Edm caused complete regression of ARH77 xenografts and significantly slowed the progression of RPMI8226 xenograft growth. Moreover, a single intravenous dose of MV-NIS led to complete regression of large (0.5 mm diameter) KAS 6/1 xenografts.

1.51 Therapy models: Noninvasive imaging of MV-NIS

Intratumoral spread of MV-NIS could be non-invasively evaluated by serial γ-camera imaging in 3 myeloma xenograft models. SCID mice bearing subcutaneous ARH77, KAS 6/1 or MM1 myeloma xenografts were injected intravenously with a single dose of MV-Edm or MV-NIS (2×10^6 IU). Three, 9 and 17 days later, ^{123}I (18.5 MBq) was administered and γ-camera imaging performed after 1 hour. All tumors treated with the control virus MV-Edm were negative by γ-photon imaging, whereas all MV-NIS treated tumors were able to concentrate radioiodine and could be visualized by γ-camera imaging. Analysis of the changing image intensity over the period of 17 days established that NIS expression peaks approximately 9 days after virus injection, presumably reflecting the maximum extent of the virus infection.

1.52 Therapy models: Radiovirotherapy

The oncolytic activity of MV-NIS is greatly enhanced by subsequent administration of ^{131}I (radiovirotherapy). To determine whether the oncolytic effect of MV-NIS could be enhanced or accelerated by high energy electron therapy resulting from intratumoral ^{131}I decay, we examined KAS 6/1 and MM1 models. The MM1 model had been previously shown to be resistant to single agent MV-NIS therapy. KAS 6/1 tumor regression was significantly accelerated when mice were treated with ^{131}I (37 MBq) administered 6 days after intravenous MV-NIS. Moreover, MM1 xenografts, which were resistant to single agent therapy with MV-Edm, MV-NIS or ^{131}I, were shown to regress completely when ^{131}I was administered 9 days after intravenous MV-NIS.

1.6 Modulating the Anti-Measles Immune Response

MV-CEA is an oncolytic measles virus expressing a soluble marker peptide (the extracellular domain of CEA) which facilitates noninvasive monitoring of viral gene expression. When MV-CEA was administered intraperitoneally to naïve measles-susceptible (CD46 transgenic IFN receptor knockout) mice, plasma CEA expression peaked after 3 days and disappeared by day 8. However, no plasma CEA was detected in mice previously vaccinated with MV-Edmonston and challenged at a later date with the same dose of MV-CEA. We therefore examined the profiles of CEA expression, anti-measles antibody responses, and susceptibility to second virus challenge in mice that received immunosuppressive cyclophosphamide therapy prior to intraperitoneal injection of 10^7 IU of MV-CEA. Cyclophosphamide treatment (250 mg/kg IP 4 hours before MV-CEA) prolonged the CEA expression profile from 8 days to 29 days, reduced the anti-measles antibody titers (measured on day 36) and resulted in significant levels of CEA gene expression 3 days post-MV-CEA rechallenge (without additional cyclophosphamide day 53).

1.7 Pre-Clinical Data: MV-NIS toxicity and biodistribution studies

1.71 Biodistribution in CD46 transgenic, interferon α/β receptor knockout mice

As part of preclinical studies to evaluate MV-NIS, we developed sensitive quantitative RT-PCR methodology in order to characterize tissue distribution of the virus in non-tumor bearing transgenic Ifnar^{KO} x CD46 Ge mice that express human CD46 with human-like tissue distribution. Groups of male and female

mice (10 mice/gender/treatment group) were given I.V. doses of vehicle or MV-NIS, 10^5 $TCID_{50}$, 10^7 $TCID_{50}$ or 10^7 $TCID_{50}$ + 125 mg/kg cytoxan. MV-NIS tissue distribution was studied non-invasively by Micro-SPECT CT imaging 4, 21 and 90 days after a dose of 0.5 mCi I- 123. MV-NIS expression in tissues was measured 2, 5, 22 and 91 days after treatment (5 mice/gender/treatment group) by quantitative RT-PCR. ***Imaging studies showed that functional NIS was not detected in tissues other than those with normal expression after administration of MV-NIS.*** Highest concentrations of MV-NIS (> 10,000 MV-N RNA copies/ µg total RNA) appeared in lung, liver, spleen and blood of both male and female mice 2 days after administration of 10^7 TCID50 +/- cyclophosphamide. ***Cyclophosphamide did not delay clearance of MV-NIS from tissues.*** Blood concentrations remained high on day 5, and fell to undetectable levels in blood on day 91. Lung and liver concentrations fell to undetectable levels by day 91. Spleen concentrations were substantially lower on day 5 and day 22, and detectable in only 5 of 24 mice given high dose MV-NIS +/- cyclophosphamide on day 91. Of note, 277 – 44093 (median, 440) copies MV-NIS/ µg total RNA were detected in brain in 3/10 mice on day 2, 2/10 mice on day 5, 3 of 10 mice on day 22, and 3 of 16 mice on day 91. The positive samples were detected only in mice treated with 10^7 MV-NIS + cyclophosphamide.

1.72 Toxicity of MV-NIS in CD46 transgenic, interferon α/β receptor knockout mice

According to the protocol 144 $Ifnar^{KO}$ x CD46 Ge mice (12/sex/dose group), approximately 6 to 8 weeks old on the first day of dosing were randomly divided into 6 dose groups and treated with one or both of the test articles (MV-NIS: Measles virus, Edmonston lineage [NSC-731414] for Groups 3, 4, 5 and 6 and cyclophosphamide [NDC# 0015-0547-41] for Groups 2 and 6) or the control article (MV-NIS vehicle [5% sucrose, 50 mM Tris-HCl, pH 7.4, 2mM $MgCl_2$] diluted as per Test Article) via an intravenous injection via the tail vein. Cyclophosphamide was at 125mg/kg given 2 days prior (Day -2) to MV-NIS in order to modulate the immune response to MV-NIS. Cyclophosphamide and MV-NIS were given as a single intravenous bolus injection through the tail vein. On study days 2, 5, 22, and 91 six mice/dose group were euthanized and a complete necropsy examination was performed by PAI personnel as described in the protocol. Protocol-specified tissues were preserved in 10% neutral-buffered formalin (NBF) and sent to PAI's Frederick, MD facility, which conducted the remainder of the analysis on those samples.

Dose Group	Day-2	Day 0	Day 2		Day 5		Day 22		Day 91		Total No. Mice
	Cyclophos-phamide (mg/kg)	MV-NIS ($TCID_{50}$)	M	F	M	F	M	F	M	F	
1	0	0*	3	3	3	3	3	3	3	3	12M/12F
2	125	0*	3	3	3	3	3	3	3	3	12M/12F
3	0	10^4	3	3	3	3	3	3	3	3	12M/12F
4	0	10^5	3	3	3	3	3	3	3	3	12M/12F
5	0	10^6	3	3	3	3	3	3	3	3	12M/12F
6	125	10^6	3	3	3	3	3	3	3	3	12M/12F

*MV-NIS Vehicle

Mayo Clinic Toxicology Core ran the in-life portion of the studies, including monitoring clinical signs and weights daily the first week post article administration, and weekly thereafter. At time of necropsy, final weights were taken, and mice were bled from the retroorbital plexus. Blood parameters analyzed included: hematology (white blood cell count, lymphocyte percent, monocyte percent, granulocyte percent, red blood cell count, mean corpuscular volume, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, hemoglobin, platelet count, mean platelet volume, and platelet distribution width); clinical chemistry (albumin, alkaline phosphatase, alanine aminotransferase, amylase, total bilirubin, blood urea nitrogen, calcium, phosphorus, creatinine, glucose, sodium, potassium, total protein, and globulin); and coagulation (prothrombin time and activated partial thromboplastin time). Plasma was also collected for anti-measles antibody titers. The in-life portion of the study started March 7th, 2005 and ended June 8th, 2005. ***There were no clinical signs or deaths considered to be related to the test articles MV-NIS or cyclophosphamide***. Body weights showed no signs of MV-NIS toxicity. ***Mice from Groups 4 and 5 developed robust anti-measles virus titers at the later time points of days 22 and 91 post-virus administration.*** In contrast, the lowest dose of virus ($1x10^4$ $TCID_{50}$) in Group 3 mice induced poor to non-detectable titers post single administration, indicating that greater than $1x10^4$ $TCID_{50}$ of MV-NIS is needed intravenously for the mice to mount and effective antibody response.

In Groups 1, 3, 4, and 5, there were no toxicologic findings in the hematology or coagulation that were considered to be related to the administration of MV-NIS. In clinical chemistry, there were sporadic mild elevations in ALT in 3 virus treated mice that were not correlated with any pathological changes in the liver. Total protein levels were mildly elevated in Groups 3, 4, and 5 as compared to control Group 1. This rise in total protein and/or globulin in virus-treated groups is likely due to the production of anti-measles immunoglobulin. Groups 4 and 5 BUN levels were mildly decreased as compared to control Group 1, but were not accompanied by any pathologic changes in the kidneys. These changes were considered related to the administration of MV-NIS, but not of significant toxicity.

In Groups 2 and 6, there were no toxicologic findings in coagulation that were considered to be related to the administration of MV-NIS. In hematology, the total WBC in Group 6 was depressed as compared to Group 2, suggesting that the additional challenge of MV-NIS to mice pre-treated with cyclophosphamide further suppressed the WBC. In clinical chemistry, there were sporadic mild elevations of creatinine considered to be related to the administration of MV-NIS, though the mice with elevated creatinine did not correspond to mice that showed changes in kidney pathology.

Upon histological analysis of mouse tissues, there were no toxicologic findings in tissues considered to be related to the administration of MV-NIS. Mice receiving pre-treatment with cyclophosphamide showed changes in the lymphoid organs (mandibular and mesenteric lymph nodes, thymus, and spleen), urinary bladder, bone marrow, testes and ovaries that were considered to be related to the administration of cyclophosphamide at the day 2 sacrifice. The cyclophosphamide-related changes showed evidence of recovery in later time points.

1.73 Imaging study of iodine biodistribution in MV-NIS treated squirrel monkeys

Two male squirrel monkeys (Saimiri sciureus) received a single intravenous dose of 10^8 TCID50 MV-NIS. NIS expression in tissues was evaluated by noninvasive SPECT/CT imaging of I-123 biodistribution at baseline and on days 3, 8, 15 and 22 after MV-NIS administration. Images were obtained at 1 and 2 hours after isotope administration. Detailed analysis of the data is not yet complete but, by naked eye examination of the serial images, ***the isotope localizes to the thyroid, stomach, salivary glands and bladder at all timepoints and the biodistribution does not appear to change following MV-NIS administration***.

1.74 Safety study of intravenous MV-NIS in squirrel monkeys

This study was performed by IIT Research Institute (IITRI) in Chicago, IL through the RAID program. According to the protocol, 12 male squirrel monkeys (Saimiri sciureus, 3/group) were intravenously dosed once with either MV-NIS or control article (saline) on study day 1. Animals in Groups II and IV were intravenously dosed once with cyclophosphamide on study day 2. Two monkeys per group were sacrificed on study day 29, and the remaining animals were sacrificed on study day 91. See table below.

All monkeys were evaluated for mortality/morbidity twice daily throughout the treatment and observation periods. All monkeys were observed for abnormal clinical signs at least once daily. Body weights were recorded on days 1, 8, 5, 29, and 91 and body temperatures were recorded pretest, 3 hours post-dosing on day 1 and on days 2 through 5 and 8. Clinical chemistry and hematology parameters were evaluated at the pretest and on days 3, 10, 15, 29, and 91. Thyroid hormone levels (TSH and T4 levels) were evaluated on days 29 and 91. Cytokine levels (IL-1, IL-6, IL-12 and TNF levels) were evaluated on days 1, 4, 8, 29 and 91. Anti-MV antibody levels were evaluated at the Mayo Clinic, Rochester, MN, on days 8, 15, 29, and 91. Samples containing epithelial cells and saliva were collected pretest and on days 1, 4 8, 29 and 91, and blood samples were collected on days 1, 4, 8, 29, and 91. MV-NIS levels were determined from these samples by PCR at the Mayo Clinic, Rochester, MN. Two monkeys/groups were sacrificed on day 29, and the remaining animals were sacrificed on day 91.

Tissues were collected, examined and fixed in 10% neutral buffered formalin at necropsy. Samples of all fixed tissues were embedded and put into blocks. Microscopic pathology was performed on all tissues. Statistical analysis of continuous data through day 29 were performed using analysis of variance with post-hoc comparisons made using Dunnett's test with a minimum significance level of $p \leq 0.05$.

There were no premature or unscheduled deaths during the study. No adverse clinical signs were observed during the study. No meaningful effects on body weights or body weight gains were noted during the study. There were no treatment-related effects noted for any clinical pathology parameters evaluated (hematology and clinical chemistry). No changes were observed in cytokine levels during the study. Lesions observed at necropsy included enlarged, dark-pigmented lymph nodes, small thymus and red focus on medial lobe of liver. All gross findings were interpreted as incidental and not treatment-related. No treatment-related histopathologic changes were observed. Pending results for thyroid hormone levels and viral levels.

Group #	MV-NIS ($TCID_{50}$)	Cyclophosphamide. (mg/kg)	Monkey #	Pre-Dose*	d1*	d2*	d8*	d15*	d29*	d91*
I	0 (Control)	0	**775**	<100	<100	<100	<100	<100	<100	
I	0 (Control)	0	**793**	<100	<100	<100	<100	<100	<100	
I	0 (Control)	0	**803**	<100	<100	<100	<100	<100	<100	<100
II	0 (Control)	31	**756**	<100	<100	1230	<100	<100	<100	
II	0 (Control)	31	**770**	<100	<100	<100	<100	<100	<100	
II	0 (Control)	31	**810**	<100	<100	<100	<100	<100	<100	<100
III	$10e^{8}$ †	0	**772**	<100	1660	<100	1455	<100	<100	
III	$10e^{8}$ †	0	**812**	<100	<100	<100	<100	<100	<100	
III	$10e^{8}$ †	0	**823**	<100	66950	<100	896500	8830	<100	<100
IV	$10e^{8}$ †	31	**817**	<100	2270	<100	988500	5880	<100	
IV	$10e^{8}$ †	31	**818**	<100	53850	955	2465000	2379870	960	
IV	$10e^{8}$ †	31	**819**	<100	150250	2520	516000	4590	690	<100

$TCID_{50}$ = tissue culture infectious dose which will infect 50% of the cell monolayers challenged with the defined inoculum.
Cyclopho. = cyclophosphamide.
* Data represents Copies of MV N-gene in 1.0 µg RNA extracted from Buccal Cheek Scrapes
† Dose = 10^{8} or the highest dose available from Mayo Clinic Viral Vector Production Facility

Preliminary Q-RT PCR on cheek swabs is summarized in table above. There was no virus detected at any time point for Groups I and II. However, in Groups III and IV there were low levels of viremia on day 1, which dropped by day 2, but increased significantly by day 8 to 15, but again dropped by days 29 and 91. Anti-measles IgG antibodies remained undetectable in Groups I and II, but in Groups III and IV became detectable by day 15 and persisted through day 29 and 91. ***These data would suggest that IV MV-NIS circulates, replicates, and clears over time and that replication is enhanced by cyclophosphamide.*** These Q-RT-PCR data also support our choice of time-points for imaging patients—that is days 8-15.

1.8 MV-NIS Translational Plans

Based on the foregoing observations, we conclude that MV-NIS is a highly promising CD46 targeted oncolytic agent that merits clinical testing in patients with multiple myeloma. Not only does the virus have an interesting and novel target specificity with associated single agent activity, but its biodistribution can also be non-invasively monitored *in vivo* allowing clinical validation of its ability to interact with its known molecular target, CD46. Furthermore, assuming that the expectation of myeloma targeting can be confirmed in this clinical study, it will be possible to further boost the potency of MV-NIS by subsequent administration of ^{131}I. Thus, MV-NIS offers the opportunity for rational clinical development.

