DCP Protocol #: MAY2016-08-01

Local Protocol #: MAY2016-08-01

A Pilot Study of MUC1 Vaccine in Current and Former Smokers at High Risk for Lung Cancer

Consortium Name: **Cancer Prevention Network (CPN)**

Name of Consortium Principal Investigator:
Paul J. Limburg, M.D., M.P.H.
Mayo Clinic
200 First Street, SW, Rochester, MN 55905
Telephone: 507-284-2511
Fax: 507-266-4371
E-mail: limburg.paul@mayo.edu

Organization: **National Cancer Institute, Division of Cancer Prevention**

Protocol Scientific and Medical Monitor:
Malgorzata (Margaret) Wojtowicz, M.D.
National Institutes of Health, National Cancer Institute,
Division of Cancer Prevention
Lung and Upper Aerodigestive Cancer Research Group
9609 Medical Center Drive, Rm 5E-104, MSC9781
Bethesda, MD 20892 (For FedEx, use Rockville, MD 20850)
Phone: 240-276-7012
Fax: 240-276-7848
Email: wojtowim@mail.nih.gov

Organization: **University of Pittsburgh**

Protocol Principal Investigator:
Arjun Pennathur, M.D. FACS *
University of Pittsburgh School of Medicine
Sampson Family Endowed Chair in Thoracic Surgical Oncology
200 Lothrop Street, Suite C-800
Pittsburgh, PA 15212
Telephone: 412-648-6271
Fax: 412-647-3104
E-mail: pennathura@upmc.edu

Organization: **University of Pittsburgh**

Co-Principal Investigator:
Olivera J. Finn, Ph.D. †
University of Pittsburgh School of Medicine
Department of Immunology
E1040 Biomedical Science Tower
Pittsburgh, PA 15262
Telephone: 412-648-9816
Fax: 412-648-9378
E-mail: ojfinn@pitt.edu

Organization: **Mayo Clinic**
Co-Investigator **David E. Midthun, M.D.**
200 First Street Southwest, Rochester, MN 55905
Phone: 507-284-2511
Fax: 507-266-4371
Email: Midthun.david@mayo.edu

Organization: **Mayo Clinic**
Statisticians: Nathan R. Foster, M.S. † and Sumithra J. Mandrekar, Ph.D. †
200 First Street, SW, Rochester, MN 55905
Telephone: 507-284-5051; 507-266-6724
Fax: 507-266-2477
E-mail: foster.nathan@mayo.edu; mandrekar.sumithra@mayo.edu

* Investigator having NCI responsibility for this protocol
† Study Contributor(s) not responsible for patient care

ClinicalTrials.gov NCT03300817
IND Sponsor: NCI/Division of Cancer Prevention

IND# #[redacted]
Agent(s)/Supplier: MUC1 peptide**,** U. of Pittsburgh/Poly ICLC adjuvant: Oncovir, Inc.
Contract # HHSN261201200042I
Protocol Version Date: January 25, 2021

Protocol Revision or Amendment # Version 5.0, Amendment 6

Participating Organizations

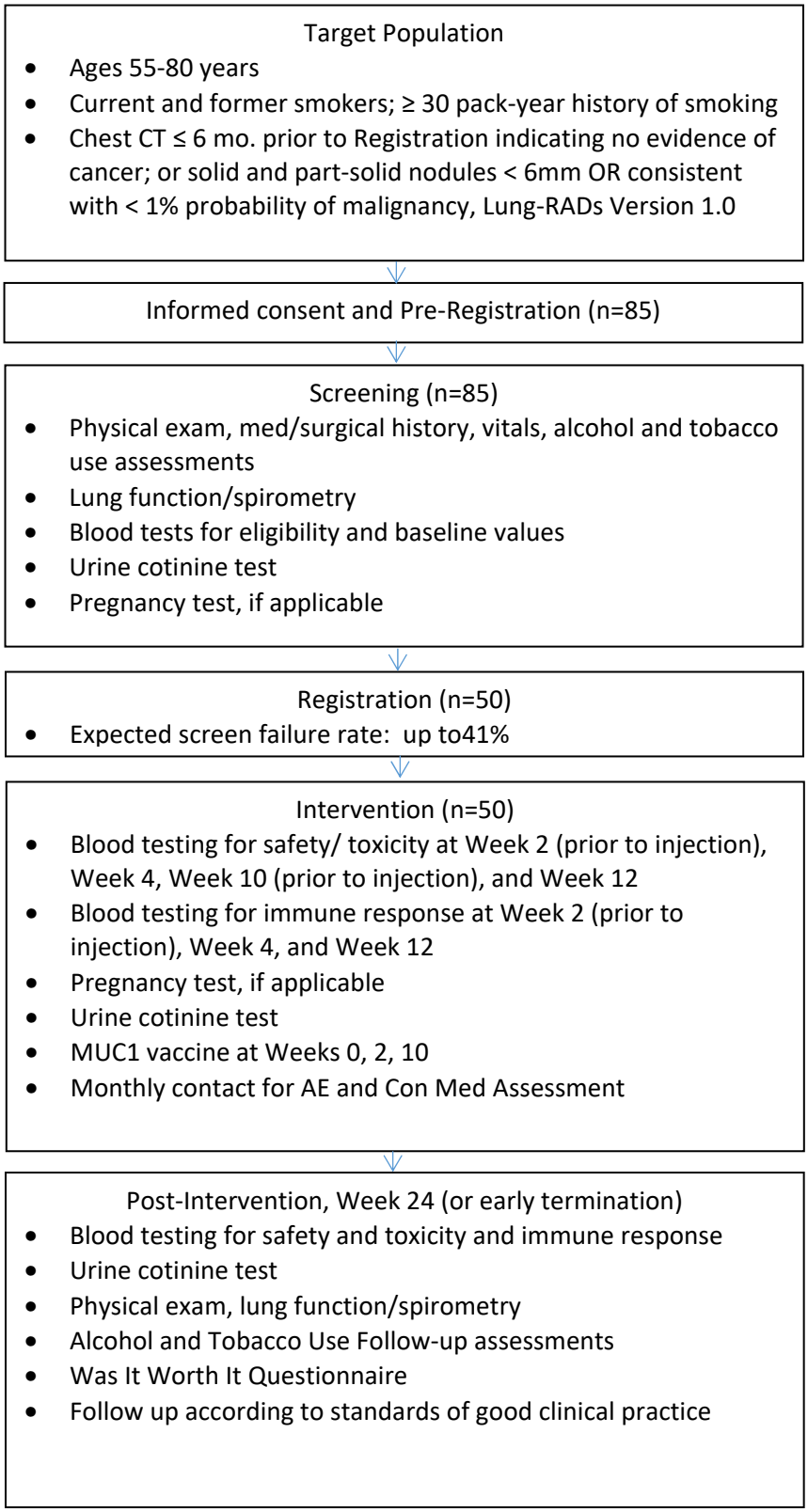
Organization and Site Investigators	
University of Pittsburgh Medical Center – PA015 **200 Lothrop Street, Pittsburgh, PA 15213** **Arjun Pennathur, M.D.** Telephone: 412-648-6271 Fax: 412-647-3104 E-mail: pennathura@upmc.edu **Rajeev Dhupar, M.D.** Telephone: 412-623-2025 Fax: 412-647-3104 E-mail: dhuparr2@upmc.edu **James Luketich, M.D.** Telephone: 412-647-7555 Fax: 412-647-3104 E-mail: luketichjd@upmc.edu **Manual Villa-Sanchez, M.D.** Telephone: 412-647-7555 Fax: 412-647-3104 E-mail: villam2@upmc.edu	**Matthew J. Schuchert, M.D.** Telephone: 412-648-6271 Fax: 412-647-3104 E-mail: schuchertmj@upmc.edu **Inderpal Sarkaria, M.D.** Telephone: 412-623-2025 Fax: 412-647-3104 E-mail: sarkariais@upmc.edu **Neil A. Christie, M.D.** Telephone: 412-623-2025 Fax: 412-647-3104 E-mail: christiena@upmc.edu **David Wilson, M.D.** Telephone: 412-687-3355 Fax: 412-647-3104 E-mail: wilsondo@upmc.edu
Mayo Clinic in Rochester, MN – MN026 **200 First Street Southwest, Rochester, MN 55905** **David E. Midthun, M.D.** Phone: 507-284-2511 Fax: 507-266-4371 Email: Midthun.david@mayo.edu	**Ryan M. Kern, M.D.** Phone: 507-284-2511 Fax: 507-266-4371 Email: kern.ryan@mayo.edu **Dante N. Schiavo, M.D.** Phone: 507-284-2511 Fax: 507-266-4371 Email: schiavo.dante@mayo.edu **Paul J. Limburg, M.D., M.P.H** Phone: 507-284-2511 Fax: 507-266-4371 Email: Limburg.paul@mayo.edu

