Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

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Protocol Synopsis

PROTOCOL SUMMARY: A Randomized, Placebo-Controlled Study utilizing high dose trivalent influenza vaccine dose with a booster compared to standard of care in patients with monoclonal gammopathies

STUDY INTERVENTION:	Fluzone® High-Dose vaccine with a 30 day booster dose
INDICATION:	All patients with a diagnosis of a monoclonal gammopathy
STUDY Type:	Randomized, double blind, placebo-controlled, Phase II Study

Background and Rationale:

Influenza is a major cause of morbidity in the US. Patients with monoclonal gammopathies are known to have increased risk of developing influenza. Furthermore, several of the medications (such as proteasome inhibitors), commonly used to treat these tumors, are known to further increase the risk of these tumors. Seasonal influenza vaccination has been shown to reduce influenza related morbidity and is approved for routine prophylaxis in US. In 2009, Fluzone® high-dose vaccine was FDA approved in 2009 for adults aged 65 and older based on the data regarding higher rates of seroprotection (defined as hemoglutination antibody inhibition (HAI) titer of 40 or higher).

Sensing of pathogens by the immune system is mediated by family of distinct pattern recognition receptors (such as toll like receptors, TLRs) that then activate immune response. In the setting of tumors involving the immune cells themselves, such as multiple myeloma, tumor cells commonly express TLRs and signaling via TLRs has been shown to regulate the growth and survival of tumor cells. This has led to the hypothesis that exposure to common pathogens may itself contribute to promoting the growth of tumor cells. Unfortunately, these patients also have immune paresis and are at increased risk for infections. Prevention of major seasonal infections may therefore have major impact not only on infection-related morbidity, but also tumor growth. In addition to potentially direct effect on tumor cells, pathogen-related morbidity also leads to interruption of therapy, which may further compromise disease control. Thus, influenza infections may cause mortality directly or indirectly by interfering with disease control. By measuring all-cause mortality at the end of an influenza season it is possible to account for all possible effects of influenza which may be related to mortality.

Although seasonal influenza vaccination is routinely employed in patients with monoclonal gammopathies, the data about its efficacy in this setting are limited and very few studies have specifically focused on this population. This is particularly true in the setting of newer agents that further reduce B cell function. Existing data suggest that routine seasonal influenza vaccination is not very effective in this population, with seroconversion rates of <20%. One approach to enhancing the efficacy of vaccination is the use of boosters. In the past 2013-2014 flu season, Hahn et al gave a standard dose influenza booster vaccine after 30 days to 25 myeloma patients and noted a doubling of serologic protection (HAI titer ≥40) from 14% to 33%. This suggests that

there may be a role for booster vaccines in these patients, however there is much room to improve. Although routinely used in adults 65 and older, there are no prospective data on high dose flu vaccine (and specifically booster) in patients with monoclonal gammopathies. Fluzone® High-Dose has been widely used since 2009 and proven to be safe. Knowing that high dose influenza vaccine increases serologic protection in adults over 65, there is a chance that our study population may benefit as well with a booster strategy including the high dose vaccine.

We recently concluded a pilot study at Yale-New Haven Hospital over the 2014-2015 influenza season, (the SHIVERING Trial), using the same proposed high dose influenza vaccine with booster strategy. While much of the data analysis (including correlative studies of immune response) is currently ongoing, preliminary findings reveal that this strategy was safe and well tolerated in this population. All 51 patients who were enrolled received both high dose vaccine and booster doses and there were no grade 2 or above adverse events attributed to the study vaccine. In addition flu infection rate was only 4% of patients compared to an expected rate of 20% in this population. The findings from the pilot study, if confirmed in the context of a randomized controlled trial as proposed here, therefore have practice changing implications for the care of patients with monoclonal gammopathies / myeloma.

Our hypothesis is that the administration of Fluzone® High-Dose with booster to all patients with monoclonal gammopathies (irrespective of age) will lead to seroconversion rates exceeding 50% and more importantly, will reduce influenza-related morbidity, reduce interruptions in cancer therapy and reduce all-cause mortality at the end of the flu season.