The risks associated with MV-NIS administration to this group of patients are considered to be acceptable. Whereas MV-NIS has not previously been administered to humans, there is a vast knowledge base concerning the toxic effects of closely related viruses in the human population. Thus wild-type measles virus causes a well-described illness characterized by fever, rash, upper respiratory tract symptoms and transient immunosuppression [32]. The case fatality rate in the United States of America is 0.1 to 0.2 %, but is higher in underdeveloped countries where opportunistic infections secondary to measles immunosuppression are a more significant problem. At the other end of the spectrum, live attenuated measles virus vaccines have been used extensively. In the USA alone, more than 550 million doses of measles vaccine have been distributed to date. Several different members of the Edmonston virus lineage have been used for measles vaccination, and all of them are capable of causing a mild measles-like illness in some variable percentage of vaccinees [33-39]. It is therefore anticipated that some MV-NIS-treated patients may develop a measles-like illness. However, in the entire history of measles vaccination, no case of reversion of vaccine strain to wild-type measles has been documented, and only 6 deaths have been reported due to uncontrolled spread of the vaccine strain virus in severely immune-compromised individuals. In contrast to their effects in non-immune subjects, neither wild-type nor attenuated measles viruses cause a measles-like illness in patients previously exposed to the virus [40, 41].

Our longer-term strategy will be to develop and test new versions of MV-NIS that have been engineered to enhance or modify their target specificity. For example, we anticipate that whereas the efficacy of the current version of MV-NIS will be due to its interaction with CD46, the dose limiting toxicity will be a measles-like illness due to its interaction with SLAM. Thus, a recombinant MV-NIS in which the H protein has been modified to ablate its interaction with SLAM may have a better therapeutic ratio than the current version.

1.9 Post-protocol updates

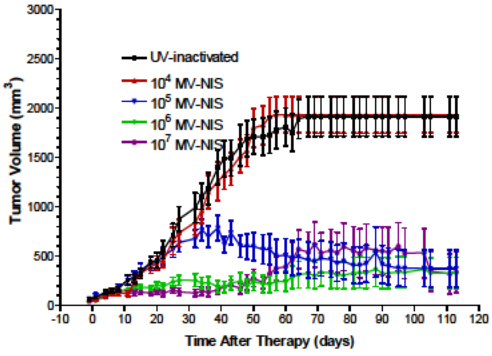
1.91 July 2011

Improved Good Manufacturing Practice to produce higher titers of MV-NIS

Due to manufacturing limitations, our clinical studies to date have used a maximum dose of 10^9 $TCID_{50}$ MV-NIS, only three times higher than the minimum effective mouse dose. Even at this low clinical dose we have shown that MV-NIS can traffic via the bloodstream to the tumor, infect the tumor cells,

amplify selectively in the tumor and then be eliminated by the immune system. There is therefore a strong rationale to push the dose of MV-NIS to higher levels.

Figure A.



Preclinical studies using intravenous MV-NIS to treat KAS6/1 myeloma xenografts are shown in figure A. Five groups of 10 irradiated SCID mice age six to eight weeks were implanted subcutaneously with 10^7 KAS-6/1 tumor cells in 100 μL of normal saline in the right flank. When tumors reached 0.5 cm in diameter, control mice received a single intravenous injection of 200 μL of UV inactivated MV-NIS. Test mice received a single intravenous injection of live MV-NIS at a dose of 10^4, 10^5, 10^6 or 10^7 $TCID_{50}$. Fig. A shows that the minimum effective dose was 10^5 (**equivalent human dose 3 x 10^8**) but tumor regression was delayed at this dose level. Rapid tumor control required a dose of 10^6 or higher (**equivalent human dose >3 x 10^9**).

Having worked intensively during the past 3 years to improve the MV-NIS manufacturing process, we are now in a position to increase the maximum dose of MV-NIS 100-fold from 10^9 to 10^{11} $TCID^{50}$. The Mayo Clinic Viral Vector Production Laboratory (VVPL), under the direction of Mark J. Federspiel, Ph.D., provides Mayo Clinic investigators the specialized resources and expertise required for product development of their promising gene and virus therapies to Phase I/II clinical trials. The Facility and Operations were audited by the National Cancer Institute (NCI) in 2004 and approved for GMP manufacture of Phase I/II products for NCI projects. The NCI auditors were impressed by the quality of the GVTSR personnel and organization. Over the past six years, the VVPL has manufactured viral products for Mayo Clinic research projects now in use in five different Phase I human clinical trials in the area of oncolytic virotherapy.

The original MV-NIS production and purification process routinely yielded 5 X 10^{10} $TCID_{50}$ infectious units, with an average titer of 2 X 10^7 $TCID_{50}$/mL and levels of residual protein and nucleic acid acceptable to the FDA. This process has been improved upon and the Federspiel production facility is now capable of of yielding supernatants with MV-NIS titers of 1-5 X 10^7 $TCID_{50}$/mL and >5 X 10^{11} $TCID_{50}$ total infectious units, a >10-fold improvement in yield. This new manufacturing process for MV-NIS with the improved overall yield and titer will enable the testing of MV-NIS doses up to 10^{11} per patient in multiple myeloma patients at significantly higher levels reaching doses expected to be in the therapeutic range.

1.92 March 2015

The Phase II portion of the trial initially allowed only the most heavily pre-treated patients to enroll. Patients had to have failed proteosome inhibition,

alkylator therapy, and immune modulatory drugs. Patients were also required to have negative measles titers both by ELISA and by neutralizing anti-body assay. Due to a lack of major responses in the first 11 treated, accrual was stopped, and the protocol was modified to include a different cohort of patients. It was felt that the safety profile seen to date made it reasonable to test the drug in less heavily pre-treated patients.

In the Phase II protocol, the first cohort will be referred to as cohort A and the second cohort as cohort B. The eligibility criteria for cohort B includes less heavily pretreated patients and the measles titer eligibility was changed to include only the ELISA testing.

1.19a Hypotheses

The primary hypothesis to be tested in our initial phase I clinical trial is as follows:

1. MV-NIS administered intravenously to patients with advanced multiple myeloma will selectively propagate in myeloma deposits throughout the body leading to tumor cell killing and reduction of tumor burden.

A secondary hypotheses is as follows:

2. Anti-measles virus antibodies (variable between patients) may sequester virus before it reaches the myeloma plasma cells and will thereby interfere with tumor cell infection and killing. Use of the immunosuppressant cyclophosphamide will abrogate this immune response.

An additional hypothesis that will be tested in a future phase I trial is:

3. ^{131}I administered at the appropriate time will synergize with MV-NIS, leading to enhanced therapeutic response through destruction of uninfected myeloma cells adjacent to the infected cells.

The reason that this hypothesis will not be tested in the initial phase I clinical trial is to allow the independent evaluation of MV-NIS toxicity, efficacy and kinetics without the additional confounding factor of ^{131}I.

2.0 Goals

2.1 Primary

2.11 Phase I:

To determine the maximum tolerated dose (MTD) of MV-NIS when administered with or without cyclophosphamide in patients with relapsed or refractory multiple myeloma.

2.12 Phase II:

Cohort A: To evaluate the confirmed response rate of MV-NIS alone in patients with relapsed or refractory multiple myeloma who have exhausted all therapeutic options.

Cohort B: To evaluate the confirmed response rate of MV-NIS alone in patients who are relapsing from VGPR or CR and have not received myeloma directed therapy for at least 12 weeks.

2.2 Secondary

2.21 Phase I:

2.211 To determine the safety and toxicity of the intravenous administration of an Edmonston vaccine strain measles virus engineered to express the thyroidal sodium iodide symporter (MV-NIS) when administered with or without cyclophosphamide in patients with relapsed or refractory multiple myeloma.

2.212 To evaluate the confirmed response rate of MV-NIS in patients with relapsed or refractory multiple myeloma

2.22 Phase II:

2.221 To further evaluate the adverse event profile of MV-NIS in patients with relapsed or refractory multiple myeloma.

2.222 To evaluate overall survival, failure-free survival and progression-free survival

2.3 Correlative (Both Phase I and Phase II)

2.31 To determine the time course of viral gene expression and virus elimination, and the biodistribution of virally infected cells at various times points after infection with MV-NIS (when administered with or without cyclophosphamide) using 99m-Tc gamma camera imaging.

2.32 To assess virus replication, viremia, viral shedding in urine and respiratory secretions, and virus persistence after systemic administration of MV-NIS (when administered with or without cyclophosphamide).

2.33 To monitor humoral responses to the injected virus.

2.34 To explore the anti-myeloma efficacy (i.e. clinical response rate, time to progression, progression free survival, duration of response) of the virus using standard myeloma response criteria as well as immunoglobulin free light chain measurements.

3.0 Patient Eligibility

3.1 Inclusion criteria

3.11 Age ≥ 18 years.

3.12 Myeloma relapsing from partial response or better
- 3.12a. Patients relapsing >18 months from transplant if not on maintenance, or
- 3.12b. If off maintenance, discontinued at least 6 months ago, or
- 3.12c. If relapsing on maintenance, at least 3 years from transplant, or
- 3.12d. Off prior myeloma therapy at least 6 months ago
- 3.12e. Sufficient tumor burden that is assessable for response
  - Serum M-spike >= 0.5 g/dL, or
  - If IgA myeloma, IgA > 1000 mg/dL, or
  - dFLC >10 mg/dL, or
  - Urine M-spike >=200 mg/24 hours, or
  - Bone marrow plasmacytosis >= 10%, or
  - Plasmacytoma >= 2 cm in diameter

3.13 The following laboratory values obtained ≤ 14 days prior to study registration
- ANC ≥1000/μL
- PLT ≥50,000/μL
- Hemoglobin ≥ 8.5 g/dl
- AST ≤2 times upper limit of normal
- Creatinine < 2 times upper limit of normal
- Total bilirubin ≤ 1.5 x upper limit of normal
- INR ≤ 1.4 x ULN at the time of registration

3.14 Ability to provide informed consent.

3.15 Willingness to return to Mayo Clinic Rochester for follow-up.

3.16 Life expectancy ≥ 12 weeks.

3.17 ECOG performance status (PS) 0, 1 or 2.

3.18 Willingness to provide all biological specimens as required by the protocol. (See section 14.0)

3.19 Negative serum pregnancy test done ≤ 7 days prior to registration for women of childbearing potential only.

3.19a Measles antibody titer on the BioRad Multiplex assay less than or equal to 1.0.

3.2 Exclusion criteria

3.21 Uncontrolled infection.

3.22 Active tuberculosis.

3.23 Any myeloma directed therapy within 12 weeks of registration including plasmapheresis or transfusion

3.24 New York Heart Association classification III or IV, known symptomatic coronary artery disease, or symptoms of coronary artery disease on systems review

3.25 Active CNS disorder or seizure disorder.

3.26 HIV positive test result.

3.27 Other concurrent chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered investigational (used for a non-FDA approved indication and in the context of a research investigation).

3.28 Previous exposure to heat inactivated measles virus vaccine (this vaccine was given to some individuals between the years of 1963-1967).

3.29a Any of the following:
- Pregnant women or women of reproductive ability who are unwilling to use effective contraception
- Nursing women
- Men who are unwilling to use a condom (even if they have undergone a prior vasectomy) while having intercourse with any woman, while taking the drug and for 4 weeks after stopping treatment.

3.29b Evidence of chronic or acute graft versus host disease or on-going treatment for graft versus host disease from prior allogenic stem cell transplantation

3.29c Exposure to household contacts ≤15 months old or household contact with known immunodeficiency.

4.0 Test Schedule

			Active Monitoring Phase						Observation
	Pre-treatment		Post-therapy (relative to MV-NIS administration; all tests ± 1day)						
Tests and Procedures	**≤ 14 days prior to Reg**	**Pre-treat-ment**	**Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 22, Day 29**	**Week 6[l]**	**3 months after treatment and Q 3 months thereafter[h]**
History and exam, wt, PS	X							X	X
AE Evaluation	X			X	X	X	X	X	X
WBC, ANC, ALC, Hgb, PLT	X		X[R, k]	X	X	X	X	X	X
aPTT, PT (INR)	X[R]			X[R]		X[R]	X[R]	X[R]	X[R]
AST, AP, Na, K, TBili, Cr, Ca	X			X	X	X	X	X	X
β2-M, LDH	X								
SPEP, IgA, IgM, IgG; 24 hr UPEP	X							X	X
Immunofix of serum & urine	X[a]							X[b]	X[b]
Immunoglobulin FLC	X		X[k,R]		X[R]	X[R]	X[R]	X	X
Anti MV IgM and IgG	X[a,R]	X[R]		X[R]	X[R]			X[R]	
Measles Neutralizing Ab[m]		X[R]			X[R]			X[R]	
HIV by EIA[R]	X								
T&B quant.: CD4, CD8		X[R]				X[R]		X[R]	
ECG	X								
BM asp/biopsy	X[a]							X[R]	
Research Blood/BM[i]		X[R]						X[R]	
Optional biopsy of affected area seen on nuclear imaging					X[O]				
Skeletal survey	X[a]								
Viral shedding:[R] mouth sample collection[c] and urine collection[d]		X		X	X	X	X[f]	X[g]	
Viremia (PBMC)[e, R]		X	X[n]	X	X	X	X[f]	X[g]	X[g]

Blood for cytokines[R]			X[k,p,R]	X[p,R]					
Blood for LPA and IFN-γ ELISPOT[R]		X[R]			X	X[R]		X[R]	
SPECT/CT[R]		See 4.1			See 4.1	See 4.1	See 4.1	See 4.1	
PET-CT[R]	X							X[q]	
Pregnancy test [R]	X[j]								

See next page for footnotes

a. ≤ 4 weeks prior to registration.
b. Only required to document complete response.
c. Patient will gargle with 15mL of Scope mouthwash for 30 seconds and fluid collected in a sterile Falcon tube (50mL). Send to Guggenheim 1802.
d. A mid-stream urine sample (15mL) to be collected in a 15mL Falcon conical tube. Send to Guggenheim 1802.
e. Collect 2.5mL of blood in each of two PAXgene containers. Send to Guggenheim 1802.
f. These studies will only be performed if there is evidence of continued viral genome presence at day 15. If at day 29, there is 10-fold increase in MV-NIS/mcg of RNA, repeat tests will be performed within 2 days to confirm the result. Weekly testing will be done thereafter until resolution to baseline.
g. Only if positive Q-RT-PCR on prior evaluation, check every 3 months by mail-out kit if no negative result at prior measurement. May be done by mail-in kit.
h. Patients will be observed at 3 months after treatment and every 3 months thereafter for a year or until progression—whichever is longer. Visits may be +/- 2 weeks. For those patients who receive alternative myeloma directed therapy, observation will be changed to "limited AE" toxicity form without additional scheduled laboratory monitoring. For those patients who have progressed but not received alternative myeloma directed therapy, laboratory tests may be done at home.
i. Blood and bone marrow can be done under IRB number of this trial or under 521-93; max of 450 mL of bone marrow and 50 cc of blood to be drawn for research purposes.
j. Necessary in women of childbearing potential ≤ 7 days prior to registration.
k. Prior to MV-NIS infusion
l. These tests may be done sooner than week 6 if patient progresses and needs to start another treatment for multiple myeloma prior to 6 week time point.
m. If patient requires other active myeloma treatment before week 6, waste serum will be retrieved from one of the clinical labs to run a neutralizing antibody test.
n. Pharmacokinetic samples will be done as follows: blood (5 mL/draw) will be taken at 6 time points: end of infusion, 30 minutes post, 60 minutes post, 120 minutes post, and 240 minutes post, and 24 hours post.
o. Biopsy may be done between day 8 and 15 if uptake observed on nuclear scans performed on day 8, if patient agrees to biopsy.
p. Cytokine samples will be taken as follows: blood (4 mL/draw into a EDTA tube), pre-MV-NIS infusion, 240 minutes post, 24 hours post (day +2), and approximately 48 hours post (day +3)
q. PET-CT will be done as indicated depending on baseline result. If markedly positive PET/CT at baseline, scan will be repeated
R. Tests drawn for research purposes only.