Contacts

Questions:	Contact Name:
Test schedule Study visits and procedures Specimen handling Adverse Events	Julie Ward *Lead Study Coordinator* University of Pittsburgh Medical Center Phone: 412-647-8583; Fax: 412-623-3143 Email: wardj@upmc.edu
Serious Adverse Events	See Protocol Section 11.2
Subject eligibility, Test schedule Adverse events, Forms completion Paraffin-embedded biospecimens	Sydney Hain CPN *Research Base* Data Manager and Pathology Coordinator Phone: 507-293-2478 E-mail: hain.sydney@mayo.edu
CPN Lead Site Coordinator Budgets and Contracts Protocol Development Forms, Checklists, Website	Sharon Kaufman CPN *Research Base* Senior Program Coordinator/CLO Lead Site Coordinator Phone: 507-293-1605 Fax: 507-266-4371 E-mail: kaufman.sharon@mayo.edu
Regulatory Administrative Recruitment	Liz Ambulay CPN *Research Base* Regulatory Affairs Specialist Phone: 507-293-1605 E-mail: Ambulay.liz@mayo.edu
Pre-Registration and Registration	CPN Registration Office (8:00 – 4:30 Central time) Phone: 507-284-4130; Fax: 507-284-0885 Email: random01@mayo.edu
Monitoring Education	Anne Holland CPN *Research Base* Compliance Coordinator Phone: 507-293-7795 Email: Holland.anne@mayo.edu
All other biospecimens BAP/Biospecimens collection and shipment	Roxann Neumann, RN, BSN, CCRP CPN *Research Base* Biospecimen Resource Manager Phone: 507-538-0602; E-mail: Neumann.roxann@mayo.edu

SCHEMA

A Pilot Study of MUC1 Vaccine in Current and Former Smokers at High Risk for Lung Cancer



Optional Follow-Up (Week 28)

- Optional telephone call to assess AEs/SAEs (and Concomitant Medications, if applicable) not resolved at the time of the Week 24 visit.

Endpoints (n=40 evaluable)

- Expected drop-out/non-evaluable rate ~20%
- Primary Endpoints:
  - Immunogenicity response (antibody titer ≥ 2-fold higher at Week 12 compared to baseline)
  - Safety, assessed throughout the trial and continued observation for 24 Weeks
- Secondary Endpoints:
  - Immunogenicity in current vs. former smokers
  - Correlation between Pre- vs. post-vaccination levels of MDSCs and response to vaccine

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

- Immunogenicity of the vaccine, assessed at week 12, based on the increase in IgG anti-MUC1 antibody titer over the pre-vaccination levels
- Safety, assessed throughout the trial and continued observation for 24 weeks

1.2 Secondary Objectives

- To explore potential differences, if any, in the immunogenicity of the vaccine (as assessed at week 12 by the IgG anti-MUC1 antibody titer ratio) in current vs. former smokers.
- To evaluate pre-vaccination levels of circulating myeloid derived suppressor cells (MDSC) and correlate with the ability to respond to the vaccine.

1.3 Exploratory Objectives

- To explore immune response at Week 24
- To explore the relationship between COPD status at pre-registration and immune response in current versus former smokers
- To explore the impact of the MUC1/Poly-ICLC vaccine on inflammation-related high sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) levels
- To explore the impact of baseline levels of hsCRP and IL-6 on the ability to successfully vaccinate with MUC1/Poly-ICLC
- To establish a biospecimen repository archive: frozen peripheral blood live cells and plasma for future more detailed and comprehensive immunologic assays, including direct testing of anti-MUC1 T cell immunity

2. BACKGROUND

2.1 Lung Cancer

Lung cancer is the most common neoplasm in the United States, and in 2017, an estimated 222,500 people in the United States will be diagnosed with lung cancer.[1] It kills more men and women than the combined incidence of the next four most common cancers, with an estimated 155,870 (lung and bronchus) deaths in 2017 in the United States.[1] Worldwide, it is estimated that 1.8 million new lung cancers were diagnosed in 2012.[2] Tobacco smoking is the most common underlying etiology for lung cancer, with an estimated 80-90% of patients having a smoking history.[3, 4] Smoking cessation is an essential component for prevention of lung cancer. However, this strategy has limitations. Smoking cessation is challenging, and even when smoking cessation is successful, it does not immediately eliminate the risk of lung cancer, although the risks decrease over time.[5, 6] Notably, more than 50% of lung cancers occur in individuals who have quit smoking.[7] This risk of lung cancer remains higher compared to never smokers even 40 years after quitting smoking.[3]

Survival is poor after diagnosis of lung cancer (15% 5-year survival), and new strategies for prevention of this deadly disease are urgently needed, such as chemoprevention. However, to date, chemopreventive

interventions for lung cancer have demonstrated inconsistent results. In a multicenter study, with participation of the University of Pittsburgh and the Mayo Clinic in Rochester, MN, oral Iloprost was investigated as a chemoprevention agent in current or former smokers. In this randomized, phase II placebo-controlled trial, Iloprost significantly improved endobronchial histology in former smokers, but no improvement was noted in current smokers.[8] A recent analysis by the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines concluded that none of the phase 3 trials with the agents b-carotene, retinol, 13-cis-retinoic acid, a-tocopherol, N-acetylcysteine, acetylsalicylic acid, or selenium demonstrated beneficial and reproducible results, and none of these agents were recommended for chemoprevention.[7]

In addition, in this analysis, other agents including Iloprost and cyclooxygenase-2 inhibitors were not recommended for chemoprevention based on the evidence published in the literature.[7] With inconsistent results of chemoprevention trials, another emerging area of interest is immunoprevention of lung cancer.[9] The presence of immune cell infiltrate has been reported to be associated with improved survival in several cancers.[10-13] We have previously demonstrated that the density of tumor infiltrating lymphocytes correlates with outcomes after resection of Stage I non-small cell lung cancer (NSCLC).[14] A higher density of tumor infiltrating lymphocytes was associated with improved disease free survival in resected large Stage I NSCLC.[14] These and other studies have sparked excitement in the investigation of immune strategies for the prevention of lung cancer.

2.2 Study Agent: MUC1/Poly-ICLC Vaccine

Vaccine antigen MUC1: Mucin 1 (MUC1) is a high molecular weight (>200,000 dalton) type I transmembrane glycoprotein that is aberrantly overexpressed in all adenocarcinomas, including lung cancer. MUC1 is expressed by normal ductal epithelial cells but in very low levels, polarized to the apical surface, and with extensive O-linked glycosylation. MUC1 expression on cancer cells is characterized by high levels of hypoglycosylated forms and loss of apical polarization (**Figure 1**).[15]

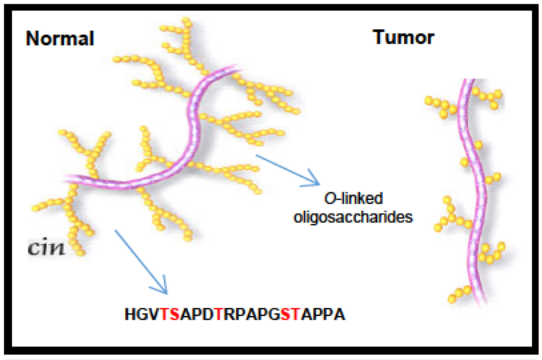


Figure 1: Abnormal MUC1 is overexpressed and hypoglycosylated. Hypoglycosylated MUC1 exposes the disaccharide T antigen and the shorter monosaccharide Tn antigen attached to the protein backbone of MUC1 molecules.

Abnormal MUC1 expression has been the target for both active and passive immunotherapy of cancer in many pre-clinical and clinical studies.[16] The greatest difference between MUC1 on normal cells and tumor cells resides in the variable number of tandem repeats (VNTR) region, the target of most MUC1-specific therapeutic antibodies and a candidate antigen for cancer vaccines. In the latest NCI workshop on tumor antigen prioritization for vaccines and other forms of immunotherapy, MUC1 was ranked as the overall #2 priority target.[17] Its priority was a result of over 25 years of preclinical studies in animal models and over 20 years of clinical trials.[18]

Therapeutic MUC1 vaccines: MUC1 proteins, peptides, glycopeptides, or DNA-based vaccines have been widely used with or without adjuvants, loaded on dendritic cells (DC), with cytokines and immune stimulatory molecules, or engineered in various viral vectors, for treatment of cancer.[18, 19] These have been administered to individuals with advanced disease and compromised immune systems. Even though the immune response induced by the vaccines was infrequent and at low levels, both humoral

and cellular responses have been reported. At the University of Pittsburgh Cancer Center, we have run seven clinical trials of a therapeutic cancer vaccine using the unglycosylated VNTR 100mer MUC1 peptide representing 5 tandem repeats, a highly immunogenic form not found on normal epithelial cells, combined with various adjuvants.