In this study, we will administer Fluzone® High-Dose vaccine with a planned booster to patients with monoclonal gammopathies irrespective of age versus a standard of care control group. Primary endpoint is composite of documented infuenza infection rate and disease progression (as defined by International Myeloma Working Group criteria) at the end of the flu season. Based on the background data, we expect a higher rate of success in the experimental arm. As such, we power for success rates of 90% and 70% in the experimental and control arms, respectively. We will also analyze several secondary endpoints including rates of influenza related morbidity, the analysis of humoral and cellular immune response to these vaccines and the rate of disease control (defined as lack of disease progression by standard international myeloma working group criteria).

By comparing this experimental approach directly to standard of care, data from estimates of effectiveness will inform the design of larger future controlled studies. As such, the data from this study can lead to practice-changing results. The data on immune correlates will also yield important information about in vivo “immune-competence” of these individuals, which in turn is important to design trials with emerging immune therapies.

STUDY Endpoints:

Primary:

1) The primary clinical endpoint of this study is: to measure a composite of documented influenza infection rate and disease progression (as defined by International Myeloma Working Group criteria) at the end of the flu season following a high dose influenza vaccine booster strategy versus standard of care.

Secondary:

1. evaluate rates of serologic protection (defined as HAI titer >40) following Fluzone® High-Dose influenza vaccine with booster dosing versus standard of care.
2. measure T cell subsets and flu-specific T cell responses following high dose influenza vaccine booster dosing strategy versus standard of care.

STUDY DESIGN:

This is a phase II randomized placebo-controlled interventional study. Patients will be randomized in a 2:1 allocation of experimental group A to standard of care group B. Experimental group will receive high dose influenza vaccine with a booster high dose flu vaccine one month later. Standard of care arm will receive a single influenza vaccine (standard dose if age <65 and high dose if age ≥ 65) and a placebo booster vaccine after one month. Both group A and B will be stratified by disease type to allow for a balanced study population. Patients can be viewed as two distinct populations, those with disease requiring therapy (defined as any plasma cell disorder having at any time required therapy) and those with early disease (defined as asymptomatic multiple myeloma, asymptomatic Waldenstrom macroglobulinemia, or monoclonal gammopathy of undetermined significance). As such, we will stratify patients by disease requiring therapy versus early disease by separately randomizing patients into the two protocol groups but with the same allocation ratio of 2:1. Patients treatment is summarized as follows:

Group (Each group stratified by disease requiring therapy and early disease)	**Randomization**	**Initial Influenza Vaccine at day 0**	**Second High Dose Influenza Vaccine at day 30** (+14 days/-7days)
Experimental (A)	2	Fluzone® High-Dose	Fluzone® High-Dose
Standard of Care (B)	1	Fluzone® High-Dose if age ≥ 65, Standard dose influenza vaccine if age < 65.	Placebo

STUDY DURATION: 2015-2016 influenza season	**TOTAL SAMPLE SIZE:** 150 Subjects (100 in experimental group A and 50 in standard of care group B)
DOSING REGIMEN: Fluzone® High-Dose trivalent inactivated influenze vaccine given on day 0 and again on month +1 (+14 days/-7 days) in the experimental group.	

Schedule of Study Assessments

Procedure	2015 – 2016 Flu Season (August to May)				
	Day of Initial Vaccine (Fluzone High Dose in experimental group A vs. standard of care in group B) **Day of Initial vaccine, study enrollment and randomization into experimental versus standard of care arm**	**Day 7 (+/- 2 days)** **Research blood draw only***	**Day of Second Vaccine (Fluzone High Dose in experimental group A vs. placebo booster in group B)** **Roughly 30 Days following Initial vaccine (+21 days/- 7 days)**	**Month 2** **Roughly 30 Days following Second Vaccine (+14 days/- 7 days)**	**End of Study Visit[4]** **(may be conducted in person, by telephone, or by email)** **(End of flu season-May 1 to May 15, 2016)**
SPEP OR IFE OR serum free light chains OR quantitative immunoglobulins [1]	X				X
Research blood draw[2]	X	*X (patients may refuse this blood draw if it creates an inacceptable burden)	X	*X (if patients are unable to receive this blood draw within the above timeframe, blood draw may be delayed up to 90 days)	*X (patients may refuse this blood draw if it creates an inacceptable burden)
Inquire and document any influenza infection[3], influenza-related hospitalization, or death during the study period	X		X	X	X
Assessment of all grade II and above adverse events [5]			X	X	
Pregnancy test for women of childbearing potential[6]	X		X		