Table 4.1 Nuclear imaging Table[a]

	SPECT/ CT[b,c]	**FDG-PET/CT**
On Study		X
Any day before MV-NIS administration, ~ 1 hour post 99m-Tc	X	
Day 8 ~1 hour post 99m-Tc	X	
Day 15 ~1 hour post 99m-Tc	X	
Day 22[c] ~1 hour post 99m-Tc	X[d]	
Day 29 [c] ~ 1 hour post 99m-Tc	X[d]	
Week 6		X[e]

a. The scheduling of the nuclear imaging will be as close to the stated time points as possible. Flexibility ± 1 day will be allowed.
b. Up to a total of six **99m-Tc** scans will be done on each patient.
c. The pre-scan and day 8 will cover 80 cm of body length (chest and abdomen); all other scans will cover 40-80 cm (chest plus or minus abdomen) depending on regions of interest.
d. These scans will be elective, based on whether there is continued uptake on prior imaging studies.
e. PET-CT will be done as indicated depending on baseline result. If marked positive PET/CT at baseline, scan will be repeated

5.0 Grouping Factors:

5.1 Stage 1: MV-NIS alone vs. Stage 2: MV-NIS + cyclophosphamide.

5.2 Phase: Phase I vs. Phase II

5.3 Cohort: Cohort A (relapsed or refractory multiple myeloma who have exhausted all therapeutic options) vs. Cohort B (relapsing from VGPR or CR and have not received myeloma directed therapy for at least 12 weeks)

Note: Cohort A patients were accrued before Addendum 21 and Cohort B patients will be accrued after Addendum 21 is implemented. Eligibility criteria were modified with Addendum 21 to reflect this change.

6.0 Registration/Randomization Procedures

Phase I

6.1 Prior to discussing protocol entry with the patient, call the Registration Office (4-2753) for dose level and to insure that a place on the protocol is open to the patient.

6.2 To register a patient fax (507-284-0885) a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through

Phase II

6.3 To register a patient, access the web page at https://mccrc.mayo.edu and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Mayo Clinic Cancer Research Consortium (MCCRC) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available by using the Help button. Prior to initiation of protocol study intervention, this process must be completed in its entirety and a MCCRC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCRC Registration Office[redacted]. If the patient was fully registered, the MCCRC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

Phase I and II

6.4 At the time of registration, the registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

The following will also be recorded:

- Patient has/has not given permission to store sample(s) for future research of multiple myeloma and gene therapy.
- Patient has/has not given permission to store bone marrow sample(s) for future research to learn, prevent, or treat other health problems.

- Patient has/has not given Mayo permission to give their sample(s) to outside researchers.
- Patient has/has not given permission to have optional biopsy.

6.5 The study coordinator should call the Clinical Research Unit to assure that there is bed availability [redacted]

6.6 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary

6.7 Translational Research: Registration Office will automatically register patients separately to the translational component of this study (see Section 14.0).

6.8 Treatment on this protocol must commence at a Mayo Clinic Rochester under the supervision of a medical hematologist/oncologist.

6.9 Treatment cannot begin prior to registration and must begin ≤14 days after registration

6.9a Pretreatment tests must be completed within the guidelines specified on the test schedule.

6.9b All required baseline symptoms must be documented and graded on the Hematology Record.

6.9c Study drug availability checked.

7.0 Protocol Treatment

This study consists of two sequential dose escalation schemes to determine the maximum tolerated dose (MTD) of MV-NIS when given with or without cyclophosphamide. These will be conducted in two separate stages. First, patients will be accrued to the various dose levels (based on the escalation rules below) for MV-NIS alone. Once the MTD is determined for MV-NIS alone, then a second stage of dose escalation will occur to determine the MTD of MV-NIS when given in combination with 10mg/kg of cyclophosphamide.

7.11 Phase I, Stage 1: Evaluating MV-NIS Alone**-Closed to accrual on December 17, 2009. Reopened on October 13, 2011 for two more dose levels and Phase II expansion**

7.12 Treatment Schedule

Agent	Dose	Route	Day
Prior to Administration of MV-NIS			
99m-Tc	20mCi (+/- 10%)	I.V.	Any time pre MV-NIS (for baseline Tc scan)
MV-NIS Administration			
MV-NIS	Assigned by the Randomization Center	I.V.	1
After MV-NIS Administration			
99m-Tc	20mCi (+/- 10%)	I.V.	Days 3, 8, and 15 of study (2 additional doses may be given for imaging based on imaging results)

7.121 The virus will be administered by slow intravenous (IV) infusion 1 hour) in 250mL of normal saline under close observation in the Clinical Research Unit (CRU) or on Hematology in-patient service.

7.122 Patients will be closely monitored in the CRU or Hematology in-patient service during infusion of the virus for acute febrile reaction to the intravenously administered virus. Patients who develop febrile or allergic responses to the infusion will be treated with acetaminophen (650 mg, PO), and diphenhydramine hydrochloride (50 mg IV or PO). For rigors, meperidine hydrochloride (50 mg IV) will be administered. Symptoms suggestive of anaphylaxis such as dyspnea, itching, dizziness or symptomatic hypotension will result in the abrupt cessation of the viral infusion and the start of aggressive supportive therapy with fluids, diphenhydramine, methylprednisone (1mg/kg IV) and epinephrine (1mg subcutaneously). Administration of these medications will be tracked.

Therapy for Acute Infusion Reactions			
Agent	**Dose**	**Route**	**Reaction**
Acetaminophen	650 mg	P.O.	Acute febrile reaction
Diphenhydramine	50 mg	I.V. or P.O.	Acute febrile reaction
Meperidine HCl hydrochloride	50 mg	I.V.	Rigors
Methylprednisolone	1 mg/kg	I.V.	Anaphylaxis
Normal saline	Prn	I.V.	Anaphylaxis
Epinephrine	1 mg	S.C.	Anaphylaxis

7.123 The *in vivo* distribution of MV-NIS infected cells and the kinetics of virus spread and elimination will be monitored by 99m-Tc SPECT/CT as

described in Table 4.1 whole body gamma camera imaging after oral IV99m-T c], and by serial measurements of viral RNA in mononuclear cells derived from blood, saliva and urine (Viral N-gene RNA copy number/μg RNA).

If at day 15 isotope uptake is observed in organs other than the thyroid, stomach and salivary glands, further imaging will be performed on day 22 (and day 29) to document elimination of the virus and virus infected cells.

7.13 MV-NIS Dose (Stage 1)

Three patients will initially be treated at each dose level. The dose of each subsequent dose level will be determined by the adverse event evaluations. NOTE: FOUR DOSE LEVELS OF STAGE 1 COMPLETED IN STAGE 1 WITHOUT DLT, SO INITIALLY CLOSED AND STAGE 2 BEGUN; HOWEVER, DUE TO NEW MANUFACTURING CAPABILITIES, STAGE 1 RE-OPENED ON October 13, 2011, FOR DOSE LEVELS 5 AND 6. AT THIS TIME, STAGE 2 WILL BE IMMEDIATELY SUSPENDED TO COMPLETE STAGE 1. STAGE 2 WILL RESUME ONCE THE STAGE 1 MODIFICATION AND PHASE II EXPANSION HAVE BEEN COMPLETED.

Dose Level	**MV-NIS ($TCID_{50}$)**
-2	$1x10^4$
-1	$1x10^5$
1*	$1x10^6$
2	1×10^7
3	1×10^8
4	1×10^9
5	1×10^{10}
6	1×10^{11}

* Starting dose level

7.2 Phase I, Stage 2: Evaluating MV-NIS in Combination with Cyclophosphamide

7.21 Treatment Schedule

Agent	Dose	Route	Day
Pre-medication prior to Administration of MV-NIS			
99m-Tc	20mCi (+/- 10%)	I.V.	Any time pre-MV-NIS (for baseline 99m-Tc scan)
Cyclophosphamide	10 mg/kg	I.V.	2 days prior to MV-NIS Administration
MV-NIS Administration			
MV-NIS	See table 7.22	I.V.	1
After MV-NIS Administration			
99m-Tc	20mCi (+/- 10%)	IV	Days 3, 8, and 15 (two additional doses may be given for imaging based on imaging results)

7.211 Cyclophosphamide will be administered 2 days prior to infusion of the virus. It should be diluted 250 mL of 0.9% sodium chloride and infused over 30 minutes.

7.212 The virus will be administered by slow intravenous infusion in 250 mL of 0.9% sodium chloride over I hour under close observation in the Clinical Research Unit (CRU) or on the Hematology in-patient service.

7.213 The *in vivo* distribution of MV-NIS and the kinetics of virus spread and elimination will be monitored as per section 7.113.

7.22 MV-NIS Dose escalation (Stage 2)

The starting dose level of MV-NIS in the Stage 2 portion (MV-NIS combined with cyclophosphamide) is the MTD as determined from the first stage evaluation of MV-NIS reduced by 2 log (i.e. 100-fold less). For example, if the MTD from the first stage evaluation for MV-NIS was 1×10^9, then the starting dose level of MV-NIS when given in combination with cyclophosphamide in this second stage of the trial will be 1×10^7.

Dose Level*	**Cyclophosphamide (mg/kg)**	**MV-NIS ($TCID_{50}$)**
**1	10	(MTD/100=10^7)
2†	10	3×10^7
3†	10	9×10^7
4†	10	1×10^9
5†	10	1×10^{10}
6†	10	1×10^{11}

*Three patients will initially be treated at each dose level.
**Dose Level 1 equals Stage 1 MTD/100 (If no DLTs were observed at any of the dose levels in Stage I, 10^9 will be used as the MTD since it would be the maximum dose delivered in Stage 1)
† Escalation will not exceed the maximum tolerated dose from Stage I.

7.3 MV-NIS Dose Escalation Rules (applicable to Phase I, Stages 1 and 2)

7.31 If DLT is not seen in any of the 3 patients at a given dose level, then 3 additional patients will be treated at the next dose level. Dose escalation will not occur until full observation period (6 weeks) has elapsed for the last patient within any given dose level cohort.

7.32 If DLT is seen in 1 of 3 patients treated at a given dose level, 3 additional patients will be entered, one by one, at the same dose level.

7.33 If no additional DLT is observed at that dose level then 3 additional patients will be treated at the next dose level.

7.34 If 2 or more subjects out of 6 experience DLT at any dose level, MTD will have been exceeded.

7.35 If MTD is exceeded at any dose level, the cohort at the next lower dose level will be expanded one by one as needed to reach a total of 6 participants.

7.36 MTD will be defined as the highest dose at which no more than one out of six participants experiences DLT OR no DLT observed out of 3 patients at the maximum dose level, provided no DLT is observed at any of the previous dose levels (see Section 7). In the case that no DLTs are observed in any of the dose levels, then the MTD will be the maximum dose delivered.

7.37 If no DLT is observed at the highest dose level (i.e. 1×10^9 for Stage 1 or 81×10^7 for Stage 2), dose escalation beyond this dose level will not occur based on MV-NIS manufacturing limitations. If the 1×10^9 dose level (for stage 1) is reached without dose limiting toxicity, this dose--the maximum feasible dose--will be used for further study.

7.38 Stage 1 only: Once MTD or maximum feasible dose is reached in stage 1, this cohort will be expanded to treat a total of 37 patients at that level as part of a Phase II expansion.

7.4 Dose De-escalation: Phase I, Stages 1 and 2:

7.41 In the Phase I, stage 1 evaluation of MV-NIS alone, if two or more patients experience DLT at dose level 1, patients will be entered at a lower dose of $1x10^5$ (see Table in Section 7.12). If two or more patients experience DLT at this dose, further patients will be accrued at the dose level of $1x10^4$ $TCID_{50}$/mL.

7.42 In the Phase I, stage 2 evaluation of MV-NIS in combination with cyclophosphamide, if two or more patients experience DLT at the starting dose

level, then the new dose level 1 will be 3 log lower than the MTD for MV-NIS alone. Re-escalation will occur according to escalation rules described in 7.3 except with this one log lower multiplier.

7.5 Phase II Treatment

7.51 Treatment Schedule

Agent	Dose	Route	Day
99m-Tc	20mCi (+/- 10%)	IV	Any time pre-MV-NIS (for baseline 99m-Tc scan)
Pre-medication prior to Administration of MV-NIS			
Acetaminophen	650 mg	orally	30 minutes prior to MV-NIS
Benadryl	50 mg	orally	30 minutes prior to MV-NIS
MV-NIS Administration			
MV-NIS	TCD50 10(11)	IV	1
After MV-NIS Administration			
99m-Tc	20mCi (+/- 10%)	IV	Days 8 and 15 (two additional doses may be given for imaging based on imaging results)

7.52 To maximize systemic delivery of the MV-NIS, patients will be asked to avoid a heavy meal 3-4 hours before treatment. In addition, patients will be kept warm at the beginning of the infusion (cover with a warm blanket). The virus will be administered by slow intravenous (IV) infusion over 1 hour in 250 mL of 0.9% sodium chloride under close observation in the Clinical Research Unit (CRU) or on Hematology in-patient service.

7.53 Patients will be closely monitored during infusion of the virus for acute febrile reaction to the intravenously administered virus. Patients who develop febrile or allergic responses to the infusion will be treated with acetaminophen (650 mg, PO), and diphenhydramine hydrochloride (50 mg IV or PO). For rigors, meperidine hydrochloride (50 mg IV) will be administered. Symptoms suggestive of anaphylaxis such as dyspnea, itching, dizziness or symptomatic hypotension will result in the abrupt cessation of the viral infusion and the start of aggressive supportive therapy with fluids, diphenhydramine, methylprednisone (1mg/kg IV) and epinephrine (1mg subcutaneously). Administration of these medications will be tracked.

Therapy for Acute Infusion Reactions			
Agent	**Dose**	**Route**	**Reaction**
Acetaminophen	650 mg	P.O.	Acute febrile reaction
Diphenhydramine	50 mg	I.V. or P.O.	Acute febrile reaction
Meperidine HCl	50 mg	I.V.	Rigors
Methylprednisolone	1 mg/kg	I.V.	Anaphylaxis
Normal saline	Prn	I.V.	Anaphylaxis or hypotension
Epinephrine	1 mg	S.C.	Anaphylaxis

7.54 The *in vivo* distribution of MV-NIS infected cells and the kinetics of virus spread and elimination will be monitored by 99m-Tc SPECT/CT as described in Table 4.1 and by serial measurements of viral RNA in mononuclear cells derived from blood, saliva and urine (Viral N-gene RNA copy number/μg RNA).

If at day 15 isotope uptake is observed in organs other than the thyroid, stomach and salivary glands, further imaging will be performed on day 22 (and day 29) to document elimination of the virus and virus infected cells

7.55 Phase II stopping rule definitions are described in section 16.521 using DLT

7.6 Toxicity Observation Period: The first 6 weeks after therapy will be considered the toxicity observation period, where any DLTs observed in this timeframe will determine whether or not accrual can continue to the next dose level. The toxicity observation period will be waved for the Phase II expansion.

7.7 Phase I only: If a patient fails to complete the initial course of therapy (i.e. registers, but does not receive therapy or lost to follow-up during first 6 weeks), the patient will be regarded as inevaluable and an additional patient will be treated at the current dose level. For these instances, a specific notation will be made for review by the Cancer Center Clinical Research Administrative Subcommittee (CCCRAS). If more than one participant must be replaced at a dose level for reasons other than toxicity, the reasons will be reported to the FDA and the trial be voluntarily halted pending comments by the FDA review team.

7.8 Anticipated toxicity

7.81 Acute febrile reaction to the intravenously administered virus may occur. Ancillary support is described in sections 7.113 and 9.2.

7.82 Measles-like illness (coryza, malaise, fever, rash, lymphadenopathy and transient suppression of the immune system). [28,29] Patients will be educated about the symptoms of measles and asked to report immediately if any of these symptoms develop.

The disease is self-limiting in normal adults but because myeloma patients are immunocompromised, treatment will be implemented:

- If the symptoms (including temperature $\geq 38.5^{o}$ C) persist for as long as 6 days, or earlier at the treating physician's discretion.
- Earlier treatment is strongly recommended if a typical measles exanthem appears.

Treatment will include immunoglobulin (500 mg/kg) and Ribavirin (10 mg/kg/day in 4 divided doses orally or 20mg/kg/day intravenously) [47, 48]. Administration of these medications will be tracked and a participant with persistent measles-like illness will be classified as having experienced a DLT (see section 7.8). Additional ancillary support is described in section 9.2.