Trials in resected pancreatic cancer were performed under the condition of minimal residual disease. In the first trial, we used MUC1 100mer peptide plus the SB-A2 adjuvant from SKB. The vaccine was safe and induced low level IgG antibody and low frequency of T cells in several participants. Two of 16 participants were alive and disease-free at 32 and 61 months of follow up, and no toxicity was seen that could be attributed to the vaccine.[20] The second Phase I/II trial used MUC1 100mer-peptide-loaded on DC.[21] The vaccine was well-tolerated and non-toxic in 12 participants enrolled. The participants were followed for over four years, and 4 of the 12 participants were alive without evidence of recurrence at 5 years. Elsewhere, a randomized phase IIB trial of Stimuvax MUC1 cancer vaccine, which consists of MUC1 25aa peptide from the VNTR formulated in liposomes (BLP25) and given with the immunoadjuvant monophosphoryl lipid A, showed efficacy (a median survival of 30.6 months vs. 13.3 months in controls) in individuals with stage IIIB and IV non-small-cell lung cancer (NSCLC).[22] This vaccine progressed to Phase III showing a similar therapeutic benefit, in a predefined subgroup treated with concurrent chemoradiotherapy, even though the overall study result (combined response in stage III and stage IV patients) was negative.[23] Therapeutic vaccines using MUC1 engineered into viral vectors are being tested primarily at NCI (pox vectors) and at a company called Transgene, in France (vaccinia vectors).

In the NCI trial, 25 individuals with various adenocarcinomas were treated with a poxviral vaccine regimen consisting of the genes for CEA and MUC-1, along with a triad of costimulatory molecules. The vaccine was well-tolerated. Low but detectable immune responses to MUC-1 (and/or CEA) were seen in 9 of 16 participants.[24] In the randomized Phase IIb portion of the TIME trial, addition of a MUC1 vaccine TG4010 to standard first-line chemotherapy in advanced non-small-cell lung cancer resulted in significant improvement in the primary endpoint of progression-free survival and in an increased proportion of patients achieving a response. Overall survival was also significantly improved in certain subgroups, including non-squamous histology, when compared with the control group of first-line chemotherapy and placebo.[25, 26]

Prophylactic MUC1 vaccines

Completed feasibility study of the MUC1 vaccine in individuals at high risk for colon cancer: When this study opened at the University of Pittsburgh in 2008,[16] it was the first time that a vaccine directed to a non-viral tumor antigen was administered to study participants without tumors. The vaccine was composed of the same MUC1 100mer peptide used previously in 7 therapeutic vaccine trials at the University of Pittsburgh from 1993 until 2008. The peptide was admixed with a TLR3 adjuvant, Poly-ICLC (Hiltonol), also used previously as adjuvant in some of our therapeutic MUC1 vaccines. Thirty-nine individuals with a previous diagnosis of advanced colon adenoma, a premalignant lesion that could progress to colon cancer if not detected on time by colonoscopy and removed, completed the trial. Participants were vaccinated at W0, W2 and W10, and their immune response specific for the MUC1 peptide was evaluated at Week 12 and compared to pre vaccination. A booster shot was administered at one year to evaluate MUC1 specific immune memory. Forty-four percent of participants made anti-MUC1 IgG in response to the vaccine, at levels much higher than ever seen with the same vaccine in cancer patients.

Most importantly, all tests to evaluate toxicity (evidence of reactivity of the vaccine-induced immune response against normal tissues) during the duration of the trial and after more than 150 injections administered, indicated only minor adverse events, and these participants have remained without any vaccine-related adverse events for over 8 years. The surprise in this study was that 56% of participants did not respond to the vaccine. We examined the most likely factors such as age, gender and HLA type, as possible correlates with response and found no correlations. However, when we examined the pre-vaccination PBMC, we saw that the non-responders had statistically significant increases in circulating myeloid-derived suppressor cells (MDSC). MDSCs can strongly suppress development of adaptive immunity.

Ongoing placebo-controlled multi-center MUC1 vaccine trial in individuals at high risk for colon cancer: Based on the data from the pilot trial (see previous section), we are currently running a larger multi-center, 1:1 placebo controlled efficacy trial of the same vaccine in participants with recently diagnosed advanced adenomas. As of the date of submission for this proposal, ninety-seven of the planned 110 evaluable participants have been accrued over the last two years. Most of them have completed the first phase of the vaccine, W0-W12, and some have already reached the one-year booster stage. Because it is expected that 48% of these individuals will have a polyp recurrence within 1-3 years from diagnosis, trial participants will be followed for at least 3 years with polyp recurrences recorded. We expect between 40-50% responders and equal number of vaccine non-responders, due to increased levels of circulating MDSCs. In the placebo control, we also expect to see around 50% of participants with increased numbers of MDSCs. Independent of the vaccine, we will also evaluate recurrence rates in MDSC high versus MDSC low individuals. The trial is storing the pre-vaccination as well as the recurrent adenomas, and we plan to study the local microenvironment and infiltrating cells to identify if and how these features affect the vaccine response, systemic immunosuppression via MDSCs, and risk for adenoma recurrence.

Proposed study of MUC-1 vaccine for prevention of lung cancer: Based on collected data and observations to date with the colorectal cancer prevention trials, our goal now is to test the feasibility of the MUC1 vaccine for prevention of other cancers. In this proposal, we have chosen individuals at high risk for developing lung cancer, age 55-80, who have ≥30 pack year smoking history and are still smoking or quit < 1 year (current smokers) or have quit 1-15 years prior to study registration (former smokers). These criteria match those individuals at high risk for lung cancer who are recommended to be screened for this malignancy by U.S. Preventive Services Task Force (USPSTF).[27] Participants are also required to have low risk for the existence of malignancy based on Lung-RADs, Version 1.0.

Preliminary data

Completed feasibility trial at the University of Pittsburgh: Between 2008 and 2012, we enrolled 40 participants who received MUC1 – Poly ICLC vaccine at 0, 2, and 10 weeks and antibody titers were evaluated prior to each vaccination and at week 12, 28 and 52.[16] In the 39 participants who received all three initial doses of vaccine, 17 (44%) had over a two-fold ratio increase at week 12, ten participants had ratios over 4.5 fold, and another 4 participants had a ratio increase from 1.4-2.0. The kinetics of the responses were similar, with peak antibody levels generally occurring after the third injection. As expected, circulating antibody levels tended to decline over the next year with clearance of the vaccine antigen. The overall response rate of 44% was much higher than 2-3% reported for most therapeutic vaccines including MUC1 vaccines. The non-responders to the vaccine, as was described above, had increased levels of circulating MDSCs that suppressed the ability of the vaccine to elicit immunity. See **Figure 2**.

Response to Booster vaccine: To test for the presence of a vaccine-induced T cell memory response, participants received a booster dose of vaccine at 1 year. Of the 16 participants who responded to the initial vaccination and received the booster, 12 (75%) had a two-fold ratio increase when comparing week 54 to week 52. Three of the 4 who did not have a two-fold elevation at week 54 had maintained high levels of antibody at week 52, hence did not manifest a 2-fold ratio increase at week 54. Overall, the results suggest that responders established a T cell memory response to the MUC1 antigen. In the proposed trial, we will not be administering a booster shot. Since all the W12 responders in the previous trial also responded to the 1-year booster shot and none of the non-responders did, W52 would not add new information. This also allows us to complete the study much faster.

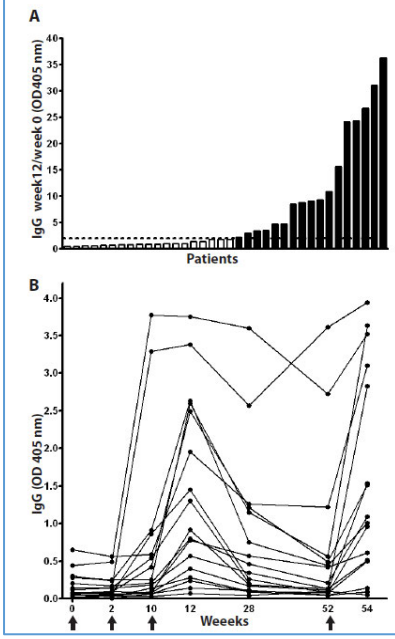


Figure 2A: Ratio response in MUC1 antibody.
Figure 2B: Kinetics of response to vaccination at 0, 2, and 10 weeks (arrows under X axis) and to booster vaccine at Week 52.

Adverse Events: Over 150 vaccinations were administered and no adverse events above grade 1 were identified or unanticipated adverse events observed. Most participants developed erythema with soreness at the injection site. Some developed short-lived fever and muscle aches, which responded well to analgesics such as Tylenol. We had nearly 100% compliance with the study protocol. Participants were monitored with immunofluorescent ANA titers pre vaccination and at 1 year. No participants have developed a change in ANA titer, and no new autoimmune diseases were observed.

Evaluation of Immune Non-Responders: Lack of response to vaccination was correlated with high levels of circulating myeloid-derived suppressor cells but not to circulating T regulatory cells.