[1] Assessment of disease status within 30 days prior to first vaccine and within 90 days of the End of Study Visit. Both patients with measurable or evaluable disease are eligible. The preferred method to monitor disease should be established at baseline and repeated at the end of study visit. For patients with measurable disease, SPEP or FLC are preferred.
[2] See Appendix A for details regarding collection of research samples and correlative studies.
[3] All subjects should be informed and reminded to present to a health care facility at the first symptoms of possible influenza infection to have DFA checked.
[4] End of treatment and 30 days following second vaccine may be merged into a single visit if they fall within 15 days of each other.
[5] See Adverse Events section of the protocol for details.
[6] Childbearing potential is defined as a sexually mature woman who 1) has not undergone a hysterectomy or bilateral oophorectomy and 2) has not been post menopause for at least 24 months. Pregnancy test to be performed within 2 weeks prior to each vaccine.

Background and Rationale

Introduction

Plasma cell dyscrasias or monoclonal gammopathies are a group of benign and malignant disorders consisting of monoclonal plasma cells which secrete monoclonal immunoglobulins[1]. These disorders include the pre-malignant entity Monoclonal Gammopathy of Undetermined Significance (MGUS), asymptomatic / active multiple myeloma, asymptomatic / active Waldenström Macroglobulinemia (WM), solitary plasmacytoma, and primary amyloidosis. Patients with monoclonal gammopathies are routinely offered influenza vaccines however there is no evidence that they are effective in preventing infections.

Influenza Vaccination

Influenza is a major cause of morbidity in the US. The most vulnerable populations include adults over the age of 65 years, those with serious co-morbidities[2]. A particularly vulnerable population are thought to be patients with hematologic malignancies, particularly multiple myeloma. A population based study in Sweden of over 9,000 myeloma patients, demonstrated that myeloma was associated with a 5.4 fold increased risk of contracting influenza infections relative to healthy controls[3].

Clearance of viral infection and vaccine responses are dependent on cell mediated immunity(CMI). The most accepted serologic measurement of antibody protection following influenza vaccine administration is hemoglutination antibody inhibition (HAI) titer of 40 or higher. However, this cutoff corresponds to an estimated 50% clinical benefit of preventing influenza infections, based on studies in young healthy adults[4,5]. It is believed that CMI declines with age, which may help explain why the elderly are more vulnerable to influenza infections. HAI titers have also been shown to be lower in the elderly compared to young adults[6]. Based on studies showing increased serologic protection, Fluzone® high-dose vaccine was FDA approved in 2009 for adults aged 65 and older.

Patients with plasma cell dyscrasias are known to have depressed immune function. Studies in myeloma have shown B cell dysfunction (hypogammaglobulinemia), functional abnormalities of dendritic and T cells, inversion of T cell CD4:CD8 ratio, abnormal T cell Th1/Th2 $CD4^+$ ratio, and dysfunction of natural killer cells[7,8,9]. Anti-cancer medications can further adversely affect the immune system. It is known that patients who received chemotherapy within 7 days of trivalent inactivated influenza vaccine have poorer responses[10]. There is no published data regarding the effects of more commonly used novel agents such as IMIDs and proteasome inhibitors on vaccine responses.

Several studies have demonstrated a poor serologic antibody response in those patients included with myeloma and WM. However, there is a paucity of prospective trials focusing exclusively on patients with monoclonal gammopathies. No studies have specifically investigated influenza

immunity in precursor states such as MGUS, although these patients may have similar risks of unresponsiveness to influenza vaccine and are known to have hypogammoglubulinemia. Based on available trial data restricted to myeloma patients, serologic protection (HAI titer ≥40) to all three influenza strains following trivalent influenza vaccine is achieved in less than 20% of myeloma patients in each trial[11, 12, 13]. There have been two trials investigating the benefit of booster vaccine in myeloma patients. In 2005 Ljungmen et al, studied 70 patients with hematologic malignancies (10 with myeloma and 4 with WM) and administered a booster dose 30 days following standard influenza vaccine booster and found no increase in serologic protection[14]. More recently, in the past 2013-2014 flu season, Hahn et al gave a standard dose influenza booster vaccine after 30 days to 25 myeloma patients and noted a doubling of serologic protection (HAI titer ≥40) from 14% to 33%[15]. This suggests that there may be a role for booster vaccines in patients with hematologic malignancies, however there is obviously much room to improve.