Therapy for Measles Persistence			
Agent	**Dose**	**Route**	**Reaction**
Intravenous immunoglobulin	500 mg/kg	I.V.	Persistent measles-like symptoms
Ribavirin	10 mg/kg/day (in 4 divided doses) Or 20 mg/kg/day (in 3 divided doses)	P.O. I.V.	Persistent measles-like symptoms Or Persistent viremia (see section 7.8)

7.83 $^{+}$99m-Tc is well tolerated. No acute toxicity is expected.

7.9 Dose limiting toxicity (DLT) will be defined as follows:

Definitions of Dose Limiting Toxicity (DLT)		
Hematologic	Neutrophils	Grade 4 ANC (<500/mm^3) 14 days
	Platelets	Grade 4 PLT (< 25,000/mm^3) $\geq$ 7 days
	All other hematologic*	Grade 3 or greater
Renal	Creatinine	Grade 3 (Serum creatinine > 3x ULN)
Vascular disorders	Hypotension	Grade 4 or greater
General	Fever	Grade 4 (> 40.0 C for > 24 hours)
Neurologic	Headache	Grade 3 lasting more than 6 hours

Other non-hematologic*	≥ grade 3
Symptomatic measles infection	Coryza, malaise, fever, rash, brassy cough; conjunctivitis; photophobia; and lymphadenopathy ≥ 6 days
Viremia (detection of viral RNA by RT-PCR in PBL).	> 10 fold increase in the copy number (copies/μg RNA) between sequential samples at least 3 days apart after day 15.

*With the exception of lymphopenia, leukopenia, anemia, febrile neutropenia, self-limited infusion reaction, and nausea, which will not be considered dose limiting toxicities.

8.0 Dosage Modification Based on Adverse Events

8.1 Given the nature of this study (i.e. a phase I trial and a phase II study with only one dose of drug administered), there are no dose modifications in this study.

9.0 Ancillary Therapy

9.1 Patients should receive full supportive care during the study including blood products, antibiotics and treatment of concurrent medical conditions and other newly diagnosed diseases.

9.2 Patients will be closely monitored as an in-patient during infusion of the virus acute febrile reaction to the intravenously administered virus. For phase II, patients will be pre-medicated with acetaminophen. Patients who develop febrile or allergic responses to the infusion will be treated with acetaminophen (650 mg, PO) and diphenhydramine hydrochloride (50mg IV or PO). For rigors, meperidine hydrochloride (50 mg IV) will be administered. Symptoms suggestive of anaphylaxis such as dyspnea, itching, dizziness or symptomatic hypotension will result in the abrupt cessation of the viral infusion and the start of aggressive supportive therapy with fluids, diphenhydramine, methylprednisone (1mg/kg IV) and epinephrine (1mg subcutaneously). Administration of these medications will be tracked.

9.3 Patients will be educated about the symptoms of measles (coryza, malaise, fever, rash, lymphadenopathy and transient suppression of the immune system[28,29]) and asked to report immediately if any of these symptoms develop.

The incubation period of measles (rubeola) averages 10 to 12 days from exposure to prodrome and 14 days from exposure to rash (range, 7 to 18 days). Prodromal symptoms of severe, brassy cough; coryza; conjunctivitis; photophobia; and fever appear 3 to 4 days before the exanthem and increase daily in severity. The nose and eyes run continuously. Koplik's spots (blue-white spots with a red halo) appear on the buccal mucous membrane opposite the premolar teeth 24 to 48 hours before the exanthem and remain for 2 to 4 days.

The rash begins on the fourth or fifth day on the face and behind the ears, but in 24 to 36 hours, it spreads to the trunk and extremities. It reaches maximum intensity simultaneously in all areas in approximately 3 days and fades after 5 to 10 days. The rash consists of slightly elevated maculopapules that vary in size from 0.1 to 1.0 cm and vary in color from dark red to a purplish hue. They are frequently confluent on both the face

and body, a feature that is such a distinct characteristic of measles that eruptions of similar appearance in other diseases are termed morbilliform. The early rash blanches on pressure; the fading rash is yellowish-brown with a fine scale, and it does not blanch.

The disease is self-limiting in normal adults but myeloma patients are immunocompromised, treatment will be implemented if the symptoms (including temperature $\geq 38.5^{o}$ C) persist for as long as 6 days, and earlier at the treating physician's discretion. Earlier treatment is strongly recommended if a typical measles exanthem appears. Treatment will include intravenous gammaglobulin (500 mg/kg) and Ribavirin (10 mg/kg/day in 4 divided doses orally or 20mg/kg/day intravenously) [47, 48]. Administration of these medications will be tracked and a participant with persistent measles-like illness will be classified as having experienced a DLT (see section 7.7)

9.4 Patients who demonstrate persistent viremia or viral shedding (10-fold increase in MV-NIS genome/mcg RNA at 4 weeks) that is confirmed on 2 consecutive samples after day 15 will also be treated with measles immunoglobulin and Ribavirin.

9.5 The disease is spread by respiratory droplets and can be communicated from slightly before the beginning of the prodromal period to 4 days after appearance of the rash; communicability is minimal after the second day of the rash. Though we would not expect the virus to be contagious to others since the majority of the U.S. population is vaccinated and all Mayo Clinic staff have measles virus immunity documented upon commencement of employment, we will require that health care personnel wear a mask at the first sign of cough; coryza; conjunctivitis; photophobia; or fever in the patient.

The vaccine strain of the measles virus (of which MV-NIS is a derivative) has been shown to be shed in the urine of normal children undergoing routine vaccination. Despite the presence of viral shedding of the vaccine strain of measles virus, transmission of has not been documented. However, since other patients on the Mayo Clinic grounds may be severely immunosuppressed, we will require that MV-NIS treated patients wear a mask when outside of their hospital room on Mayo Clinic grounds while they are shedding virus (tested by RT-qPCR).

If a patient is found to be shedding the virus in urine or throat gargle specimens(s), family members (or close personal contacts) who don't have documentation of immunity, will be offered testing to assess anti-measles virus immunity by Enzyme Immunoassay for the presence of MV-NIS. Measles vaccination will be offered to seronegative individuals, as per standard clinical practice.

9.6 Patients enrolled in this study will not be eligible for concurrent enrollment in any other study involving a pharmacological agent (drugs, biologicals, immunotherapy, gene therapy) whether for therapeutic intent or symptom control.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event monitoring and reporting. The CTC v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov/CTC3/ctc_ind_term.htm). All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next,

determine whether the event is expected or unexpected (refer to Section 15.0 and/or product literature) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2) or as part of the routinely reported clinical data.

Expedited adverse event reporting requires submission of a written report, but may also involve telephone notifications. Telephone and written reports are to be completed within the timeframes specified in Section 10.2. All expedited adverse event reports should also be submitted to the local Institutional Review Board (IRB).

10.12 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the investigational agent(s).
Probable - The adverse event *is likely related* to the investigational agent(s).
Possible - The adverse event *may be related* to the investigational agent(s).
Unlikely - The adverse event *is doubtfully related* to the investigational agent(s).
Unrelated - The adverse event *is clearly NOT related* to the investigational agent(s)

10.13 Expected vs. Unexpected

- The determination of whether an AE is expected is based on agent-specific adverse event information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific adverse event information provided in Section 15.0 of the protocol.

10.14 When a study includes both investigational and commercial agents, the following apply:

- When an investigational agent(s) is used in combination with a commercial agent(s) the combination is considered investigational. Expedited reporting of adverse events follows the guidelines for investigational agents.

10.2 Expedited Adverse Event Reporting Requirements

	Grade 4 or 5[1] Unexpected with Attribution of Possible, Probable, or Definite	Other Grade 4 or 5 or Any hospitalization during treatment[6]	Secondary AML/MDS[2, 4]
Submit written report within 5 working days[3, 5]	X		
Submit Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days.[4]		X	
Submit Serious Adverse Event Reporting Form for Human Gene Transfer Clinical Studies [5, 6]	X		

1. Includes all deaths within 30 days of the last dose of investigational agent regardless of attribution or any death attributed to the agent(s) (possible, probable, or definite) regardless of timeframe.
2. Reporting for this AE required during or after treatment.
3. Use *Adverse Event Expedited Report – Single Agent* or *Multiple Agents* report form. Submit to the Cancer Center SAE Coordinator for further processing (see footnote 7)
4. Submit the report by fax [redacted] to the MCCC SAE Coordinator. If Adverse Event Expedited Report – Single Agent or Multiple Agents report form was completed, this form does not need to be completed.
5. Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.
6. This reporting is in addition to all other reporting. Submit form to the Office of Recombinant DNA Activities, NIH, MSC 7010, 600 Executive Boulevard, Suite 302, Bethesda MD 20892-7010; Phone [redacted]. Submit copies of the report to the Cancer Center PDC for IRB reporting and to the Cancer Center SAE Coordinator for further processing (see footnote 7).

10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per (CTCAE) v3.0 grading unless otherwise stated in the table below:

Table 10.3a

Category	Adverse event/Symptoms	Baseline	Each Evaluation
BLOOD/BONE MARROW	Leukocytes (total WBC)	X	X
	Platelets	X	X
METABOLIC/LABORATORY	Creatinine	X	X
CONSTITUTIONAL	Fever	X	X
	Rigors/chills	X	X
DERMATOLOGIC	Rash/desquamation	X	X
RESPIRATORY	Cough	X	X
GASTROINTESTINAL	Baseline # of stools	X	
	Diarrhea (patients w/o colostomy)	X	X
	Vomiting	X	X
	Nausea	X	X
ENDOCRINE	Thyroid function , low (hypothyroidism	X	X

Table 10.3b

Upon receiving alternative myeloma directed therapy, only limited adverse events as indicated below will be monitored until 1 year after MV-NIS therapy

Category	Adverse event/Symptoms	Observation
CONSTITUTIONAL	Fever	X
RESPIRATORY	Cough	X
INFECTION	Upper airway NOS	X
	Febrile neutropenia	X

10.31 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic as applicable) the following AEs experienced by a patient and not specified in Section 10.3:

10.311 Grade 2 AEs deemed possibly, probably or definitely related to the study treatment or procedure.

10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.313 Grade 5 AEs (Death)

10.3131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.3132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also

be submitted as a grade 5 AE, with a CTCAE type and attribution assigned.

10.32 Refer to the instructions in the forms packet (or electronic data entry screens as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

11.1 Terms and definitions

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

  Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.
  - M-proteins migrating in the β-region (usually IgA M-proteins)
  - Cases in which the M-spike is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
  - Cases in which there are multiple peaks of same monoclonal protein (aggregates or dimers)

  If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-spike values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

  Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

  FLC estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), progressive disease (PD) and relapse from CR (RFCR).

  In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without

the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

Measurable disease: Patients who have a measurable serum or urine M-protein.

- Serum M-protein ≥1 g/dl
- Urine M-protein ≥ 200 mg/24 h
- Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal
- Bone marrow plasma cells ≥ 30%

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. ***Patients included on the study on the basis of FLC alone (i.e. no measurable serum/urine) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results.***

- **Evaluable disease**: Patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike.

- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-spike or urine M-spike, but has had a detectable monoclonal protein in his/her serum and/or urine and/or measurable serum free light chain.

- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable monoclonal protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

Table 11.2

Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])

On Study Baseline Value	SPEP	24 hr UPEP[2]	Ig FLC	BM Bx
Serum M-spike ≥1 g/dl, and urine M-spike≥ 200 mg/24 hrs	X	X		
Serum M-spike ≥ 1 g/dl, but urine M-spike < 200 mg/24 hrs	X			
Serum M-spike<1 g/dl, and urine M-spike≥ 200 mg/24 hrs		X		

Serum M-spike < 1 g/dl, urine M-spike < 200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X	
Serum M-spike < 1 g/dl, urine M-spike < 200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow ≥30% plasma cells				X[3]

[1] ***Immunofixation studies of both serum and urine*** *are required to document CR regardless of registration values, and in addition* ***FLC*** *measurement and* ***bone marrow immunophenotyping*** *is required to document sCR.*

[2] *For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category*

[3] *Bone marrow biopsyresults do not need to be confirmed (i.e. repeated after documented response).*

11.3 Confirmed response

In order to be classified as a hematologic response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document or confirm CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response.
- Radiographic studies are not required to satisfy these response requirements, however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.2

11.4 Bone progression

Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the study chair before removing the patient from the study.

11.5 Response and Progression

Criteria for response and progression are listed in Table 11.2. Progressive disease for all patients as defined in Table 11.2. Although the definition for "relapse from CR (or sCR) is listed, this will be documented as a response category in ONLY those protocols evaluating disease free survival.

Table 11.5	
CATEGORY	**RESPONSE CRITERIA [a]**
Stringent complete response (sCR)	• CR as defined below plus all of the following • Normal serum FLC ratio • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence [b]
Complete response (CR)	• Negative immunofixation of the serum and urine • < 5% plasma cells in bone marrow • Disappearance of any soft tissue plasmacytomas • If at on study, the only measurable non-bone marrow parameter was FLC, normalization of FLC ratio
Very good partial response (VGPR)[e]	• PR as defined below plus all of the following: • Serum and urine M-component detectable by immunofixation but not on electrophoresis or • If at on study, serum measurable, ≥ 90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h • If at on study, the only measurable non-bone marrow parameter was FLC, ≥ 90% or greater reduction in the difference between involved and uninvolved free light chain levels
Partial Response (PR)	• One of the following: ▪ If at on study, serum and urine measurable, a ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to <200 mg per 24 h ▪ If at on study, only serum measurable (but urine not), a ≥ 50% reduction of serum M-protein ▪ If at on study, urine measurable (but serum not), a reduction in 24-h urinary M-protein by ≥ 90% or to <200 mg per 24 h ▪ If at on study, only the only measurable non-bone marrow parameter was FLC, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels ▪ If at on study, the bone marrow was only measurable parameter, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30% • In addition to the above criteria, if a plasmacytoma present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minor Response (MR)	• ≥25% but < 49% reduction of serum M-protein and reduction in 24h urine M-protein by 50-89%, which still exceeds 200 mg per 24 h • In addition to the above criteria, if a plasmacytoma present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR or progressive disease
Progressive disease (PD)	Any one or more of the following: • Increase of 25% from lowest confirmed response in: ▪ Serum M-component (absolute increase must be ≥ 0.5 g/dl)[c] ▪ Serum M-component increase ≥ 1 g/dl, if lowest M component was ≥ 5 g/dl

	▪ Urine M-component (absolute increase must be ≥ 200 mg/24 h) [c] ▪ If at on study, only the only measurable non-bone marrow parameter was FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl) [c] ▪ Bone marrow plasma cell percentage (absolute % must be ≥10%)[c] Or any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder ▪ Development of new soft tissue plasmacytomas or bone lesions ▪ Hypercalcemia (≥11.5 mg/dl) ▪ Decrease in hemoglobin of ≥2 g/dl ▪ Serum creatinine level ≥2 mg/dl
Relapse from CR or sCR [d]	Patient who has achieved confirmed CR who has any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥ 5% plasma cells in the bone marrow [f] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

[a] All response categories require two consecutive assessments made at anytime before the institution of any new therapy; complete and PR, MR and SD 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. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u"] to designate first time point at which response category MAY have been achieved if confirmed.

[b] Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ 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/λ of >4:1 or <1;2.

[c] Positive immunofixation alone in a patient previously classified as CR will not be considered progression.

[d] This category will ONLY be used on a protocol specific basis, i.e. only those protocols looking at disease free survival.

[e] This response category is not available for those patients being followed by bone marrow only.

[f] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

11.6 Criteria for engraftment (for hematopoietic stem cell transplant studies only)

Engraftment is defined as:

- The first day of three consecutive days on which the absolute neutrophil count (ANC) >500/mm^3
- The first of three consecutive days with an untransfused platelet count >20,000/mm^3.

12.0 Descriptive Factors:

12.1 Number of prior treatments and what type

12.2 Disease status: Primary responsive, primary refractory, chemosensitive relapse, chemoresistent relapse, untested relapse.

12.3 Prior stem cell transplant: Yes vs. no

12.4 Date of last therapy

12.5 Date of myeloma diagnosis and Durie Salmon Stage at diagnosis.

12.6 At diagnosis was serum M-spike ≥1 g/dL: Yes vs. no.

12.7 At diagnosis was urine M-spike ≥ 200 mg/24 hours: Yes vs. no.

12.8 Durie Salmon Stage at entry

12.9 Measles IgG and IgM titers at entry

12.9a Pre-treatment disease measurements: serum M-spike ≥1 g/dL; urine M-spike ≥ 200 mg/24 hours; immunoglobulin free light chain ≥ 10 mg/dL; bone marrow ≥ 30% plasma cells.