O*ngoing randomized placebo controlled multi-center trial:* The MAY2013-01-01 trial started in 2014 and in two years completed accrual of 102 evaluable participants, most of whom received the full course of the vaccine, W0, W2, W10, and were evaluated for post-vaccine IgG titers at W12. Our preliminary data show over 30% responders so far and 70% non-responders who are either bona-fide non-responders or are in the placebo group (50%). We have also evaluated MDSC levels and find a wide range, with some individuals having very high levels of circulating MDSC. These are very preliminary results that will be possible to interpret only when the trial is unblinded. What we can say with confidence at this point is that we have seen no adverse events.

Abnormal MUC1 expression in bronchial dysplasia: Even though abnormal MUC1 expression has been reported on various types of lung dysplasia, we wanted to confirm that in our laboratory. From the Cancer Prevention Network (CPN), we obtained paraffin-fixed tissue sections from bronchial dysplasia biopsies that were collected in the context of the "Randomized, Phase IIb Trial of Sulindac in Smokers with Bronchial Dysplasia," DCP Protocol # MAY03-1-02. We received 8 samples, 4 of mild and 4 of moderate dysplasia. By immunohistochemistry using two different anti-MUC1 antibodies, we found increased expression (as seen by antibody HMPV) and abnormal glycosylation (antibody 4H5) in all samples. **Figure 3** shows two examples of MUC1 expression in moderate dysplasia.

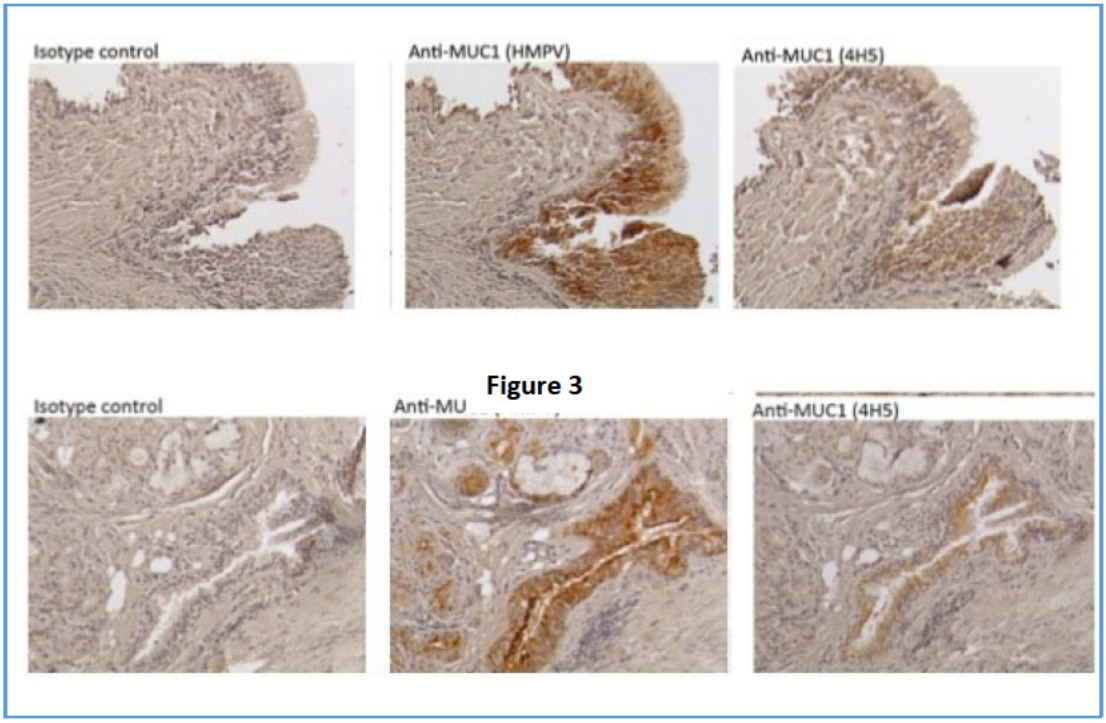


Figure 3

2.3 Rationale

Immunotherapy targeting antigens known to be aberrantly expressed on lung cancer and on premalignant lung lesions offers the potential for a relatively non-invasive and non-toxic prevention strategy. Because of the specificity of the immune response and its long-term memory, it offers potential for prolonged protection from cancer progression. Data suggest that aberrant expression of tumor cell antigens is subject to immune surveillance. Vaccines intended to boost anti-tumor immune responses have been tested in patients with many types of cancer and advanced metastatic disease.[28] Even when an increase in post-vaccination immunity was achieved (albeit at lower than expected levels), it rarely had an effect on the clinical outcome. The limited effect of vaccine therapy in established cancer is known to be due to numerous immunosuppressive mechanisms that develop in the cancer patient over time, caused by the presence of the tumor and its microenvironment, the immunotoxicity of standard cancer therapy, or both.[29, 30]

An opportunity to bypass these barriers is presented by the discovery that many antigens that are abnormally expressed on tumor cells and have been targeted by cancer vaccines are also abnormally expressed and could be targets on precursor lesions.[31] These lesions include adenomatous polyps as precursors to colon cancer, PanINs to pancreatic cancer, CINs to cervical cancer, or pre-malignancies for smokers (e.g. those with a substantial history of smoking), including bronchial dysplasia (for squamous cell cancer) and atypical adenomatous hyperplasia (for adenocarcinoma). This suggests that immunization of these patients, before the tumor and cytotoxic therapy have had the chance to suppress the immune system, might be possible and even preferred.[32] We have been testing this possibility since 2008 in the well-elucidated pathway of premalignant to malignant progression-adenomatous polyp to colon cancer.

The vaccine is based on the MUC1 antigen[15] abnormally expressed on colon cancer and precancerous polyps, described in detail below. The vaccine was administered to healthy individuals with an increased risk for colon cancer due to the history of adenomatous polyps.[16] Based on the data from this pilot study, we have undertaken a multi-center, placebo-controlled efficacy trial of the same MUC1 vaccine and in the same type of high-risk individuals for colon cancer following removal of an advanced adenoma. This ongoing trial is sponsored by NCI DCP and coordinated by CPN at the Mayo Clinic in Rochester, MN. The endpoints of the trial are safety, immunogenicity, and reduction of polyp recurrence. Because MUC1 is abnormally expressed in lung cancer as well as pre-invasive and premalignant dysplasia,[33] we propose to test this vaccine in current and former smokers who are considered to be at an increased risk for developing dysplasia that can progress to lung cancer.

Chronic inflammation is a well-recognized hallmark of cancer.[34] Cigarette smoking is a major risk factor for lung cancer development. Among the mechanisms by which smoking increases risk of lung cancer is increase in chronic inflammation. An abundance of data demonstrates that chronic inflammation induces an immune-inhibitory environment conductive to cancer development. Release of immunosuppressive cytokines e.g. IL-6 or IL-10 is one of the mechanisms involved. High sensitivity C-reactive protein (hsCRP) is another marker of inflammation and individuals with elevated hsCRP concentration have been shown to have increased risk of several inflammation-related cancers, especially lung cancer.[35-37]

Results of a recent trial of anti-inflammatory therapy with canakinumab inhibiting interleukin 1β (IL-1β) reported reduction in lung cancer incidence among individuals with elevated hsCRP and IL-6 levels.[38] In this report, those with increased concentrations of hsCRP and IL-6 had the highest risk for lung cancer and smokers along with those who had greatest reductions in hsCRP and IL-6 levels seemed to benefit most from canakinumab. Therefore, we plan to examine in an explanatory fashion whether or not MUC1/Poly-ICLC has an impact on hsCRP and interleukin-6 (IL-6) levels when assessed at Week 24 compared to baseline. In addition, we will explore if baseline concentration of both inflammation-related markers have any impact on ability to successfully vaccinate with MUC1/Poly-ICLC. These data, along with other exploratory studies planned in this trial, will inform selection of study target population for the next generation investigations.

Increasing evidence suggests that tobacco and alcohol use are risk factors in the development of intraepithelial neoplasia and cancer. In addition, tobacco and alcohol use may adversely affect agent intervention, for example by altering the safety profile or metabolism of a drug. Standardized assessments of tobacco and alcohol use during clinical trials will aid in understanding the potential relationship between the use of these products and clinical endpoints or cancer prevention biomarkers. Therefore, NCI, DCP is including assessment of tobacco and alcohol use at baseline and Week 24, to determine the potential impact of tobacco and alcohol use on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

3. SUMMARY OF STUDY PLAN

We propose to start with a pilot study that will test immunogenicity and safety of the vaccine in individuals at high risk for lung cancer. Even though the two trials described above have given us information about immunogenicity and safety of this vaccine in individuals at risk for colon cancer, we cannot assume the same for individuals at risk for lung cancer. We expect that smoking has led to the establishment of a long-term chronic inflammation in the lung of most potential participants, which is likely to lead to an increase in circulating MDSCs that could affect the response to the vaccine. Many of

the individuals eligible for the vaccine are expected to have ongoing chronic obstructive pulmonary disease (COPD), which has already been shown to expand numbers of circulating MDSCs creating an immunosuppressive microenvironment.[39] This does not allow us to predict either the rate of the immune response or the level of vaccine immunogenicity in this population. It is also possible that the extent of inflammation in the lung could make the lung more vulnerable to the effects of a strong adaptive immune response. Based on the safety profile of this vaccine in lung cancer trials, where the cancer-bearing lung is also a chronically inflamed organ, we do not expect any adverse effects. However, in none of these trials has very strong immunity been elicited by the vaccine. Thus, immunogenicity and safety have not yet been properly tested in this population. This pilot study will provide us with the safety and immunogenicity data that will decide whether testing of this vaccine could subsequently proceed to the placebo-controlled efficacy trial(s) for the prevention of lung cancer.