Although routinely used in adults 65 and older, no one had studied high dose flu vaccine specifically in patients with monoclonal gammopathies. Fluzone® High-Dose has been widely used since 2009 and demonstrated to be safe. Knowing that high dose influenza vaccine increases serologic protection in adults over 65, our study population may benefit as well, given the similar but more significantly depressed cellular immunity in patients with monoclonal gammopathies. With this in mind, we have already designed the recent SHIVERING Pilot study at Yale New Haven Hospital over the 2014-2015 flu season. In this pilot study, all patients received Fluzone® High-Dose with a second booster dose after 30 days. Enrollment has closed and data analysis is ongoing. However, preliminary data revealed that all 51 patients enrolled tolerated the two vaccine doses well and no grade 2 or above adverse events related to vaccine were reported. In addition, with very close follow-up 2/51 patients (4%) patients developed documented flu infections despite an expected rate of 20% in this population (manuscript in preparation).

Rationale for Treatment in this Setting

Sensing of pathogens by the immune system is mediated by family of distinct pattern recognition receptors (such as toll like receptors, TLRs) that then activate immune response. In the setting of tumors involving the immune cells themselves, such as multiple myeloma, tumor cells commonly express TLRs and signaling via TLRs has been shown to regulate the growth and survival of tumor cells. For example, infectious particles can activate TLRs and cause proliferation of myeloma cell lines and secretion of IL-6 (a potent myeloma growth cycokine)[16]. This has led to the hypothesis that exposure to common pathogens may itself contribute to promoting the growth of tumor cells. Unfortunately, these patients also have immune paresis and are at increased risk for infections. Prevention of major seasonal infections may therefore have major impact not only on infection-related morbidity, but also tumor growth. In addition to potentially direct effect on tumor cells, pathogen-related morbidity also leads to interruption of therapy, which may further compromise disease control.

Ultimately if this novel vaccine strategy proves to be more effective, an important question will be if mortality will also be improved. As discussed above influenza infections are associated both with their own morbidity and mortality, and may have a negative impact on disease control, thereby indirectly increasing mortality. All-cause mortality as a clinical endpoint will take into account all possible relation of influenza infections to mortality. One year estimates are known for patients with plasma cell disorders. The most recent SEER data of one year survival for newly diagnosed myeloma, based on patients diagnosed in 2009 is 79.2%.[17] Relapsed refractory patients have lower survival depending on many risk factors and is estimated as low as 60-66%.[18,19] MGUS patients are not believed to have much of a decrease in survival compared to age-matched controls and one-year survival is estimated to be 98%.[20] Most of the patients seen at Smilow cancer Hospital are relapsed/refractory multiple myeloma patients. We anticipated that more than 2/3 of patients enrolled will be relapsed / refractory and less than 1/3 will be MGUS or newly diagnosed plasma cell disorder patients. As would be expected, relapsed patients have reduced time to progression with each successive line of therapy. Kumar, et al[21] followed 355 myeloma patients who have had at least two lines of therapy and showed that time to progression shortened with each line of therapy from 9.9 months after first therapy to 7.3 months after second therapy to less than 4 months after sixth line of therapy (see Figure 1 below). In our population of patients of relapsed patients mixed with newly diagnosed and early disease patients a conservative estimate of the proportion who would relapse from the time of initial vaccine to the end of the influenza season (which may range from roughly 4-8 months depending on when the patient receives their initial vaccine) is 10%. Considered together with an expected influenza infection rate of 20%, we would expect our control arm to have a combined disease progression and influenza infection rate of 30% (10%+20%).