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 The investigator may discontinue individual patients from the study at any time for the following reasons: a) if the patient develops adverse events that in the judgment of the investigator preclude further exposure to the study agent; b) if a patient develops an intercurrent illness that is not consistent with the protocol requirements, that patient may be withdrawn from the study; c) if the patient is not compliant with the study plan.

13.2 Phase I only: Indications for replacing a patient include: a) If a patient fails to complete the initial course of therapy (defined as 1 cycle of drug administration and 6 weeks observation) for reasons other than toxicity (e.g. intercurrent illness, patient refusal, or patient non-compliance), the patient will be regarded as inevaluable and an additional patient will be treated at the current dose level (see Section 7.6). If more than one participant must be replaced at a dose level for reasons other than toxicity, the reasons will be reported to the FDA and the trial be voluntarily halted pending comments by the FDA review team.

13.3 Patients who have disease progression, refuse further observation, or go on to receive alternate therapy will be monitored by Q-RT-PCR for N-gene according to test schedule until Q-RT-PCR becomes negative. This can be done through mail-in kits.

13.4 Patients who discontinue treatment due to unacceptable toxicity as defined in Section 7 will be actively monitored in Observation and will follow the test schedule per Section 4.0 until progression and until Q-RT-PCR for N-gene becomes negative. This will be done according to test schedule and can be accomplished through mail-in kits.

13.5 If a patient is registered to this trial and refuses further participation prior to receiving treatment (and is classified as a cancel), it is not necessary to provide follow-up information. On-study material is to be submitted. No further follow-up information is necessary.

13.6 For the purposes of this study, patients will be evaluated for clinical response at 6 weeks and 12 weeks and every 3 months thereafter while on observation. Blood, urine, bone marrow and skeletal radiography will be performed as outlined in Section 4.0.

14.0 Pharmacologic/Ancillary studies (Mandatory) and Optional Biopsy

14.1 Assessment of viremia and viral shedding. Mononuclear cells will be isolated from blood, throat washings and urine from all study patients on days 3, 8, 15. Additional samples on days 22 and 29 might be collected (depending on the viral RNA profile) and all will be tested for a) viral replication (quantitative RT-PCR to determine virus RNA copy number and co-culture on Vero cells for virus isolation). Testing will be performed in Dr S.J. Russell's laboratory (Guggenheim 1802) under the supervision of Dr Dispenzieri.

If a patient is found to be shedding the virus in urine or throat gargle specimens(s), family members (or close personal contacts) who don't have documentation of immunity, will be offered testing to assess anti-measles virus immunity by Enzyme Immunoassay for the presence of MV-NIS. Measles vaccination will be offered to seronegative individuals, as per standard clinical practice.

14.2 Assessment of immune competence will be performed by evaluation of immunoglobulin levels, CD4 and CD8 counts

14.3 Assessment of the peripheral immune response to viral administration. MV specific immunity will be evaluated at baseline and on day 42 by (a) measuring anti MV specific antibodies (IgG) and (b) by performing lymphocyte proliferation assays, and IFN-g ELISPOT assays on peripheral blood. These latter tests will also be performed on day 8 and day 15; and (c) cytokine levels around the time of MV-NIS administration.

14.4 Appraisal of baseline bone marrow CD46 and SLAM expression by flow cytometry.

14.5 Assessment of baseline bone marrow's infectivity ex vivo.

14.6 Assessment of day 42 bone marrow syncytia formation and levels of measles virus N mRNA within bone marrow cells.

14.7 Evaluation of MV-NIS biodistribution using SPECT/CT. Table 4.1.

14.8 Pharmacokinetic studies will be done during Stage 2 and Stage 1 patients at dose levels 5 and 6 of trial on all patients as well as all Phase II patients

14.9 Optional biopsy of area of interest will be performed by Dr. Stephanie Carlson (or colleagues) to biopsy "area of interest" if uptake seen on SPECT scan day 8 to confirm presence of virus in lesion. The biopsy of the lesion will be done per usual image-guided techniques using CT-guidance (see Section 17).

Summary of Research blood and bone marrow

Sample	Tube (volume); #tubes	Timing	Destination	Total trial
APTT	Citrate (5 mL)	5x	Routine coagulation lab [redacted]	25 mL
FLC	Red top (1 mL)	6x	Routine immunology lab [redacted]	6 mL
Anti MV IgM & IgG	Red top (0.5 mL)	2x	Routine serology lab	1 mL
Measles neutralizing Ab	Red top (2 mL)	2x	Guggenheim [redacted]	4 mL
Cytokines	EDTA (4 mL)	4x	Guggenheim [redacted]	16 mL
T & B quantitation (CD4 & CD8)	EDTA (5 mL)	3x	Routine cell kinetics lab [redacted]	15 mL
PBMC for viremia	PAXgene x2 (2.5 mL per tube)	10 to 15 x (baseline, PK x 6; day 8, 15, 42, and possibly days 22 and 29, and month 3, 6, and 12)	Guggenheim [redacted]	50-75mL
Blood for LPA and IFN-γ ELISPOT	CPT tube (10 mL x 4)	4x	Guggenheim [redacted]	160 mL
Bone marrow aspirate & biopsy	40 mL (IRB 521-93)	2x entire study	Guggenheim [redacted]	80 mL
Mouth rinse		4 to 6 x/ cycle 1 and once per cycle thereafter	Guggenheim [redacted]	
Mid-stream urine	400 mLin sterile 50 mL Falcon tube	4 to 6 x/ cycle 1 and once per cycle thereafter	Guggenheim [redacted]	
Optional biopsy of lesion*			Guggenheim [redacted]	

- Cores of the tissue (either bone or soft tissue depending on the lesion and if it is associated with a soft tissue mass or not) will be acquired using a biopsy needle (ranging in size from 12-guage to 20-guage depending again on lesion site, consistency, and size). As per usual practice a core and smears will be sent to cytology and pathology for analysis and confirmation of the malignancy (charge to grant, not to patient). One core of tissue (and an associated cytology smear) will go to Dr. Stephanie Carlson's lab (Guggenheim 18)

15.0 Drug Information

15.1 MV-NIS **(recombinant Edmonston measles virus carrying the human NIS gene)**

15.11 Background: MV-NIS is an attenuated measles virus, engineered to express the human thyroidal sodium-iodide symporter (NIS). The virus is selectively oncolytic, targeting and destroying tumor cells through CD46, a membrane regulator of complement activation that is known to be overexpressed on human malignancies. Multiple myeloma cells are selectively infected and killed by attenuated measles viruses of the Edmonston vaccine lineage

15.12 Formulation: MV-NIS infusions yield doses ranging from 1×10^4, 1×10^5, 1×10^6, 1×10^7, 1×10^8, 1×10^9, to 1×10^{11} $TCID_{50}$. See Section 1.91 for a more complete description of the production and purification process

15.13 Administration: The virus will be administered by slow intravenous (IV) infusion (1 hour) in 250ml of normal saline under close observation in the Clinical Research Unit (CRU) or on the Hematology in-patient service. (See Appendix I)

15.14 Known potential toxicities: MV-NIS has not been tested in the clinic and therefore, we do not know the potential toxicities. However, the virus was rescued from a derivative of the Edmonston B vaccine strain of measles virus and we anticipate that the most common toxicities will be similar to those experienced after the administration of the measles vaccine [44]. The main reaction associated with measles vaccination is a mild measles-like syndrome that occurs in 2-3% of recipients usually 1 week after vaccination. Thus patients might experience moderate fever up to 39.4°C and rash (minimal) within the first 5 to 12 days after virus injection. However it should be noted that this vaccine related measles like illness has been described only in measles-naïve subjects.

Not uncommon reactions:

- Moderate to high fever lasting 1 – 2 days, starting within a week or two of vaccination
- A rash, lasting 1 – 2 days
- Cough and rhinitis
- Erythema multiforme
- Arthritis

Unexpected and rare reactions associated with the vaccine:

- Allergic reactions including anaphylaxis
- Reactions at the injection site such as a wheal, flare or urticaria
- Thrombocytopenia
- Diarrhea
- Giant cell pneumonia
- Inclusion body encephalitis
- Guillain-Barré syndrome
- Vasculitis
- Otitis media
- Optic neuritis
- Ataxia

We will be particularly vigilant for symptoms suggestive of either giant cell pneumonia or inclusion body encephalitis that have been rarely observed in immunocompromised patients who were administered the vaccine.[43] If symptoms suggestive of persistent measles or either pneumonitis or encephalitis develop, the patients will be treated aggressively with anti-measles virus immune globulin and ribavirin and all the supportive care necessary as the situation might dictate.[42]

15.15 Risks to caretakers and other Mayo Clinic Patients
Viral transmission between patient and his/her contacts is thought to be unlikely, unless the patient develops florid measles infection. The vaccine strain of the measles virus (of which MV-NIS is a derivative) has been shown to be shed in the urine of normal children undergoing routine vaccination. Despite the presence of viral shedding of the vaccine strain of measles virus, there has been only 1 case of symptomatic measles virus presumptively transmitted from a vaccinated individual (Rota et al J. Clin Microbiology 2005). However, since other patients on the Mayo Clinic grounds may be severely immunosuppressed, we will require that MV-NIS treated patients wear a mask when outside of their hospital room on Mayo Clinic grounds while they are shedding virus (tested by RT-qPCR).

15.2 **Radioactive technetium –99m-Tc**

15.21 Generic or Common Drug Name (others such as Brand, Alpha-numeric): Sodium Pertechnetate Tc 99m, Mo-99/Tc-99m generator, TechneLite® (Technetium Tc 99m Generator), Ultra-TechneKow™ DTE Generator.

15.22 **Background**: Mechanism of action, drug family.

The pertechnetate ion distributes in the body similarly to the iodide ion but is not organified when trapped in the thyroid gland. Pertechnetate concentrates in the thyroid gland, salivary glands, stomach and choroid plexus. After intravenous administration it gradually equilibrates with the extracellular space. A fraction is promptly excreted via the kidneys.

15.23 **Formulation**: How supplied, available strengths, excipients.

Supplied in a Mo-99/Tc-99m generator which contains the amount of molybdenum Mo-99 at the date and time of calibration stated on the label.

The sterile, non-pyrogenic solution used to elute the generator column contains 0.9% sodium chloride. The eluant does not contain an antimicrobial agent.

The generator should not be used after the expiration date stated on the label. The expiration time of the Sodium Pertechnetate Tc 99m solution is not later than 12 hours after time of elution. If the eluate is used to reconstitute a kit, the radiolabeled kit should not be used after 12 hours from the time of generator elution or after the expiration time stated on the labeling for the prepared drug, whichever is earlier. (BUD assignment for prepared drug is based on radiopharmaceutical package insert or internal validated SOPs)

15.24 **Preparation and storage**: admixture instructions, light sensitivity, temperature for storage, product specific information.

Store generator and Sodium Pertechnetate Tc 99m solution at controlled room temperature 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature], and such generator system should be eluted in an ISO Class 8 or cleaner air environment to permit special handling, shielding, and air flow requirements [see USP <797> "Radiopharmaceuticals as CSPs"].

15.25 **Administration:** Intravenous rates, details for oral administration.

Sodium Pertechnetate Tc 99m is usually administered by intravascular injection but can be given orally..
The suggested dose range employed for various diagnostic indications in the average ADULT PATIENT (70kg) is:

Vesico-ureteral Imaging 18.5 to 37MBq (0.5 to 1mCi)
Brain Imaging 370 to 740MBq (10 to 20mCi)
Thyroid Gland Imaging 37 to 370MBq (1 to 10mCi)
Salivary Gland Imaging 37 to 185MBq (1 to 5mCi)
Placenta Localization 37 to 111 MBq (1 to 3mCi)
Blood Pool Imaging 370 to 1110MBq (10 to 30mCi)
Nasolacrimal Drainage System Max. 3.7MBq (100µCi)

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration of the dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The solution to be administered as the patient dose should be clear and contain no particulate matter.

15.26 **Pharmacokinetic information**:
a) Absorption –
b) Distribution –
c) Metabolism –
d) Excretion –

After intravascular administration Sodium Pertechnetate Tc 99m remains in the circulatory system for sufficient time to permit blood pool, organ perfusion, and major vessel studies. It gradually equilibrates with the extracellular space. A fraction is promptly excreted via the kidneys.

15.27 **Potential Drug Interactions**:

None

15.28 **Known potential toxicities**:

Radiation risks associated with the use of Sodium Pertechnetate Tc 99m are greater in pediatric patients than in adults and, in general, the younger the patient the greater the risk owing to greater absorbed radiation doses and longer life expectancy. These greater risks should be taken firmly into account in all benefit risk assessments involving pediatric patients.

Long-term cumulative radiation exposure may be associated with an increased risk of cancer.

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether Sodium Pertechnetate Tc 99m may affect fertility in males or females.

Allergic reactions including anaphylaxis have been reported infrequently following the administration of Sodium Pertechnetate Tc 99m.

15.28a **Drug procurement:** Identify source of drug.

The Mo-99/Tc-99m generator is currently available from two FDA licensed manufacturers:

[redacted]

15.29 **Nursing Guidelines:**

15.291 **Pregnancy Category C**

Animal reproductive studies have not been conducted with Sodium Pertechnetate Tc 99m. It is also not known whether Sodium Pertechnetate Tc 99m can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Sodium Pertechnetate Tc 99m should be given to pregnant women only if the expected benefits to be gained clearly outweigh the potential hazards.

Ideally, examinations using radiopharmaceutical drug products - especially those elective in nature - of women of childbearing capability should be performed during the first ten days following the onset of menses.15.292 **Nursing Mothers**

Technetium Tc-99m is excreted in human milk during lactation, therefore, formula-feedings should be substituted for breast-feedings.

15.3 **Cyclophosphamide (Cytoxan®, Neosar®, CTX)**

15.31 **Background**: Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell

cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.

15.32 **Formulation**: Commercially available for oral administration as:
Tablets: 25 mg, 50 mg

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature preferably below 25ºC (77ºF). This product will withstand brief exposure to temperatures up to 30ºC (86ºF), but should be protected from temperatures above 30ºC (86ºF). Dispense in a tight container as defined in the USP/NF. Refer to labeling on the bottle for expiration date of the commercial tablets.

15.34 **Administration:** Refer to the treatment section for specific administration instructions. Tablets are not scored and should not be cut or crushed. To minimize the risk of bladder irritation, do not administer tablets at bedtime.

15.35 **Pharmacokinetic information**:
Distribution: V_d: 0.48-0.71 L/kg; crosses placenta; crosses into CSF (not in high enough concentrations to treat meningeal leukemia)
Protein binding: 10% to 60%
Bioavailability: >75%
Time to peak, serum: Oral: ~1 hour
Metabolism: Hepatic to active metabolites acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard
Half-life elimination: 3-12 hours
Excretion: Urine (<30% as unchanged drug, 85% to 90% as metabolites)

15.36 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CYP2A6 (minor), 2B6 (major), 2C9 (minor), 2C19 (minor), 3A4 (major); **Inhibits** CYP3A4 (weak); **Induces** CYP2B6 (weak), 2C8 (weak), 2C9 (weak)
Increased Effect/Toxicity: Allopurinol may cause an increase in bone marrow depression and may result in significant elevations of cyclophosphamide cytotoxic metabolites. CYP2B6 and CYP3A4 inducers may increase the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inducers. Etanercept may enhance the adverse effects of cyclophosphamide. Cyclophosphamide reduces serum pseudocholinesterase concentrations and may prolong the neuromuscular blocking activity of succinylcholine and mivacurium.
Decreased Effect: Cyclophosphamide may decrease the absorption of digoxin tablets. CYP2B6 and CYP3A4 inhibitors may decrease the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inhibitors.
Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors.