This is a pilot trial designed to evaluate co-primary endpoints: the preliminary immunogenicity in response to the MUC1 vaccine against abnormal MUC1 (assessed at 12 Weeks) and the safety (assessed at up to 24 weeks) in current and former smokers, who are at high risk for development of lung cancer. Immune response will also be evaluated at Week 24. We expect to consent and screen up to 85 participants in order to have approximately 40 evaluable participants with baseline and 12-week immunogenicity assessments. This includes a 41% rate of ineligibility and 20% rate of drop out/otherwise not evaluable. The projected rates of ineligibility, dropout, and otherwise not evaluable are based on experience with the prior MUC1 protocol and other engagements with the proposed target population. If the projected rates of ineligibility and drop out prove to be optimistic, it should be noted that even with 30 evaluable participants, statistical power will be sufficient for the purposes of this pilot study.

4. PARTICIPANT SELECTION

4.1 Pre-Registration Inclusion Criteria

4.1.1 Smoking history of ≥30 pack-years AND either current smoker (still smoking or quit < 1 year prior to pre-registration) OR former smoker (quit 1-15 years prior to pre-registration). Note: Pack years is determined by multiplying the number of packs smoked per day by the number of years smoked.

4.1.2 Ages 55-80 years

4.1.3 ECOG performance status ≤1 (See Appendix A)

4.1.4 CT scan of the chest done ≤ 6 months prior to pre-registration showing either negative findings (no nodules) OR solid or part-solid nodules < 6 mm in size OR consistent with < 1% probability of malignancy, Lung-RADs Version 1.0

4.1.5 Willingness to employ adequate contraception, if applicable. Note: the effects of MUC1/Poly-ICLC on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

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

4.2 Pre-Registration Exclusion Criteria

4.2.1 History of any malignancy. Exceptions: Non-melanoma skin cancer or CIS of the cervix

4.2.2 Known Hepatitis B or C

4.2.3 Receiving any other investigational agents

4.2.4 Any prior investigational immune therapy, such as for lung cancer prevention or treatment or for CIS of the cervix

4.2.5 Use of oral or systemic steroids or other systemic anti-immune therapy ≤ 90 days prior to pre-registration. Note: Use of inhaled/nasal steroids and local steroid injections for pain control are not exclusionary.

4.2.6 Known HIV

4.2.7 Known autoimmune disease

4.2.8 Known Non-alcoholic steatohepatitis (NASH) or Non-alcoholic fatty liver disease (NAFLD)

4.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MUC1/Poly-ICLC

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

4.3 Registration Inclusion Criteria

4.3.1 Participants must have normal organ and marrow function as defined below:

Leukocytes (WBC)	≥ 3,000/microliter
Neutrophils (ANC)	≥ 1,500/microliter
Platelets	≥ 100,000/microliter
Total bilirubin	≤ 1.5 x institutional upper limit of normal (ULN) Note: Higher total bilirubin levels (≤ 3 mg/dL) can be allowed if due to known benign liver condition, i.e. Gilbert's.
AST (SGOT)	≤ 1.5 × institutional upper limit of normal (ULN)
ALT (SGPT)	≤ 1.5 × institutional upper limit of normal (ULN)
Creatinine	≤ institutional upper limit of normal (ULN)

4.4 Registration Exclusion Criteria

4.4.1 Any positive ANA titer above 1:160, even in an asymptomatic individual. Note: Weakly positive ANA defined as ANA titers up to 1:160 maximum (≤ 1:160) will be acceptable in an asymptomatic individual who is otherwise eligible for the study.

4.2.2 Pregnant or breast feeding. Note: Pregnant women are excluded from this study because the MUC1/Poly-ICLC vaccine may have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with MUC1/Poly-ICLC vaccine, breastfeeding should be discontinued if the mother is treated with the vaccine.

4.5 Inclusion of Women and Minorities

Both men and women (as applicable) and members of all races and ethnic groups are eligible for this trial. Please refer to the Recruitment, Retention, and Adherence (RR&A) Plan for details.

4.6 Recruitment and Retention Plan

Each Participating Organization will be required to develop and submit a study- and site-specific RR&A plan for the purposes of insuring equal access to the clinical trial by individuals of all genders, races, and ethnic groups and for attaining the organization's accrual target. Participating Organizations will use the RR&A Plan Worksheet as the basis for their plans. At a minimum, these plans will be reviewed annually.

In summary, participants will be identified from the lung health, smoking, thoracic clinics, and/or CT screening programs at The University of Pittsburgh Medical Center and the Mayo Clinic in Rochester, Minnesota. Individuals at high risk for developing cancer but at low risk for having cancer will be recruited by the site study teams according to their site-specific RR&A plans and utilizing recruitment materials approved by NCI, DCP, the CIRB, and any applicable local entities. Accrual will be closely monitored by the Consortium Lead Organization and NCI, DCP. Accrual plans will be revised regularly and as needed to complete the study in an acceptable time frame.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

The MUC1 peptide is manufactured at the FDA certified peptide facility of the University of Pittsburgh. The vaccine will consist of 100 micrograms of the MUC1 100mer peptide dissolved in 50 micro-liters of sterile saline, admixed with 500 micrograms of the adjuvant poly-ICLC (Hiltonol®) in 250 microliters volume, for a total injection volume of 300 microliters. Poly-ICLC is a TLR3 agonist, a synthetic, non-replicating dsRNA with no specific genetic message, which acts as a viral-mimic and activator of diverse elements of both the innate immune response and of adaptive immunity.[40]

5.2 MUC1/Poly-ICLC Vaccine Administration

The vaccine will be administered by appropriate site personnel subcutaneously in the upper arm (preferably) or in the anterior thigh approximately 20 cm inferior to the inguinal ligament, if injection in the upper arm(s) is not possible. The vaccine will be administered into the same upper arm on all 3

occasions for vaccine delivery. The vaccine site may demonstrate erythema and/or tenderness after administration. This erythema and/or tenderness can persist even to the timing of the next vaccine dosing. Erythema is not a contraindication to repeat vaccination. However, persisting injection site tenderness (and/or other local injection site reaction) may, at the discretion of the investigator, be a reason to administer subsequent, scheduled vaccine into the opposite upper arm. Similarly, the 3rd vaccine administration can be given into the same upper arm as the previous (2nd) vaccine or into the opposite upper arm (the same upper arm where the initial 1st vaccine was given). Also, at the discretion of the investigator, repeat vaccination may be delayed, but not to exceed the protocol limits (See section 7.1). It is also possible to inject the vaccine into the thigh(s), if necessary.

5.3 Run-in Procedures

Not applicable.

5.4 Contraindications

If a study participant is prescribed corticosteroids, immunomodulators, or any medications listed as exclusionary (Section 4.2) during the course of the study, the participant will be taken off agent (no further vaccine administrations) but followed per protocol through the Follow Up telephone call.

5.5 Concomitant Medications

All medications (prescription and over-the-counter), and vitamin, herbal, and mineral supplements taken by the participant will be documented on the concomitant medication CRF and will include: start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g.*, biopsy) will also be included.

5.6 Dose Modification

There will be no dose reductions. A vaccine administration can be withheld:

- At any time deemed appropriate, based on the best clinical judgment of the treating physician. Vaccine administration can be withheld for up to a week.
- For any Grade 2 increases in liver function tests, pancreatic function tests, or ANA titers, vaccine administration should be withheld until test results resolve to Grade 1 or baseline.
- The second vaccine administration can be withheld for up to one week and the third vaccine administration can be withheld for up to 2 weeks. These individuals will still be considered evaluable for the primary endpoint.
- If dose 2 is delayed by ≤ 1 week, dose 3 will still be scheduled at week 10. If dose 2 is not administered within 1 week of the scheduled time point, the participant will be considered “off agent” but will be followed per protocol. Dose 3 will not be given if dose 2 was not administered within the planned schedule.

5.7 Adherence/Compliance

5.7.1 All vaccine will be administered by appropriately trained personnel at each site. Vaccine administration will be documented on the Intervention Administration CRF.

5.7.2 Individuals who receive the Week 0, Week 2, and Week 10 injections will be considered evaluable for the primary endpoint. If subjects receive at least 1 but not all 3 injections, they will still be considered evaluable for secondary endpoints.