To the authors' knowledge, there have not been any prior influenza vaccine studies in patients with monoclonal gammopathies, which have looked at clinical endpoints other than our pilot SHIVERING trial. Clinical endpoints which we plan to assess include number of influenza infections, influenza-related hospitalizations / deaths, and efficacy related to prior therapy. While prior studies have measured serologic response to influenza vaccines in patients with monoclonal gammopathies, there have not been any trials correlating T cell responses. We plan to try to better understand cell mediated immunologic response by looking at T cell functional assays.

Our **hypothesis** is that the administration of Fluzone® High-Dose with booster to <u>all patients</u> with monoclonal gammopathies (irrespective of age) will lead to seroconversion rates exceeding 50% and more importantly, will reduce influenza-related morbidity, prevent interruptions in cancer therapy and reduce disease progression at the end of the influenza season.

In this study, we will administer Fluzone® High-Dose vaccine with a planned booster to patients with monoclonal gammopathies (randomized into the experimental group versus standard of care). The experimental group will receive Fluzone® High-Dose vaccine with a second booster dose after 30 days, regardless of age. In the standard of care group, patients will receive influenza vaccine based on current standard of care clinical practice. Standard of care depends on age; patients ≥65 receive a single high dose influenza vaccine, patients <65 receive a single

standard dose vaccine. In addition, patients in the standard of care group will receive a placebo vaccine after 30 days, which will aid in the blinding between groups and allow for stricter comparison between groups.

Primary endpoint is a composite of documented influenza infection rate and disease progression (as defined by International Myeloma Working Group criteria) at the end of the flu season. We will also analyze several secondary endpoints including rates of influenza related morbidity, analysis of humoral and cellular immune response to these vaccines, and rate of disease control (defined as lack of disease progression by standard international myeloma working group criteria).

By comparing this experimental approach directly to standard of care, data from estimates of effectiveness will inform the design of larger future controlled studies. As such, the data from this study can lead to practice-changing results. The data on immune correlates will also yield important information about in vivo "immune-competence" of these individuals, which in turn is important to design trials with emerging immune therapies.

Study Objectives

Endpoints

Primary endpoints

The primary clinical endpoint of this study is to measure a composite of documented infuenza infection rate and disease progression (as defined by International Myeloma Working Group criteria) at the end of the flu season following a high dose influenza vaccine booster strategy versus standard of care. Please see sections under biostatistical considerations for details.

Secondary study endpoints

The secondary endpoints are 1) rates of serologic protection (defined as HAI titer >40) following Fluzone® High-Dose influenza vaccine after booster dosing and 2) measurement of T cell subsets and flu-specific T cell responses.

Investigational Plan

Study vaccine description

Fluzone® High-Dose

Proper Name: Influenza Virus Vaccine
Trade Name: Fluzone® High-Dose Vaccine
Manufactuer: Sanofi Pasteur, Inc, License #1725
Indication: Fluzone High-Dose is indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Fluzone (Influenza Virus Vaccine) for intramuscular injection is an inactivated influenza virus vaccine, prepared from influenza virusespropagated in embryonated chicken eggs. The virus-containing allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a nonionic surfactant, Octylphenol Ethoxylate (Triton®X-100), producing a "split virus".

The split virus is further purified and then suspended in sodium phosphate buffered isotonic sodium chloride solution.

Fluzone is standardized according to United States Public Health Service requirements and is formulated to contain HA of each of the following three influenza strains recommended for the current influenza season, including two A subtypes (H3N2 / HINI) and one influenza B subtype.

Dosage form

Fluzone® High Dose is supplied in 0.5 mL for intramuscular injection

Adverse events:

In adults 18 through 64 years of age, the most common injection-site reaction was pain (>50%); the most common solicited systemic adverse events were headache and myalgia (>30%).

In adults>65 years of age, the most common injection-site reaction was pain(>20%); the most common solicited systemic adverse events were headachemyalgia, and malaise (>10%)

Post Marketing Experience

The following events have been spontaneously reported during the post-approval use of Fluzone.