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Dermatologic: Alopecia but hair will usually regrow although it may be a different color and/or texture. Hair loss usually begins 3-6 weeks after the start of therapy.
Endocrine & metabolic: Fertility: May cause sterility; interferes with oogenesis and spermatogenesis; may be irreversible in some patients; gonadal suppression (amenorrhea)
Gastrointestinal: Nausea and vomiting, usually beginning 6-10 hours after administration; anorexia, diarrhea, mucositis, and stomatitis are also seen
Hematologic: Thrombocytopenia and anemia are less common than leukopenia

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Facial flushing
Central nervous system: Headache
Dermatologic: Skin rash

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Cyclophosphamide may potentiate the cardiac toxicity of anthracyclines. Other adverse reactions include anaphylactic reactions, darkening of skin/fingernails, dizziness, hemorrhagic colitis, hemorrhagic ureteritis, hepatotoxicity, hyperuricemia, hypokalemia, jaundice, malaise, neutrophilic eccrine hidradenitis, radiation recall, renal tubular necrosis, secondary malignancy (e.g., bladder carcinoma), SAIDH, Stevens-Johnson syndrome, toxic epidermal necrolysis, weakness.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 Nursing Guidelines:

15.391 Myelosuppression is common. Monitor CBC including platelets. Instruct patient on signs/symptoms of infection and to inform health care team of any unusual bruising, or signs of bleeding.

15.392 Instruct patient to drink 2-3 liters of fluid per day for 2-3 days following treatment and to void frequently, not greater than every three hours to facilitate keeping the bladder clear of drug.

15.393 Instruct patient to report any urinary urgency, frequency, dysuria, or hematuria. Administer mesna with high dose cytoxan to prevent hemorrhagic cystitis. It may be necessary to catheterize and provide constant bladder irrigation.

15.394 Advise patient in possible strong metallic taste associated with Cytoxan and suggest hard candy with a strong flavor (cinnamon, peppermint) to alleviate it.

15.395 Administer antiemetics as necessary to minimize nausea and vomiting, which usually occurs 6-8 hours after administration.

15.396 Report and record any complaint of lightheadedness, facial "heat sensation," diaphoresis during administration.

15.397 Use of an ice cap may be helpful in preventing or limiting alopecia.

15.398 Corticosteroids, phenothiazine, imipramine, vitamin A succinylcholine, digoxin, thiazide diuretics, warfarin and allopurinol may inhibit Cytoxan metabolism and modify its' effect. They may also increase bone marrow suppression.

15.399a Advise female patients of possible menstrual changes or amenorrhea.

15.399b Patients on anticoagulant therapy should have INR levels carefully monitored as cytoxan increases their effect.

15.399c Monitor electrolytes and for signs/symptoms of SIADH and tumor lysis syndrome.

15.399d Monitor digoxin levels closely as cytoxan may decrease these levels.

15.399e Cytoxan may potentiate doxorubicin-induced cardiomyopathy. Instruct patient to report any chest pain.

16.0 Statistical Considerations and Methodology

16.1 Overview: This is a Phase I/II study designed to evaluate the toxicity and efficacy of MV-NIS. The phase I portion will determine in a sequential manner the MTD of MV-NIS when administered with or without cyclophosphamide. This will be done in two stages (MV-NIS alone and then MV-NIS with cyclophosphamide), where each evaluation will use the standard 'cohort of three' design used in phase I clinical trials. Toxicity and pharmacokinetics (viral spread, expression and elimination) of MV-NIS in the treatment of multiple myeloma will be evaluated in each of the stages. Once the MTD has been determined in Stage 1, the phase II portion will assess the efficacy of MV-NIS alone in 2 cohorts (Cohort A: relapsed or refractory multiple myeloma who have exhausted all therapeutic options and Cohort B: relapsing from VGPR or CR and have not received myeloma directed therapy for at least 12 weeks). The same one-stage design with an interim analysis will be used to evaluate efficacy in each cohort independently.

16.11 Sample Size, Accrual and Study Duration for Phase I: The first stage of this study (MV-NIS alone) may involve as few as 9 patients (DLTs in at least 2 patients observed in first three patients at the starting dose level and 6 at dose level -1 if deemed MTD) and as many as 24 patients (6 each at dose levels 1 through 4).

ADDENDUM 10: The number of patients needed for Stage 1, is recalculated based on the knowledge that only 12 patients were required for dose levels 1-4 since not DLT observed; Re-opening Stage 1 for dose levels 5 and 6 (new manufacturing capabilities)

could require 6-12 patients depending on whether dose-limiting toxicity is seen at this level.

The second stage of the Phase I study (MV-NIS with 1 dose of cyclophosphamide) may involve as few as 3 patients (DLTs in at least 2 of the first 3 patients at the starting dose level and decision not to de-escalate) and as many as 30 (6 per dose level).

ADDENDUM 10: The number of patients needed for Stage 2, is recalculated based on the knowledge that for Stage 2, dose levels 1 and 2 required only 6 patients since no DLT observed at these levels. With the revised dose-escalation scheme of 10-fold rather than 3-fold increases per dose level, there would be a total of six Stage 2 dose levels, for a minimum and maximum number of patients on Stage 2 of 18 and 30, respectively, assuming Stage 1 maximum tolerated dose is equivalent to maximum feasible dose. If not, the Stage 2 patient numbers would drop to a minimum of 12 and a maximum of 18 patients.

At trial inception, the overall the minimum number of patients to be enrolled was 12 and the maximum number of patients was 54. After Amendment 10, the revised estimates of overall minimum and maximum are 30 and 54. For Stages 1 and 2, the accrual rate for this study is expected to be about 3 patients per month. Assuming each patient cohort will require approximately 5 weeks to follow for dose-limiting toxicity after the last patient has been accrued (see Section 7.5), each cohort of 3 patients in Stage 1 or 2 will require about 2 months for accrual, treatment, and observation to determine incidence of DLTs and whether or not dose escalation can proceed.

Therefore, the accrual period for Phase I is expected to be at most 72 months, taking into account the time needed to assess toxicity in each cohort.

ADDENDUM 17: As of June 16, 2014, 32 patients had been accrued to Phase I. With the interesting responses seen in Stage I, dose level 6, Stage II (escalation with addition of cyclophosphamide) was suspended to move to a Phase II single agent MV-NIS trial. A minimum of 12 and a maximum of 37 evaluable patients will be accrued in phase II. We anticipate accruing 4 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, we expect to accrue a maximum of 41 additional patients for 73 patients overall. The expectation is to start accruing patients in August 2014 at a rate of 4 per month, with an anticipated accrual time of 10 months for the Phase II trial. The phase II analysis can begin after the last patient accrued has been followed for 3 months

ADDENDUM 21: As of March 2015, 44 patients have been accrued to this study (32 phase I and 12 phase II cohort A). Due to lack of major responses seen in phase II cohort A, accrual to cohort A will be suspended. Cohort B will be added to evaluate the efficacy of this regimen in less heavily pretreated patients. A minimum of 12 and a maximum of 37 additional evaluable patients will be accrued to cohort B in phase II. We anticipate accruing 4 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, we expect to accrue a maximum of 41 additional patients in cohort B for 85 patients overall. The expectation is to start accruing patients at a rate of 2 patients per month once Addendum 21 is implemented, with an anticipated accrual time of 20 months for cohort B of the Phase II trial. The phase II analysis can begin after the last patient accrued has been followed for 3 months

16.12 General Statistical Considerations: The trial is designed to provide data about pharmacokinetics (biodistribution, targeting, viral gene expression and viral elimination), safety and biological activity of MV-NIS in patients with myeloma. Data related to toxicity and pharmacology will be presented using descriptive statistics due to the exploratory nature of the study. The data will be presented in table formats listing the mean, standard deviation and number of patients per group for continuous data, or listing count and percentages for categorical data as appropriate. All the relevant data will be used both in exploratory and hypothesis generating fashions to examine factors related to toxicity and pharmacology.

16.2 Phase I Portion

16.21 Primary outcome analyses: Maximum Tolerated Dose (MTD): The MTD will be defined as the highest safely-tolerated dose level where at most one patient out of six experiences DLT or no DLT observed out of 3 patients at the maximum dose level, provided no DLT is observed at any of the previous dose levels (see Section 7). In the case that no DLTs are observed in any of the dose levels, then the MTD will be the maximum dose delivered for each stage. MTD determination: See Section 7.0

16.22 Secondary endpoints: The following secondary endpoints will be evaluated for each stage independently. In addition, differences in dose levels with and without cyclophosphamide may also be explored where appropriate.

16.221 The number and severity of toxicity incidents will indicate the level of myeloma. For each of the stages, non-hematologic toxicities will be evaluated via the CTCAE v. 3 standard toxicity grading. Hematologic toxicity measures such as anemia, neutropenia and thrombocytopenia will be assessed using continuous variables as the outcome measures (nadir and percent change from baseline values) as well as categorization via CTCAE v. 3 standard toxicity grading. Frequency distributions and other descriptive measures will form the basis of the analysis of these variables

16.222 Clinical Response: The number of clinical responses may provide useful preliminary data on the efficacy of this treatment regimen in this patient population. A clinical response in this setting will be defined as noted in Section 11.0. The number of responses (CR, VGPR, PR, or MR) will be summarized by simple descriptive summary statistics across all patients in each group as well as by dose level.

16.223 Tolerability of this regimen will be explored in an ancillary manner through time-related variables including time until any treatment related toxicity, time until treatment related grade 3+ toxicity and time until hematologic nadirs (WBC, ANC, platelets). Simple summary statistics will be supplemented with Kaplan-Meier survival estimates and related confidence intervals. The effect of dose and ancillary dichotomized covariates such as age will be explored using logrank testing involving one covariate at a time. Again the small sample size restricts the generalizability of such testing, but the results will provide preliminary indications for subsequent research in Phase II clinical trials.

16.23 Correlative Analyses

16.231 Data will be collected for a number of laboratory correlative variables as discussed before (e.g. viral replication and shedding). Descriptive statistics and scatterplots will form the basis of presentation of these variables. Correlations between the laboratory values and other outcome measures will be carried out by standard parametric and non-parametric tests (e.g. Pearson's and Spearman's rho). Data obtained from gamma camera imaging of MV-NIS following ^{123}I consumption (or after revised protocol 99m-Tc administration) will be used to determine the bio-distribution and kinetics of virus spread and NIS gene expression in vivo and correlate it with tumor distribution. We will also estimate the radiation dose that could be delivered to the bone marrow as well as critical organs such as the liver, lungs and kidneys if I-131 were to be administered using MIRDOSE 3 program. Where patterns of correlation are indicated, ordinary and partial correlation coefficients (controlling for dose levels) will be calculated. Inferential testing for significant shifts in the correlative laboratory data results across dose levels will be carried out only as a hypothesis generating exercise.

16.3 Phase II Portion (to be evaluated in each cohort independently)

16.31 Statistical Design:

16.311 Decision Rule: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 5%, representing a response by chance alone. The smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 20%. The following one-stage design with an interim analysis is based on a Simon optimal design and uses 12 or 37 patients to test the null hypothesis that the true success proportion in a given patient population is at most 5%.

16.3111 Interim Analysis: Enter 12 patients into the study. If no successes are observed in the first 12 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 1, we will continue accrual.

16.3112 Final Decision Rule: Enter an additional 25 patients into the study. If 3 or fewer successes are observed in the first 37 evaluable patients, we will consider this regimen ineffective in this patient population. If 4 or more successes are observed in the first 37 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

16.3113 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

Analyses involving over accrued patients are discussed in Section 16.413.

16.3114 NOTE: We will not suspend accrual at the interim analysis to allow the first 12 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.312 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10, i.e. there is a 10% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping after the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.05	0.10	0.15	0.20	0.25
Then the probability of declaring that the regimen warrants further study is…	0.10	0.45	0.75	0.90	0.96
And the probability of stopping after the interim analysis is…	0.54	0.28	0.14	0.07	0.03

16.313 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.4 Analysis Plan for Phase II Portion (to be evaluated in each cohort independently)

16.41 Primary Outcome Analyses:

16.411 Definition: The primary endpoint in the phase II portion of this trial is the proportion of confirmed response. A confirmed response is defined as a PR or better noted as the objective status on two consecutive evaluations. Confirmed response will be evaluated using all cycles. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for confirmed response.

16.412 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients Ninety-five percent confidence intervals for the true success proportion will be calculated according to the method of Duffy and Santner.

16.413 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used

in any decision making processes; however, they will be included in final endpoint estimates and confidence intervals.

16.42 Secondary Outcome Analyses

16.421 Overall survival is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier.

16.422 Time to progression is defined as the time from registration to the earliest date with documentation of disease progression If a patient dies without a documentation of disease progression, the patient will be considered to have had tumor progression at the time of their death unless there is sufficient documented evidence to conclude no progression occurred prior to death. The distribution of time to progression will be estimated using the method of Kaplan-Meier.(Kaplan and Meier 1958) The progression-free rate at 1 year and 2 years will be assessed.

16.423 Failure-free survival is defined as the time from registration to the earliest of progressive disease, alternative treatment for myeloma, or death due to any cause. The distribution of failure-free survival will be estimated using the method of Kaplan-Meier.

16.424 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.43 Correlative Analyses

16.431 Data will be collected for a number of laboratory correlative variables as discussed before (e.g. viral replication and shedding). Descriptive statistics and scatterplots will form the basis of presentation of these variables. Correlations between the laboratory values and other outcome measures will be carried out by standard parametric and non-parametric tests (e.g. Pearson's and Spearman's rho). Data obtained from gamma camera imaging of MV-NIS following 99m-Tc infusion will be used to determine the biodistribution and kinetics of virus spread and NIS gene expression in vivo and correlate it with tumor distribution. We will also estimate the radiation dose that could be delivered to the bone marrow as well as critical organs such as the liver, lungs and kidneys if I-131 were to be administered using MIRDOSE 3 program. Where patterns of correlation are indicated, ordinary and partial correlation coefficients (controlling for dose levels) will be calculated. Inferential testing for significant shifts in the correlative laboratory data results across dose levels will be carried out only as a hypothesis generating exercise.

16.5 Data & Safety Monitoring:

16.51 Monitoring: Members of the study team will review the study regularly to review the progress of this protocol and be kept aware of efficacy and toxicity issues. This study will be monitored according to the MCCC Data Safety Monitoring Plan that is currently in place, and if necessary will report to the MCCC Data Safety Monitoring Board. Indications for temporary stopping the study include: a) unexpected toxicity of any of the drugs; b) unexpected difficulties with production of MV-NIS; and c) unexpected difficulties with any of the assays required to monitor patient safety (QT-PCR monitoring).

16.52 The principle investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.521 Adverse Event Stopping Rules (to be evaluated in each cohort independently in the phase II portion): The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

· if 5 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

· if after the first 15 patients have been treated, 33% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on

ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is approximately 15 months after the implementation of Addendum 21. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 3 months (and allowing 2 months for data entry).

16.7 **Subset Analyses for Women and Minorities**:

16.71 This study will be available to all eligible patients, regardless of race, ethnic origin, and gender. There is no information currently available regarding differential effects of this regimen in subsets defined by race or gender, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on gender and racial groupings, the sample size is not increased to provide additional power for subset analyses.

16.72 Since women typically comprise 45% of this patient population, the number of women enrolled in this trial is expected to be at most approximately 38 depending on the number of patients needed to establish the MTD.

16.73 In prior Mayo Clinic studies in this disease, approximate 3% of all patients were classified as ethnic minorities. Therefore, it is likely that only 1 or 2 patients classified as ethnic minorities will be enrolled in this trial.