6. PHARMACEUTICAL INFORMATION

6.1 MUC1 Vaccine (IND # [redacted], NCI, Division of Cancer Prevention)

MUC1 Peptide

The MUC1 peptide is composed of 100 amino acids (aa), representing five 20aa-long tandem repeats of the MUC1 VNTR region: H_2N-(GVTSAPDTRPAPGSTAPPAH)$_5$-$CONH_2$. The peptide is synthesized on a rapid multiple peptide synthesizer (Dupont NEN) in a dedicated facility under a strict and fully certified procedure and using reagents with a defined expiration date. The peptide is highly hydrophilic and for testing as well as injection, it is dissolved in sterile saline. The peptide is tested for pyrogenicity and safety in guinea pigs, mice, and rabbits in accordance with an FDA approved protocol in a commercial facility. Once tested negative, it is aliquoted in small freezer vials containing one injection volume (100 mcg lyophilized peptide in 0.05 mL of sterile saline). Two percent of vials are sampled randomly for sterility testing in the University of Pittsburgh Medical center Microbiology Laboratories. Both 7 and 14-day sterility results are recorded. Peptide synthesis procedure, safety, pyrogenicity and sterility are contained in detail in Dr. Schoen's IND application to the FDA cross referenced by NCI, DCP. This peptide and all these procedures have been previously examined and approved by the FDA six times in six different IND applications. For administration as a vaccine, the peptide will be admixed with the POLY-ICLC adjuvant described above and below and injected subcutaneously as described above.

Poly ICLC

Poly-ICLC is supplied by Oncovir in vials containing 1 mL of 2 mg/mL opalescent white suspension. Poly-ICLC is withdrawn from the vial under sterile conditions and is to be administered intramuscularly, subcutaneously or intranasally as supplied. It can also be diluted with normal saline.

Each vial Poly-ICLC will be labeled with the following information:

- Drug Name
- Concentration
- Lot Number
- Date of Manufacture
- Manufacturer
- Investigational Use Statement

Low-dose Poly-ICLC administered IM or SC or intranasally has been well tolerated in clinical trials of patients with brain tumors, other cancers, multiple sclerosis, and in normal volunteers. Multiple additional trials have used it in combination with various cancer or HIV vaccines. The most common adverse events experienced in these studies have been transient discomfort at the injection site and transient malaise. Subcutaneous injection may result in a transient erythematous skin reaction. Preliminary findings from these trials suggest that low-dose Poly-ICLC may be effective in treating various tumors and further study is warranted.

Poly ICLC synthesis, procedure, safety, pyrogenicity, and sterility are contained in detail in the Oncovir IND and DMF to the FDA cross-referenced by NCI, DCP.

6.2 Reported Adverse Events and Potential Risks

A preliminary human clinical study with the MUC1 100mer vaccine was conducted in subjects with a history of advanced adenoma.[16] Forty subjects received 100 μg of MUC1 100mer admixed with polyinosinic-polycytidylic acid-poly-L-lysine carboxymethylcellulose (Poly-ICLC) adjuvant at 0, 2, and 10 weeks; antibody titers were evaluated prior to each vaccination and at weeks 12, 28, and 52. More than 150 vaccinations were administered in this study. No adverse events (AEs) above CTCAE (v3.0) grade 1 were identified, and no unanticipated AEs were observed. AEs related to vaccination included erythema, experienced by 87.5% of subjects (35 out of 40), discomfort at the injection site (80%, 32 subjects), and flu-like symptoms (37.5%, 15 subjects), which responded well to analgesics such as Tylenol. No subjects developed a change in *anti*-nuclear antibody (ANA) titer at one year, and no new autoimmune diseases were observed.

The MUC1 vaccine was also assessed in 16 pancreatic cancer patients who were candidates for curative resection due to early diagnosis.[20] These patients were considered better vaccine candidates because of a lower tumor burden and no immunotoxicity from previous chemotherapy. Subjects received four different doses of the MUC1 100mer peptide vaccine (100, 300, 1000, and 3000 μg, four subjects/group) admixed with SB-AS2 adjuvant every three weeks for three doses. The vaccine was well tolerated with most subjects experiencing mild AEs, including flu-like symptoms (grade 1, 25%), and tenderness (grade 1, 38%) and erythema (grade 1, 31%; grade 2, 6%) at the injection site. No grade 3/4 AEs were reported.

A phase 1 trial with MUC1 105mer peptide vaccine accrued 63 subjects with advanced colon, pancreatic, and breast cancers.[41] Subjects were vaccinated with 100 μg of a MUC1 peptide, consisting of 105 amino acids representing a little more than 5 tandem repeats from the extracellular VNTR, admixed with BCG as adjuvant. Two booster vaccines were administered at three-week intervals. The vaccine was well tolerated, with most subjects (98%) experiencing local ulceration at the injection site, fever, chills, and night sweats, all related to BCG, which is no longer used as adjuvant.

MUC1 100mer plus Poly-ICLC vaccine was previously tested in a phase 1/2 trial in metastatic prostate cancer. In this trial, Poly-ICLC was used in two different ways, as an adjuvant as well as an immune modifier. Patients were pretreated for two weeks prior to the MUC1/poly-ICLC vaccination with an intravenous injection three times/week with one of two high doses of Poly-ICLC, 25 μg/kg or 50 μg/kg; this was continued until disease progression. Two weeks after starting intravenous Poly-ICLC, patients were given the MUC1 vaccine with Poly-ICLC as adjuvant, as a low dose of 500 μg total per injection, subcutaneously; three injections were administered at three-week intervals. A total of 14 patients were treated; 88% experienced grade 1 toxicity, the most common being injection site reaction (93%). Eight patients experienced grade 2 toxicity (fatigue and fever), and two patients had grade 3 toxicity (fever and transient neurological symptoms) correlating with the start of iv injections of high doses of Poly-ICLC prior to vaccination. These symptoms were readily controlled and resolved. There were no grade 4/5 AEs.

MUC1/Poly-ICLC vaccine was administered to three patients with advanced lung cancer and quickly progressing disease. Two patients received only one injection before succumbing to their disease. The third patient received boosters every three months for a total of three years, and developed anti-MUC1 antibodies while experiencing only grade 1 toxicity (redness and inflammation at the injection site).

One patient with metastatic lung cancer is currently being treated on an expanded access protocol and is receiving the MUC1/Poly-ICLC vaccine on the same schedule as the one followed in the prophylactic setting in advanced adenoma (week 0, 2, and week 10). The patient has generated a good antibody response and is now getting regular boosters every three months. The only reported AEs are grade 1 toxicity at the injection site, and long-term disease stability is reported.

An NCI, DCP-sponsored randomized, double-blind, placebo-controlled trial of MUC1-Poly ICLC vaccine in participants with newly diagnosed advanced adenomas is ongoing. Subjects are randomly assigned to receive either MUC1-Poly ICLC vaccine or normal saline injections at week 0, 2, and 10, with a booster injection at week 53. In 103 subjects evaluable for toxicity to date, the most commonly reported AEs were grade 1/2 injection site reactions (29 subjects, 28.2%) and grade 1 influenza-like illness (eight, 7.8%).

In one subject given the MUC1 vaccine in the DCP adenoma study, grade 1 elevated liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were observed two weeks after the initial injection. The DCP Medical Monitor considered this to be a serious adverse event (SAE), possibly related and unexpected for the study agent, thus qualifying it as an IND safety report. The data in this case suggest that the increased hepatic enzymes may be related to MUC1 vaccine and/or the adjuvant poly-ICLC (Hiltonol).

The Poly-ICLC Investigator's Brochure provides data from high dose (unspecified) Poly-ICLC cancer trials indicating that modest reversible hepatic enzyme elevations can occur after drug administration. In a trial of intravenous Poly-ICLC (about 100 µg/kg) administered to multiple sclerosis (MS) patients, transient, modest elevations of AST and ALT occurred after 84% of 127 infusions, and increased lactate dehydrogenase (LDH) and alkaline phosphatase occurred after 52% of the infusions. The event in this DCP-sponsored trial was considered unexpected because the adjuvant dose was much lower (3.95 µg/kg) and administered via a different route (subcutaneous) than in the MS study, as well as administered with the MUC1 vaccine. Also, although the subject had a relevant past history of nonalcoholic steatohepatitis (NASH) with a risk factor of obesity, the MUC1 vaccine and/or the adjuvant Poly-ICLC could not be ruled out as a cause of the event due to the timing. No similar events have been reported in the study or in the four prior completed studies described in the Investigator's Brochure. Individuals with a diagnosis of NASH and a NAFLD (nonalcoholic fatty liver disease) activity score (NAS) ≥5 are excluded from the current study in response to this event. Other SAEs reported in the ongoing DCP study are considered not related to study agent.

Possible Side Effects of the MUC1/Poly-ICLC vaccine*:

Common, Some May Be Serious In 100 people receiving the injection, more than 20 may have:
• Redness at injection site (erythema) • Pain/soreness at injection site • Painful, red swelling at injection site • Flu-like symptoms, which may include fever chills, headache, fatigue, muscle pain, and joint pain • Night sweats • Loss of appetite • Low albumin blood test result (a type of protein in the blood) • Fever • Tiredness

The redness and soreness generally resolve within a few days to a week. Generally, acetaminophen (Tylenol®) is sufficient for pain relief. The flu-like symptoms generally resolve within 12-24 hours. Acetaminophen (Tylenol®) generally helps with these symptoms if they occur.