- Blood and Lymphatic System Disorders: Thrombocytopenia, lymphadenopathy.
- Immune System Disorders: Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- Eye Disorders: Ocular hyperemia

- Nervous System Disorders: Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination),dizziness, paresthesia
- Vascular Disorders: Vasculitis, vasodilatation/flushing•
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, pharyngitis, rhinitis, cough, wheezing, throat tightness
- Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome
- General Disorders and Administration Site Conditions: Pruritus, asthenia/fatigue, pain in extremities, chest pain
- Gastrointestinal Disorders: Vomiting

Screening and Eligibility

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 2, Schedule of Study Assessments and may take place on or < 30 days before the day of first vaccine administration.

Approximately 150 of subjects with monoclonal gammopathies will be screened for enrollment and must meet the eligibility criteria below. 100 patients will be randomized into the experimental group and 50 subjects will be randomized into the standard of care group. During screening, patients will be identified by disease type as having either disease requiring therapy or early disease. In order to maintain balanced stratification, patients of each disease type will be separately allocated in the same ratio of 2:1 experimental to control group. If a patient dies or discontinues their participation for any reason, we will not add another patient in their place.

Inclusion Criteria

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

Inclusion criteria

1. Understand and voluntarily sign an informed consent form.
2. Age ≥18 years at the time of signing the informed consent form.
3. Diagnosis of any monoclonal gammopathy: Monoclonal Gammopathy of Undetermined Significance (MGUS), asymptomatic / active multiple myeloma, asymptomatic / active Waldenström Macroglobulinemia (WM).

Exclusion criteria

1. Any serious egg allergy or prior serious adverse reaction to an influenza vaccine.

2. Use of any other influenza vaccine for the 2015 to 2016 flu season.
3. Women who are pregnant or plan to become pregnant in the study period.

Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Section 2 Table of Study Assessments.

At the end of the 2015-2016 flu season between May 1 to May15, subjects will undergo off study evaluations per the Schedule of Assessments.

Vaccine Administration

5.4.1 Treatment assignments

Individuals will be randomized at an allocation of 2:1 experimental to standard of care arm. The experimental group will receive high dose influenza vaccine with a booster high dose flu vaccine one month later. The standard of care group will receive a single influenza vaccine (standard dose if age <65 and high dose if age ≥ 65) and a placebo booster vaccine after one month. All study injections, whether vaccine or placebo will be redrawn into a fresh syringe to assist in blinding. Only the research pharmacist will have a record of the contents of each study injection.

5.4.2 Dosing regimen

The planned vaccine administration for investigation for experimental group is:

1) Fluzone® high-dose vaccine after flu vaccines are available (starting August 2015);

2) Fluzone® high-dose vaccine as a second booster dose to all subjects in each cohort.

The planned vaccine administration for investigation for standard of care group is:

1) Fluzone® high-dose vaccine if age ≥65 or standard dose trivalent inactivated influenza vaccine if age <65. Vaccines will be administered based on standard of care practice after flu vaccines are available (starting August 2015);

2) Placebo normal saline injection as a second booster dose to all patients in this group.

5.4.4 Record of administration

Accurate records will be kept of all vaccine administration.

Discontinuation of Study Treatment

Follow up will continue until the last study visit or the occurrence of any of the following events.

- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Withdrawal of consent
- Lost to follow up
- Death

Adverse events

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

Because any attribution of an adverse event from a vaccine would be expected to occur immediately or within several days, adverse events will only be recorded for a period of 30 days from each study vaccine. Within this time frame, all adverse clinical experiences grade 2 or higher, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the study vaccine, and the patient's outcome.

Following the 30-day window after the booster vaccine, survival data will be collected for the remainder of the influenza season in addition to any influenza-like illnesses and documented influenza infections.

Serious Adverse Event (SAE) Definition

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability or incapacity[2]
- Is an important medical event[3]

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

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

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

Protocol Amendments/Deviations

Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and IRB.

Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol per IRB Policy 710.

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

Data Management

Analyses and Reporting

Clinical data will be coded and blinded from the study investigators after randomization. Data will be analyzed and reported after all accrual is completed. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

Data Monitoring Committee

The study team will monitor the data on a regular basis. There is no formal DMC for this minimal risk study.

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency [monthly]. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator, the Institutional Review Board (IRB), Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. In the unlikely event that such events occur, Reportable Adverse Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or unanticipated problems involving risks to subjects or others will be reported in writing to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies per IRB policy 710. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project [via email as they are reviewed by the principal investigator.]