16.74 Expected sizes of ethnicity and race by gender subsets are shown in the following table:

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	38	47	0	85
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	38	47	0	**85**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	2	2	0	4
Native Hawaiian or other Pacific Islander	0	0	0	0
White	36	45	0	81
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects	38	47	0	**85**

Ethnic Categories:
Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories:
American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations:

17.1 Optional biopsy of area of interest will be performed by Dr. Stephanie Carlson (or colleagues) to biopsy "area of interest" if uptake seen on SPECT scan day 8 to confirm presence of virus in lesion. The biopsy of the lesion will be done per usual image-guided techniques using CT-guidance

18.0 Records and Data Entry Procedures

Forms	Active-Monitoring Phase (Compliance with Test Schedule)						At Each Occurrence		
	Initial Material	Follow-up material							
	≤2 weeks after registration	At each evaluation	At end of treatment	Observation: 3 months after treatment and Q 3 months thereafter[1,7]	At PROG	Death	ADR/AER	New Primary	Grade 4 or 5 Non-AER Reportable Events/ Hospitalization
On-Study Form	X								
Baseline Adverse Events Form	X								
Other Laboratory Form		X	X						
Measurement Form	X	X	X	X[5]					
Evaluation/Treatment Form		X	X						
Nadir/Adverse Event Form		X	X	X					
End of Active Treatment/Cancel Notification Form	X[3]		X						
Bone marrow biopsy report	X	X[7]	X[7]	X[7]					
SPEP, UPEP, FLC, Immunofixation reports	X	X[8]	X[8]	X[8]					
Skeletal Survey	X			X[7]					
Event-Monitoring Form					X	X		X	
Therapy for Acute Infusion Reaction Form		X[4]							
Evaluation/Observation Form		X[2]		X[2]					
PK Specimen Submission Form		X[6]							
Cytokine Samples Submission Form		X[9]							
Concurrent Treatment Log	X	X	X						
ADR/AER (See Section 10.0)							X		
Secondary AML/MDS Report Form (See Section 10.0)							X		
Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form (See Section 10.0)									X

Footnotes on the following page.

1. If a patient is still alive 1 year after completing therapy, no further follow-up is required.
2. Complete at each evaluation during Observation (see Section 4.0).
3. Submit this form only if withdrawal/refusal prior to beginning protocol therapy.
4. See section 7.113.
5. Only to be done until patient progression.
6. Specimens collected as per Sections 4.0 and 14.07. Upon receiving alternative myeloma directed therapy, only limited to adverse events as indicated in Table 3b will be monitored until 1 year after MV-NIS therapy
7. Only when required by the test schedule (see section 4.0)
8. Submission of these reports is only required for documentation of CR (including sCR) or progression. For documentation of CR, submit all of these reports at the first confirmation of CR. For documentation at first signs of progression, submit reports to the QAS for MC038C.
9. Specimens collected pre-MV-IS infusion, 240 minutes post, 24 hours post (day +2), and approximately 48 hours post (day +3) as per Section 4.0.

19.0 Budget

19.1 Costs charged to patient: Routine clinical care.

19.2 Patients enrolled in the study will not be billed for room and board or nursing charges while in the CRU or Hematology in-patient service. However, participants may be billed for ancillary expenses such as any oral medications prescribed at the time of discharge.

19.3 Tests that will be research funded: All nuclear imaging costs (nuclear medicine personnel, FDG-PET/CT, and SPECT /CT imaging will be charged to either [redacted] All other research costs (, Cyclophosphamide, follow up bone marrow biopsy, tests pertaining viral status and shedding, tests of immune function, thyroid hormone measurements, and serial immunoglobulin free light chain levels.) will be charged to [redacted]. According to CMS guidelines, baseline, FDG-PET/CT will be covered by Medicare for patients who are on Medicare. Subsequent FDG-PET will be charged to the grant.

19.4 Cost of MV-NIS production will be charged to [redacted] and [redacted]

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Appendix I

GUIDELINES FOR MV-NIS ADMINISTRATION AND DAY 1 AND 2 PHARMACOKINETICS BY NURSING STAFF

Synopsis: Patients have been asked to take part in this study because they have evidence of recurrent or refractory MM that has progressed through established treatments. We are trying to find new treatments that may be more effective at treating MM. The "drug" used in this trial is a modified version of the measles virus used to vaccinate children. The virus has been altered by having extra gene added for a protein called NIS inserted into it. NIS is normally found in the thyroid gland and helps the body concentrate iodine. Having this additional gene will make it possible to track where this virus goes in the body

1.0 Drug Information

MV-NIS is a live, tissue culture adapted measles virus engineered to express the human thyroidal sodium iodide symporter (NIS). The virus was constructed by inserting the NIS gene (cDNA) into a full-length infectious molecular clone of an attenuated Edmonston lineage measles virus (MV-tag). This virus is not a vaccine. MV-NIS propagates on Vero cells with kinetics equivalent to the parental strain of virus. It propagates selectively in human cancer cells that it infects by binding preferentially to CD46, a membrane protein that is overexpressed in tumor cell lines including myeloma. The virus is directly cytopathic to tumor cells leading to the formation of multinucleated syncytia that die by apoptosis. MV-NIS infected tumor cells express NIS, a membrane ion channel that actively transports iodide into cells. Radioiodine uptake by cells expressing NIS provides the basis for in vivo radioiodine imaging that can reveal the profile of MV-NIS gene expression and the location of MV-NIS infected cells during virus spread and elimination.

1.1 Preparation and storage:

MV-NIS will be prepared at the Virus and Vector Production Laboratory (VVPL) of the Molecular Medicine Program at Mayo Clinic and stored at -80°C. The virus will be thawed and mixed with normal saline prior to administration according to good practice guidelines for any Biohazard Level 2 biological. A leak proof box, preferably equipped with a gasket seal lid, should be used for transport of MV-NIS from one location to another

- The MV-NIS product will be dispensed with intravenous tubing attached that is primed with the base solution used for preparation of the medication. The product will be dispensed in leak-proof packaging and contain a label indicating safe handling precautions are required.
- The drug, dose, dilution, drug diluent, final product concentration, labeling and documentation of the preparation are checked by a pharmacist prior to dispensing.

1.2 Administration:

1.2.1 General precautions

- Pregnant, breastfeeding, and/or immunosuppressed healthcare workers must not enter the room (place a sign on door)
- Contact Isolation
- Hazardous Medication Precautions
- Protective Environment Precautions
- Patient to wear mask (N95) when out of patient room post MV-NIS infusion
    - **Patient education point**: since other patients on the Mayo Clinic grounds may be severely immunosuppressed, we will require that you wear a mask when you are outside of your hospital room on Mayo Clinic grounds. The results of these tests will determine how long you should wear a mask when in public.

1.2.2 Patient preparation

- Patient to avoid heavy meal 3-4 hours prior to MV-NIS infusion
- Patient to be NPO for 30 minutes prior to CRU nurse collecting mouthwash sample (see below)
- Saline Lock X2 (one in each arm) if no central line access
- Notify Pharmacy 1 hour before you are ready for the drug
- Have emergency red box at nursing station during infusion
- Cover patient with warm blanket(s) pre and during infusion
- Continuous Pulse Oximetry during treatment and for 24 hours after treatment
- Cooling Blanket prn fever >39.0 post infusion

1.2. 3 Preparation for infusion and pharmacokinetic studies

- Do not start MV-NIS infusion until mobile CRU (clinical research unit) mobile staff has drawn baseline bloodwork and taken urine and mouthwash samples. They will come at 0800 the day of treatment to collect these samples. If questions call 6-2302 and ask for mobile CRU nurse.
    - Mouthwash sample: **Pt must be NPO for 30 minutes prior to collecting this sample**
    - Please verify the Scope mouthwash is ordered and sent from pharmacy the evening before so ready for the CRU mobile nurse visit day of treatment
    - If pt needs to void just prior to mobile CRU nurse arrives, save urine in hat or urinal (need 100cc or more)
- Notify Hematology Research Nurse 127-16808 with infusion start/estimated stop time (this is needed to coordinate for the post infusion lab samples). Hematology Research Nurse will come draw the

post infusion PK lab samples (end of infusion, 30 min post, 60 min post, 120 min post, 240 min post and 24 hours post infusion)

1.2. 4 MV-NIS Infusion

- The MV-NIS product will be administered by slow intravenous infusion in 250mL of 0.9% sodium chloride under close observation in the Clinical Research Unit (CRU) or at Rochester Methodist Hospital.
- Prior to administration of MV-NIS, two chemotherapy prepared RNs will verify the drug and dose against the orders and the CDM, and the identity of the patient to receive the drug.
- RN will remain in room with the patient during the one hour infusion. Continue to monitor them closely.
- PPE including gloves, gowns, mask and eye protection should be worn when handling the MV-NIS product. Protective eyewear must be worn at all times the product is handled, and in the event that splashing or spraying is anticipated, a mask or protective shield must be used. Protective eyewear should cover the eyes and areas above and below the eyes, and protection to the sides of both eyes. Face shields that extend from over the eye area to below the chin may be used.
- If acute febrile or allergic reaction occurs or if the patient develops rigors, contact the primary service and treat per orders.
- If symptoms suggestive of anaphylaxis such as dyspnea, itching, dizziness or symptomatic hypotension occur, stop the infusion, call the primary service and treat per orders.
- <u>Upon completion of medication administration flush tubing by the following procedure:</u>
    1. Attach your flush bag to the secondary medication tubing set-up, prime tubing and turn clamp off.
    2. Attach secondary IV set to the main IV tubing at the first port directly below the drip chamber.
    3. When the MV-NIS gets just below the air check valve and above the first port, lower the MV-NIS bag on the hook found in the secondary medication set-up and continue running at the same rate of infusion, **change the volume to be infused to 15 and continue running until the pump reads 0. This will be the end of the infusion.**
    4. While wearing PPE, cover IV site with 4x4 and disconnect the infusion from the saline lock. Dispose of bags and tubing in red bag. Flush saline lock with 10cc NS (and other flushes required for type of line prn).

1.3 Post infusion support, monitoring and pharmacokinetics (PK)

1.3.1 Vital signs

During and post-infusion, the schedule of vital sign monitoring will change from "Baseline on admission and then every 8 hours until infusion of MV-

NIS" to schedule shown below. Vitals may be done by Hematology Research staff, LPN or non-chemotherapy nurse. May be preferred for Hematology Research Staff to do the time points that coincide with PK blood draws (Post-infusion time points: 30 minutes, 1 hour, 2 hours, and 4 hours)

- Every 15 minutes during infusion
- End of Infusion
- 30 minutes post end of infusion (research nurse may perform)
- 1 hour post end of infusion (research nurse may perform)
- 2 hours post end of infusion (research nurse may perform)
- 4 hours post endo of infusion (research nurse may perform)
- Every 2 hours while awake, then every 4 hours

1.32 Pharmacokinetics and cytokine measurements

The Hematology research staff will be responsible for these blood draws

- End of Infusion (PK only)
- 30 minutes post end of infusion (PK only)
- 1 hour post end of infusion (PK only)
- 2 hours post end of infusion (PK only)
- 4 hours post end of infusion (PK + cytokine)
- 24 hours post end of infusion (PK + cytokine)
- 48 hours post infusion (cytokine only)

1.33 Other post-infusion support

- IV Fluids (see orders) to start 2 hours after completion of MV-NIS infusion
- Fever typically begins about 2 hours after infusion: support with acetaminophen, meperidine, and cooling blanket as needed
- Nausea is not unusual so anti-emetics will be available

1.4 Other precautions:

- In the hospital setting, utensils (e.g., bedpans, urinals) are cleaned with an institutionally approved detergent and rinsed twice following each use.
- In the inpatient setting, the toilet is covered with a white professional towel (plastic side up) and flushed twice. The white professional towel is disposed of in a red biohazard bag or biohazard waste container.
- Disposable patient care items contaminated with blood or body secretions are placed in a red biohazard bag or biohazard waste container.
- Soiled linen is placed in a clear plastic bag or a designated plastic chemotherapy bag and then put into a regular linen bag.

- Eating and drinking are prohibited in the patient's room during the infusion, and extreme precautions are taken while handling needles and other sharp instruments.

- All spills should be reported.

- Cytotoxic Spill kits (MC115455) are available from Central Service at Rochester Methodist Hospital (RMH) or by paging the General Par Stock pager (127-05232) at Saint Marys Hospital (SMH). In the outpatient setting spill kits are obtained from the MIC Warehouse through the Lawson ordering system. A spill kit should be obtained and available on a patient care unit/area prior to a patient receiving spillable (non-solid) cytotoxic medications.

- In case of a blood or body fluid exposure, thoroughly wash skin with soap and water; backbleed when appropriate; thoroughly rinse mucous membranes with water. Promptly report all exposures to management and Employee Health Services. Within 48 hours of the exposure, an Employee Incident Report should be completed.

1.5 Known potential toxicities of MV-NIS:

MV-NIS was rescued from a derivative of the Edmonston B vaccine strain of measles virus and we anticipate that the most common toxicities will be similar to those experienced after the administration of the measles vaccine. The most common side-effects seen with high doses of MV-NIS have been high fever that lasts for a couple to several days, nausea and headache. These tend to be most severe within a couple of hours after completing infusion. Thus patients might experience moderate fever up to 39.4°C fever and rash (minimal) within the first 5 to 12 days after virus injection. However it should be noted that this vaccine related measles like illness has been described only in measles-naïve subjects.

Not uncommon reactions:
- Moderate to high fever(with rigors) lasting 1 – 2 days, starting within a week or two of vaccination
- Nausea and vomiting
- Headache
- Cough and rhinitis
- Arthralgias
- Thrombocytopenia
- Lymphopenia
- Anemia
- A rash, lasting 1 – 2 days

Unexpected and rare reactions associated with the vaccine:
- Allergic reactions including anaphylaxis
- Reactions at the injection site such as a wheal, flare or urticaria
- Diarrhea
- Erythema multiforme
- Giant cell pneumonia
- Inclusion body encephalitis
- Guillain-Barré syndrome
- Vasculitis
- Otitis media
- Optic neuritis
- Ataxia

Viral transmission between patient and his/her contacts is thought to be unlikely, unless the patient develops florid measles infection. The vaccine strain of the measles virus (of which MV-NIS is a

derivative) has been shown to be shed in the urine of normal children undergoing routine vaccination. Despite the presence of viral shedding of the vaccine strain of measles virus, there has been only 1 case of symptomatic measles virus presumptively transmitted from a vaccinated individual (Rota et al J. Clin Microbiology 2005). However, since other patients on the Mayo Clinic grounds may be severely immunosuppressed, we will require that MV-NIS treated patients wear a mask when outside of their hospital room on Mayo Clinic grounds while they are shedding virus (tested by RT-qPCR).

We will be particularly vigilant for symptoms suggestive of either giant cell pneumonia or inclusion body encephalitis that have been rarely observed in immunocompromised patients who were administered the vaccine. If symptoms suggestive of persistent measles or either pneumonitis or encephalitis develop, the patients will be treated aggressively with anti-measles virus immune globulin and ribavirin and all the supportive care necessary as the situation might dictate.

Appendix II

APPENDIX II: Pre-Screening Process, Script, and Minimal Risk HIPPA Consent for Patients Who Initiated Contact Regarding Protocol Participation for inclusion/exclusion of MC038C, "A Phase I/II Trial of Systemic Administration of (Edmonston Strain) of Measles Virus, Genetically Engineered to Express NIS, with or without Cyclophosphamide in Patients with Recurrent or Refractory Multiple Myeloma"

AIMS, PURPOSE, OR OBJECTIVES:

To provide better service to patients by allowing a level of pre-screening prior to their investment in traveling to Rochester, MN to be screened for trial participation. This will be accomplished by contacting them, running through a checklist of eligibility criteria, and sending them a blood kit which can be completed locally and returned to the trial team. Patients have already contacted the study team expressing interest in the trial, so they have made first contact.

REASONING:
The reason is that there are more patients interested in the trial than there are doses of drug. We are going through the list on a first contact, first serve basis to exclude those subjects who will not be eligible and save them unnecessary financial costs.

The logistics of the pre-screening process are as follows:

1. The list of patients who have made contact have been collated and organized by date of contact.
2. Subjects who have expressed interest will be contacted by phone in the order in the spreadsheet. The telephone script (**Appendix II-1**) and oral consent (**Appendix II-2**) will be used to run through the eligibility check list.
3. If patients appear to be eligible based on the check list, we will instruct them that they will be receiving a kit for a mail-in blood test to check for measles virus anti-body titers along with a HIPAA Authorization to Use and Disclose Protected Health Information Form. The blood can be drawn at the time of a routine blood test. The kit will come with a self-paid mailing label. Cover letter is contained in **Appendix II-3** and HIPPA form is **Appendix II-4**).
4. Patients will be informed of the results of their measles titers. If titers are positive, the patients will be told that they are not eligible for the trial, but that they are welcome to come to Mayo at any time for a consultation and/or participation in other clinical trials. If negative, the patients will be told that they are a potential candidate and offered an appointment. We will keep track of doses of drug, availability of beds at CRU and on Hematology in-patient service.
5. If there are more eligible patients than there are slots in the trial, we will call and/or mail these patients informing them of the trial status without running through the checklist and without sending them the blood kit. We will ask them that if there is further expansion to the trial whether they would like to be contacted again at that time.