Occasional, Some May Be Serious In 100 people receiving the injection, 4 to 20 may have:
• Low white blood cell count (cells that fight infections) • Low platelet count (cells that help the blood clot in order to stop bleeding) • Anemia (which may cause tiredness, or may require blood transfusion) • Abnormal liver function test results

Rare, Some May Be Serious In 100 people receiving the injection, 3 or fewer may have:
• Hives, shortness of breath, or an allergic reaction that is life-threatening • Immune reaction to his or her own tissue (autoimmune diseases) or if present, may be made worse.

* MUC1 vaccine IB (Edition 2, 15Nov2017) and Hiltonol/Poly-ICLC IB (Edition 14, 25Jan2018)

6.3 Availability

MUC1 100mer peptide and Poly-ICLC will be supplied by the University of Pittsburgh and sent to each participating site's research pharmacy upon receipt of a completed CPN Study Agent Order Form. The vaccine injection will be prepared by each participating organization's pharmacy (or other appropriate designated personnel) within 8 hours prior to clinical administration. The dose will be mixed and prepared as per the pharmacy instructions. Study agent will be supplied by and shipped from:

Olivera Finn, Ph.D., E1040 Biomedical Science Tower, Pittsburgh, PA 15262
Telephone: 412-648-9816; Fax: 412-648-9378; E-mail: ojfinn@pitt.edu

6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of CIRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents using NCI Drug Accountability Record Form (DARF) or comparable institutional form. The investigator or designee is required to maintain adequate records of receipt, dispensing, and final disposition of study agent. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity, and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility will be delegated to the Participating Organization pharmacist. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Packaging and Labeling

The participating organization pharmacy personnel will be required to label the injection supplied for each participant. Each injection should be labeled according to institutional guidelines. The label should define the injection as MUC 1 100mcg/0.05mL w. poly-ICLC 500mcg/0.25mL. The label should also include the date of preparation, the route of administration, and the study name. The label may also include other information, such as the time of expiration, as required by local or state regulations.

6.7 Storage

The MUC-1 vaccine will be stored frozen at-70 to -80^{o} C until mixed for injection. MUC1 Vaccine will be shipped on dry-ice overnight to each site. Participating organizations are required to store the vaccine in a -70 to -80^{o} freezer upon receipt.

Poly-ICLC is stable at room temperature for brief periods (days). It is normally refrigerated at about 40^{o}F (2-8°C) but should not be frozen. Poly-ICLC will be shipped at ambient temperature overnight to each participating site. It is to be stored in the refrigerator upon receipt.

6.8 Pre-Registration and Registration

6.8.1 Participant Pre-Registration

6.8.1.1 To pre-register a participant, the participating site will send the completed, signed, and dated Pre-Registration Eligibility Checklist, to the CPN Registration Office (Email: random01@mayo.edu; Fax: 507-284-0885) to pre-register all participants. The CPN Registration Office will enter the information into the CPN-hosted database. A unique participant identification number (PID) will be assigned. No study-related activities may take place until pre-registration has taken place.

6.8.1.2 At the time of pre-registration, the following will also be verified:

- CIRB (local context subcommittee) approval for the registering institution
- Participant eligibility (including existence of a signed informed consent document)
- Existence of a signed authorization for use and disclosure of protected health information (USA Institutions only)
- Study agent is available and Drug Shipment Authorization has been granted to the registering site
- The following will also be recorded:
    - Participant has/has not given permission for blood samples to be collected and that these samples and related information may be used for optional laboratory studies.
    - Participant has/has not given permission for the study doctors to contact them or their physician to see if they wish to learn about the results from the optional studies.
    - Participant has/has not given permission for blood samples and related information to be kept in a Biobank for use in future health research.
    - Participant has/has not given permission for information from their alcohol and tobacco use assessments to be used for future health research
    - Participant has/has not given permission to send blood sample(s) and related information to researchers at outside institutions.
    - Participant has/has not given permission to their study doctors (or their representative) to contact them to see if they wish to participate in research in the future.

6.8.1.3 Baseline (screening) evaluations must be completed within the guidelines specified on the Schedule of Events (See Section 7.1).

6.8.1.4 Registration Office personnel will automatically register participants separately to the translational components of the study (See Section 13).

6.8.2 Registration

6.8.2.1 To register a participant, the participating site will send the completed, signed, and dated Registration Eligibility Checklist to the CPN Registration Office (Email: random01@mayo.edu; Fax: 507-284-0885). The CPN Registration Office will enter the information into the CPN-hosted database. For randomization details, see Section 13.2.

6.8.2.2 Intervention on this protocol must commence at a CPN institution under the supervision of a CPN clinician.

6.8.2.3 Intervention cannot begin prior to Registration and must begin ≤ 14 days after Registration.

6.8.2.4 Descriptive Factors:

- Participating organization: University of Pittsburgh versus Mayo Clinic
- Gender: Male versus female
- Smoking status: Current versus former

6.9 Blinding and Unblinding Methods

Not applicable

6.10 Agent Destruction/Disposal

At the completion of investigation or after completion of the site pharmacy final close out visit report by the CPN Compliance Coordinator, all unused study agent will be returned to the University of Pittsburgh. The University of Pittsburgh will supply instructions, shipping supplies, shipping bills, and other items necessary for the return shipment.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Study Visit/Event	Pre-Registration	Screening	Registration/ Day 0	Week 2 (+/- 4 days)	Week 4 (+/- 4 days)	Week 10 (+/- 4 days)	Week 12 (+/- 4 days)	Weeks 16 and 20 (+/- 4 days)	Week 24 (or early termination, +/- 7 days)	Week 28 (+/- 14 days)
Informed consent	X									
Physical exam		X							X	
Vital signs[1]		X	X	X		X			X	
Med/Surg history		X								
Alcohol and Tobacco Use Assessment		X							X	
Baseline symptoms		X								
Con Meds		X	X	X	X	X	X	X	X	
Hematology tests[2]		X		X	X	X	X		X	
Blood chemistry[3]		X		X	X	X	X		X	
Urine cotinine		X					X		X	
Pulmonary function[4]		X							X	
Immunological testing[5]		X		X	X		X		X	
Blood testing for exploratory endpoints[6]		X							X	
Pregnancy test, urine, if applicable		X	X	X		X				
Vaccine administration[7]			X	X		X				
AE assessment			X	X	X	X	X	X	X	
Phone call[8]								X		X
WIWI Questionnaire									X	

1. Vital signs include height (screening only), weight, temperature, blood pressure, heart rate, respiratory rate.
2. Hematology testing (evaluated at local labs) includes CBC with 5-part differential and platelets.
3. Blood chemistry tests (evaluated at local labs) include: potassium, sodium, chloride, bicarbonate, creatinine, serum glucose, BUN, total bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT, uric acid, amylase, lipase, and albumin. At the screening, Week 4, and Week 24 visits only, blood testing will also include antinuclear antibody (ANA). Optional research blood will be collected at screening and Week 24, if participant consent is provided.
4. Testing (evaluated locally) includes spirometry, including graphic record, total and timed vital capacity, expiratory flow rate measurement, with or without maximal voluntary ventilation, and pulmonary diffusing capacity.
5. Immunological testing for antibody responses to MUC1 (See Section 9.1).
6. All blood testing for secondary and exploratory endpoints will utilize plasma remaining after the immunological studies are complete with the exception of high sensitivity C-reactive protein (hsCRP). For individuals accrued prior to protocol Amendment 2, levels of hsCRP will be tested at baseline and Week 24 using frozen plasma remaining from the blood draw for immunological studies (See footnote #5 above). Beginning with Amendment 2, one extra blood specimen will be collected, processed into serum, and stored until the end of the study for hsCRP.
7. Where applicable, blood draws and AE assessments will precede vaccine administration (See Section 7.4).
8. If any adverse events have not resolved at the time of the Week 24 visit, an optional follow up phone call may take place at Week 28 (+/- 7 days).

7.2 Baseline Testing/Pre-study Evaluation

After participants have been informed about the study and have signed the informed consent document, they will be pre-registered and assigned a unique participant identification number (PID).

They will then undergo initial screening tests and procedures. The order in which these tests and procedures is conducted is flexible within the designated study timelines and should be consistent with good clinical practice and institutional policies and procedures. These tests and procedures include a physical exam, documentation of medical/surgical history, alcohol and tobacco use assessments, review of clinical CT imaging, and documentation of any existing baseline symptoms, allergies, concomitant medications, and baseline blood tests. Baseline blood tests include ANA, CBC with 5-part differential and platelets, potassium, sodium, chloride, bicarbonate, creatinine, serum glucose, BUN, total bilirubin, alkaline phosphatase, uric acid, AST/SGOT, ALT/SGPT, albumin, amylase, lipase, and an optional additional specimen for future research. Blood will also be drawn at baseline/screening for the immune assays and exploratory endpoints. A urine cotinine test will be performed. Pulmonary function testing includes spirometry, including graphic record, total and timed vital capacity, expiratory flow rate measurement, with or without maximal voluntary ventilation and pulmonary diffusing capacity. A urine pregnancy test will be administered, if applicable.