Biostatistical Considerations

The primary endpoint of this randomized Phase II study is a composite measure of two clinical endpoints. A patient is considered a treatment failure if either of the following events occur during the 2015-6 flu season:

- Progression of the underlying plasma cell disorder
- Any documented flu infection

We plan to enroll 50 patients in the standard care group and 100 in the vaccine group for a total of 150. Patients will be separately allocated in this 1:2 ratio based on their disease type of early disease versus active disease in order to maintain balanced stratification between the groups. For each disease type, this 1:2 ratio will be performed in blocks of three in order to maintain balance in the study at all times. A randomization schedule will be prepared by the study biostatistician, Dr Yao, in advance of the trial beginning. If the standard care group has 0.70 probability of success (defined above) and the vaccinated group has probability of success equal to 0.90 then the power of this design is 0.93. As another example, if the standard care group has 0.75 probability of success and the vaccinated group has 0.90 probability of success then the power of

our design is 0.78 at significance level 0.1. Patient deaths which are not related to influenza or disease progression will be censored for efficacy analysis.

Yale University's online OnCore system will be used to randomize the patients. Randomization will be performed by the clinical trials office of Yale University and the information released only to the research pharmacist.

We will monitor the study for the toxicity of the vaccine. The unacceptable toxicities include any serious adverse event grade 3 or higher which is believed to be related to the study vaccine. The tolerability will initially be tested in the first 20 patients in the vaccine arm. We will consider the vaccine tolerable if the rate of vaccine related toxicity is 10% or less and intolerable if 30% or more. If, in the first 20 patients, we observe 5 or more patients with vaccine related toxicity, then the cohort will be terminated early. With this design, the probability of terminating the cohort early is 0.04 if the true but unknown toxicity rate is 10% and 0.76 if the true rate is 30%.

Regulatory Considerations

Institutional Review Board/Ethics Committee approval

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

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

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

Informed consent

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

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original

consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

Subject confidentiality

The principle investigator affirms the subject's right to protection against invasion of privacy.

Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; original signed informed consents, etc) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after study closes).

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Appendices

Appendix A – Correlative Studies and Collection of Research Samples

Timing:

Blood:

30 ml in heparin anticoagulant (4 green tops)

- Day of first vaccine ± 1 week
- 7 Days after first vaccine ± 2 days (optional)
- Day of second vaccine ± 1 week
- 30 Days after second vaccine (-1 week, + 90 days)
- End of study blood draw between May 1 to May 15, 2016 (optional)

Correlative studies:

The Dhodapkar lab will process the research samples for performance of the following assays:

- Measurement of T cell subsets, including CD4+/CD8+, NK cells (Flow cytometry)
- Influenza-specific T cell response (intracellular cytokine analysis)
- HAI titers for influenza A and B
- Temporarily freeze PBMCs for cell mediated immune studies. Samples will be destroyed of after all testing is completed and the study is closed.

Appendix B – Figures and Tables

*Figure 1: Gradual decrease in the response duration of myeloma patients with increasing order of treatment regimen

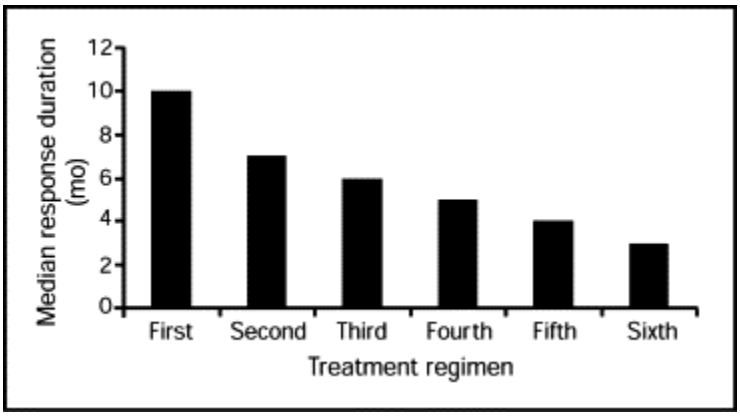

*Figure from Kumar, et al. Mayo Clin Proc 2004. Response duration is defined as time to death or start of a new therapy.