Mayo Clinic: Office for Human Research Protection
Telephone Script

APPENDIX II-1: Pre-Screening Process, Script, and Minimal Risk HIPPA Consent for Patients Who Initiated Contact Regarding Protocol Participation for inclusion/exclusion of MC038C, "A Phase I/II Trial of Systemic Administration of (Edmonston Strain) of Measles Virus, Genetically Engineered to Express NIS, with or without Cyclophosphamide in Patients with Recurrent or Refractory Multiple Myeloma"

Introduction:

Hello, this is _____ calling from the Mayo Clinic in Rochester, Minnesota (if out of state). May I please speak to _____?

***If the participant is there continue with the script.

***If the participant is not there, ask when it would be a good time to speak with _____?

Describe the Reason for the Call:

(Example of phone call to potential participant)

I am calling you because in May/June 2014 you expressed interest in our Phase II clinical MV-NIS trial for patients with relapsed refractory myeloma. As we shared with you previously, the clinical trial will re-open in August/September 2014. There was tremendous interest in this treatment trial with more than 1000 inquiries. Since the Phase 2 trial will have a maximum of 37 slots available, we have generated a list of patients and are making contact to see if these individuals still have interest in participating in this trial.

Are you still interested?

Please understand that your current or future medical care at the Mayo Clinic will not be jeopardized if you choose not to participate.

If no*: Thank them for their time and stop the recruitment process.*

If yes*:* Since you are still interested in enrolling on the measles (MV-NIS) for myeloma clinical trial, we would like to make things as convenient for you as possible. As the case for all clinical trials, there are 'eligibility 'criteria, which means that there are certain requirements about you and your medical condition that are necessary to make you a candidate. To save you time and travel, I would like to run through several of these criteria with you.

If we find that you are ineligible, you are still welcome to make an appointment to be seen at the Mayo Clinic to receive care/recommendations about your multiple myeloma and/or participate in another clinical trial.

If the screening questions would suggest that you are eligible, the next step would be to determine if you have existing immunity to the measles virus. Our studies show that if you have existing antibodies to measles (as measured by a blood test), it is almost a guarantee that the MV-NIS will not provide you with any benefit, so the absence of measles titers is an eligibility criterion.

For your convenience, we can send you a blood test kit that you can bring to your local laboratory to draw and mail back to us. If the test shows that there are no antibodies, then you will likely be eligible for the trial. If the test is show antibodies to measles, then you would not be a candidate for the trial. Once again, you are still welcome to make an appointment to be seen by one of our myeloma specialists; however, if the only reason that you would consider coming to the Mayo Clinic in Rochester at this time would be to participate on this particular trial, then we will have saved you the trip.

There is no payment for your travel expenses. The standard of care myeloma therapy will not be covered by the trial, but all of the extra blood work and scans related to the trial will be free of charge. There are several days of testing followed by admission to our clinical research unit for a day and a night during which time you would get the therapy and be monitored for side-effects. Additional blood work and scans are done 2, 7, 14 and 42 days after treatment in all patients. Some patients also require testing 21 and 28 days after treatment.

There is no guarantee that this treatment will help your myeloma, but we are hopeful that it will. Are you interested in hearing more and going through the checklist to see if you may be eligible?

If no: *Thank them for their time and stop the recruitment process.*

If yes: I would like to receive your formal permission to ask you questions and to potentially offer you the opportunity to have a blood test kit sent to you for further testing to see if you are potentially eligible.

Go to **ORAL CONSENT SCRIPT (Appendix II-2)**.

Once consented, start the check list

Inclusion criteria		
3.11	Are you older than 18 years?	
3.12	Is your myeloma progressing now?	
	Was your last response called a “very good partial response” or better? That would also include a complete response (CR) or stringent complete response?	
	Has it been 12 weeks or more since your last myeloma therapy (drugs like pamidronate (Aredia) or zolendronic acid (Zometa) are allowed?	
	Do you have measurable disease as defined as: - Serum M-spike >= 0.5 g/dL, or - If IgA myeloma, IgA > 1000 mg/dL, or - dFLC >10 mg/dL, or	

	- Urine M-spike >=200 mg/24 hours, or - Bone marrow plasmacytosis >= 10%, or - Extramedullary plasmacytoma >= 2 cm in diameter	
3.13	The following laboratory values obtained ≤ 14 days prior to study registration	
	• ANC ≥1000/μL	
	• PLT ≥50,000/μL	
	• Hemoglobin ≥ 8.5 g/dl	
	• AST ≤2 times upper limit of normal	
	• Creatinine < 2 times upper limit of normal	
	• Total bilirubin ≤ 1.5 x upper limit of normal	
	• INR ≤ 1.4 x ULN at the time of registration	
3.15	Are you willing to return to Mayo Clinic Rochester for follow-up? For the study, you will need to be here for treatment and testing days 1, 3, 8, 15 (possibly 22 and 29) and day 42 (6 weeks after treatment)?	
3.17	Are you up and about for at least 50% of the day?	
3.18	Are you willing to provide all blood and bone marrow specimens as required by the protocol?	
Exclusion criteria		Answers should all be "no"
3.21	Do you have an uncontrolled infection?	
3.22	Do you have active tuberculosis?	
3.23	Have you been off therapy for at least 12 weeks?	
3.24	Do you have symptomatic heart disease?	
3.25	Do you have active brain problem or seizure disorder?	
3.26	Have you been told that you have tested positive for HIV (the AIDS virus)?	
3.28	Were you immunized with the heat ***inactivated*** measles virus vaccine (this vaccine was given to some individuals between the years of 1963-1967)?	
3.29	[If appropriate] Are you pregnant?	
	[If appropriate] Are you nursing?	
	Will you be willing to use contraception for at least 4 weeks if you are having intercourse?	
	Have you had a prior ***allogeneic*** hematopoietic stem cell transplant and have active GVHD?	
	Do you have household contacts ≤15 months of age or a household contact with known immunodeficiency?	

If they are not eligible*: Thank them for their time and stop the recruitment process.*

If yes*:* We will send you a mail-in kit. You should receive it within a week and then you should hear from us within 1-2 weeks after we receive the blood test.

Closing

Thank you for participating in our research study. Please understand that your answers will remain confidential. If you have any additional questions, please call [redacted].

Mayo Clinic: Office for Human Research Protection
Oral Consent Script

Protocol Title: Minimal risk, first pass screening consent for MV-NIS trial eligibility: survey and blood test

IRB #: 06-005263
Principal Investigator: Angela Dispenzieri

You are being asked to answer questions in order to screen you for eligibility for the MV-NIS (measles for myeloma) Phase II clinical trial. If the answers to the questions suggest that you may be eligible for the clinical trial, we will invite you to have a blood test done at home to see if you have antibodies to the measles virus. If you do have immunity to the measles virus, there would not be any potential advantage for you to participate on the treatment trial.

If you agree to participate you will be asked to answer about 30 questions. You will not receive any payment for your participation.

The risks associated with the first pass screening portion of this research study are time burden and discomfort during interviews. Using sensitive questions during the oral consent process is common and can often lead to discomfort. You could also experience some discomfort during the blood draw. Otherwise, there are no known physical risks to you from taking part in the screening portion of this research study.

The benefits which may reasonably be expected to result from this screening are possible eligibility for the MV-NIS (measles) for myeloma trial.

Please understand your participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty. Specifically, your current or future medical care at the Mayo Clinic will not be jeopardized if you choose not to participate.

If you have any questions about this research study you can contact me at [redacted] If you have any concerns, complaints, or general questions about research or your rights as a participant, please contact the Mayo Institutional Review Board (IRB) to speak to someone independent of the research team at [redacted]

Mayo Clinic: Office for Human Research Protection
Contact Letter Template

(Date}

{ Name}
{Street Address}
{City, State Zip}

RE: *{ first name} { last name}*
MC#: *{mc #}*

Protocol Title: Minimum Risk Screening Process for Patients Who Initiated Contact Regarding Protocol Participation for inclusion/exclusion of MC038C, "A Phase I/II Trial of Systemic Administration of (Edmonston Strain) of Measles Virus, Genetically Engineered to Express NIS, with or without Cyclophosphamide in Patients with Recurrent or Refractory Multiple Myeloma

IRB #: 06-005263
Principal Investigator: Dr. Dispenzieri

Dear *{Mr., Ms, or Mrs.}*

You are being asked to participate in a pre-screening research study for the Phase I/II measles trial for patients with myeloma. You previously contacted the Mayo Clinic stating that you would like information or were interested in participating in the MC038C trial. This pre-screening process is being done to find out if you do/do not qualify for potential participation in the measles for myeloma Phase I/II trial without you having to physically travel to Mayo Clinic and incur unnecessary financial costs.

Please understand your participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty. Specifically, your current or future medical care at the Mayo Clinic will not be jeopardized if you choose not to participate.

If you agree to participate, you will be asked to sign the enclosed authorization form and have 10 cc (2 teaspoons) of blood drawn (kit enclosed) from a vein in your arm during your next routine clinical lab work up at your local treating medical facility. This lab kit will be mailed back to us by that facility for processing. This process can take up to two weeks. You will be notified of the results by either phone or mail.

If you do qualify, you will be invited for an appointment for further medical evaluations and formal trial screening for the measles for myeloma Phase I/II trial. There is no guarantee that you will still meet the qualifications at that time.

All information related to your multiple myeloma disease including current treatments, labs, past vaccines) obtained from you during this pre-screening process from the research team will be kept confidential. If you do not qualify or if you chose later not to participate, all information obtained from you up to that point will be destroyed immediately by the research team.

There is a blood draw associated with this pre-screening. The risk associated with this is that even though you are giving a blood sample, you still may not qualify for this study. In addition, you may experience pain or bleeding from the blood draw site. Rarely, infection may occur.

The benefits which may reasonably be expected to result from this research study are to determine whether you are eligible to participate without incurring the expense of traveling to Mayo Clinic Rochester prior to knowing whether you are a candidate.

If you decide to participate, please read and sign the HIPAA Authorization to Use and Disclose Protected Health Information form and return it in the postage paid envelope provided as we are not allowed to use the answers without your signature on the HIPAA Authorization to Use and Disclose Protected Health Information form. An extra copy is included for your records.

Contact me at [redacted] if you have any questions about:

- Study tests and procedures
- Research-related injuries or emergencies
- Withdrawing from the research study
- Materials you receive
- Research related appointments

If you prefer, you may write to me at the address given below:

[redacted]

Contact the Mayo Institutional Review Board (IRB) to speak to someone independent of the research team at [redacted] or toll free at [redacted] if you have questions about:

- Rights of a research participant
- Use of your Protected Health Information
- Stopping your authorization to use your Protected Health Information

Research-related questions not listed above, or any research-related complaints may also be addressed to me. If you prefer to speak with someone independent of the research team, you may contact the Mayo Institutional Review Board (IRB).

If you do not wish to participate, please indicate on the next page and return this letter since it will make a follow-up telephone call unnecessary. Thank you very much for your time and consideration.

Sincerely,

_____

RE: *{first name} {last name}*

MC#: *{mc #}*

☐ I am **enclosing** the HIPAA **Authorization to Use and Disclose Protected Health Information form** only. Please call me.

Your name: _____
Telephone number: (___)___-_____
Today's date: __/__/__
Best time to call: ☐ Morning ☐ Afternoon ☐ Evening
Best day(s) to call:_____

☐ I am **not** willing to participate in this research study.

Click here to access further instructions and details http://intranet.mayo.edu/charlie/mics-patient-provided-information-rst/ppi-forms/

MAYO CLINIC

Authorization for Mayo Clinic to Disclose Protected Health Information

Your privacy is important to us, and we want to protect it as much as possible. By signing this form, you authorize Mayo Clinic to disclose information as requested by the individual(s) you list below. This information may include, but is not limited to, verbal or written information relating to psychiatric/psychologic, sickle cell anemia, alcohol and drug diagnosis and treatment, billing information, and information from its affiliated entities.

Please complete, sign, and date this form. Be sure to include any individuals and/or specific details you may have listed previously, if appropriate, as any prior versions of this form will become inactive upon receipt of this completed form.

1) Write the name of the person(s) to receive information here:

_____

Relationship to Patient: ☐ Parent(s) ☐ Spouse ☐ Child(ren) ☐ Sibling(s) ☐ Domestic Partner ☐ Other _____

2) Write the name of the person(s) to receive information here:

_____

Relationship to Patient: ☐ Parent(s) ☐ Spouse ☐ Child(ren) ☐ Sibling(s) ☐ Domestic Partner ☐ Other _____

3) Write the name of the person(s) to receive information here:

_____

Relationship to Patient: ☐ Parent(s) ☐ Spouse ☐ Child(ren) ☐ Sibling(s) ☐ Domestic Partner ☐ Other _____

I understand the information to be released may include records related to behavior and/or mental health care, alcohol and drug abuse treatment, HIV/AIDS, and genetics. This authorization may be revoked at any time except to the extent that action has been taken in reliance upon it. Revocation must be made in writing to the provider/facility releasing the information. The provider/facility will not condition treatment on whether I sign the authorization. **I may be charged for copies in accordance with state law.** Information used or disclosed pursuant to this authorization may be subject to redisclosure by the recipient and may no longer be protected by federal law.

This authorization will expire one year from the date of signing unless I indicate an earlier date or event here: _____

ATTENTION: This is a legal document. Please read carefully. By signing, you agree that you understand and accept the terms on this form.

- **If the patient is 18 years of age or older**, the patient must sign and date the form.
- **If the patient is 18 years of age or older and is incapable of signing**, a legally authorized substitute may sign and date the form. Please indicate your legal authority, and include documentation of your relationship:
  ☐ **Legal Guardian or Conservator** ☐ **Healthcare Agent (Healthcare Power of Attorney)**
- **If the patient is 17 years of age or younger**, the patient's parent or legal guardian must sign and date the form, unless an exception exists under state or federal law. Please indicate your relationship:
  ☐ **Parent** ☐ **Legal Guardian**

Signature (Required)	Date Signed (Required) - *(Month DD, YYYY)*
Printed Name of Person Signing (if not patient)	

MC0072-34rev1112

7691

MAYO CLINIC

HIPAA Authorization to Use and Disclose Protected Health Information

Name and Clinic Number

TITLE		IRB #
Phase I/II Trial of Systemic Administration of Edmonston Strain of Measles Virus, Genetically Engineered to Express NIS, with or without Cyclophosphamide, in Patients with Recurrent or Refractory Multiple Myeloma		06-005263
RESEARCHER **Dr. Angela Dispenzieri and colleagues**	PROTOCOL LAST APPROVED BY IRB **January 20, 2014**	THIS FORM APPROVED **NOT YET APPROVED**

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission. You will be given a copy of this form.

Health information may be collected about you from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

This information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was done correctly.

If the results of this study are made public, information that identifies you will not be used.

Your health information may be used or shared with:

- Mayo Clinic research staff involved in this study.

Your health information may also be shared with:

- The Mayo Clinic Institutional Review Board that oversees the research.
- Researchers involved in this study at other institutions.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- The sponsor(s) of this study and the people or groups it hires to help perform this research.
- A group that oversees the data (study information) and safety of this research.

MAYO CLINIC

HIPAA Authorization to Use and Disclose Protected Health Information

Protection of your health information after it has been shared with others:

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study. Your decision won't change the access to medical care or any other benefits you get at Mayo Clinic now or in the future.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

You can cancel your permission to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
[redacted]

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate
[redacted]

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission lasts until the end of this study, unless you cancel it. Because research is an ongoing process, we cannot give you an exact date when the study will end.

MAYO CLINIC

HIPAA Authorization to Use and Disclose Protected Health Information

Printed Name of Participant		Mayo Clinic Number
Signature of Participant **X**		Date of Signature
Printed Name of Representative Signing for Participant (if applicable)	Representative's Relationship to Participant (if applicable)	
Signature of Representative Signing for Participant (if applicable) **X**		Date of Signature