If participants are eligible and willing to participate, they will be registered to the study.

7.3 Evaluation During Study Intervention

Vaccine will be administered at Weeks 0, 2, and 10. Participants will be monitored for at least 30 minutes after each injection for possible emergent side effects.

Prior to vaccine administration:

- Females of childbearing potential will be required to document negative pregnancy test.
- Blood will be drawn for safety and/or immune response, as applicable (See Section 7.1 and see below).
- Adverse events and concomitant medications will be assessed (See Section 11.1 for details).
- Vital signs will be evaluated (temperature, blood pressure, heart and respiratory rates, and weight)
- Blood testing results will be reviewed by the treating physician for clinical significance and possible indications of toxicity.

Immune response will be tested at Weeks 2, 4, and 12. A repeat ANA titer will be drawn at Week 4. Blood tests to monitor toxicity will be conducted at Weeks 2, 4, 10, and 12. Urine cotinine will be monitored at Week 12.

Adverse events will be evaluated during all contacts with the participants, with emphasis on AE evaluation two weeks after each injection (See Section 11.1 for details). Possible adverse events and concomitant medication information will be captured by telephone at Weeks 16 and 20.

7.4 Evaluation at Completion of Study Intervention (or early termination)

The post-intervention evaluation will take place at Week 24 (+/- 7 days). The order in which these tests and procedures is conducted is flexible within the designated study timelines and should be consistent with good clinical practice and institutional policies and procedures. These tests and procedures include a physical exam, review of adverse events, and concomitant medications, alcohol and tobacco use follow-up assessments, and blood tests. Blood tests include CBC with 5-part differential and platelets, potassium, sodium, chloride, bicarbonate, creatinine, serum glucose, BUN, total bilirubin, alkaline phosphatase, uric acid, AST/SGOT, ALT/SGPT, albumin, amylase, lipase, and ANA. Blood will also be drawn for the immune assays and exploratory endpoints. An optional additional blood specimen will be collected for future research, if consent was provided. A urine cotinine test will be performed. Pulmonary function testing includes spirometry, including graphic record, total and timed vital capacity, expiratory flow rate measurement, with or without maximal voluntary ventilation, and pulmonary diffusing capacity. The Was It Worth It (WIWI) Questionnaire will also be administered. If the participant provides consent, the data from this questionnaire will be included in the central Quality of Life database (along with demographic information) that is accessible to non-study investigators after CIRB approval.

7.5 Post-intervention Follow-up Period

If any adverse events have not resolved at the time of the Week 24 visit, a follow up phone call may take place at Week 28 (+/- 14 days). Concomitant medications will be recorded. Adverse events will be followed according to institutional standards of good clinical practice.

7.6 Methods for Clinical Procedures

See Section 5.2 for vaccine preparation and administration procedures.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

See Section 13.4.

8.2 Secondary Endpoints

See Section 13.5.

8.3 Off-Agent Criteria

Participants may stop taking the study agent due to: completion of the planned intervention period, development and/or continuation of an adverse event or serious adverse event, inadequate agent supply, noncompliance, use of concomitant medications, medical contraindication, refusal, ineligibility (see Section 8.4), major treatment violation (see Section 8.4) or alternative treatment. Participants will continue to be followed, if possible, for safety according to the intended schedule of events (see Section 7).

Participants discontinuing the planned intervention prematurely will be encouraged to complete the Post-Intervention Evaluation tests and procedures as appropriate (if participant does not refuse, is not lost to follow-up, or unless it is clinically contraindicated). See Section 8.4 for further details as to data submission for participants deemed Ineligible after starting treatment or classified as a Major Treatment Violation (i.e., protocol requirements regarding intervention during the first week post-registration were severely violated). In such cases, all data and all on-study materials, collected up until the point of confirmation of ineligibility or major violation status must be submitted.

8.4 Off-Study Criteria

Participants may go "Off-Study" for the following reasons: development or continuation of an adverse event or serious adverse event, death, lost to follow-up, participant withdrawal, physician decision, protocol violation, completion of study, or other (with detailed comments provided). Reason(s) will be noted in the participant's research records, with the primary reason clearly identified. The participant will be classified as (Off Study/Off Agent). Data submission and follow-up after participants are determined to be a screen failure or "Off-Study/Off-Agent" for specific situations is noted below:

Ineligible: A registered participant is deemed ineligible if the participant does not satisfy each and every eligibility criterion for study entry.

- If participants received study intervention, on-study materials and all data up until the point of confirmation of ineligibility will be submitted.
- If participants did not receive study intervention, on-study materials must be submitted. No further data submission is necessary. No follow-up is required.

Major Treatment Violation: A registered participant is deemed as being in major treatment violation by the coordinating center, if the participant's very first treatment/intervention administration is so grossly administered in error, that the participant's data can no longer be used for the primary endpoint. These cases are typically rare.

- On-study material and all data up until the point of confirmation of a major violation must be submitted.

Cancel: A registered participant is deemed a cancel if he/she refuses the study before any study intervention is given.

- On-study material must be submitted. No further data submission is necessary. No follow-up is required.

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

The most appropriate biomarker of vaccine efficacy is the immune response. We will measure the major T cell dependent anti-MUC1 antibody IgG isotype that requires MUC1 specific T cells to promote isotype switching by B cells from IgM. We will largely focus on IgG, as that antibody isotype is easier to measure and more reproducibly induced. The biospecimen repository archive will include plasma and PBMC for immunologic and other assays, such as the frequency and quality of antigen-specific T cells induced by the vaccine, and changes in the serum cytokine and chemokine profiles.

The MUC1 ELISA is an established assay that has been used to monitor many clinical trials as well as IgG response in large cohorts of patients on other studies. It has been validated as highly reproducible. The set-up includes positive and negative control anti-MUC1 antibodies that allow comparison of results between different studies. Nevertheless, in this trial, each patient will also be his/her own control as we will compare post-vaccination titers with pre-vaccination baseline. All time points will be assayed simultaneously and multiple times.

Immune Assays: Upon receipt of the overnight shipment or immediately after collection, heparinized blood will be centrifuged over a density gradient (Ficoll) to separate the plasma and PBMC. Plasma will be collected, aliquoted, and stored at -20ºC. PBMC will be washed several times, aliquoted, slowly frozen to -70 to -80ºC in human serum with 20% DMSO and stored in the vapor phase of liquid nitrogen.

Measurement of the vaccine-induced anti-MUC1 IgG will be determined by the **E**nzyme-**L**inked **I**mmunosorbent **A**ssay (ELISA) that was established in Dr. Finn's laboratory and successfully used to measure anti-MUC1 responses in humans and mice. The procedure is as follows: Immulon 4 (Thermo-Fisher Scientific, MA) microtiter plates are coated overnight at 4ºC with 1µg of synthetic MUC1 100mer peptide (vaccine antigen) dissolved in 0.9% Dulbecco phosphate buffered saline (PBS). Corresponding control plates receive PBS but no antigen. The plates are washed three times with and incubated with 2.5% bovine serum albumin (BSA) in PBS (PBS-BSA) to fully coat the microtiter plate wells with protein and block non-specific binding. PBS-BSA is removed and plasma diluted in PBS-BSA added to the wells. After one-hour incubation at room temperature the plates are washed five times with PBS with 0.1% tween-20 (Sigma-Aldrich, MO), and alkaline phosphatase-conjugated anti-human IgG secondary antibody (Sigma-Aldrich) in PBS-BSA added. Following one-hour incubation, the plates are washed five times and the substrate, p-nitrophenyl phosphate (Sigma-Aldrich), added to each well. The reaction is terminated after one hour by adding 0.5M NaOH. The results are read at optical density (OD) 405nm on a spectrophotometer. The OD values from the control wells containing no antigen are subtracted from the OD values in test wells coated with peptide. Every sample is assayed multiple times at multiple dilutions, in at least triplicate wells. The results can be expressed wither as OD values or control antibody of a known titer, included in the assay, is used to convert the OD values to titers.

For detecting Myeloid-Derived Suppressor Cells (MDSC), PBMC will be thawed and stained with APC-labeled mouse anti-human CD11b antibody (clone: ICRF44, BD Biosciences), PE-Cyanine 7 (PE-Cy7) labeled mouse anti human CD14 antibody (clone: M5E2, BD Biosciences), PE -labeled mouse anti human CD33 antibody (clone: WM53, BD Biosciences) and FITC-labeled mouse anti human HLA-DR antibody (clone: G46-6, BD Biosciences). MDSC will be defined by flow cytometry as $CD11b^{+}$ $CD33^{+/low}$ $HLA\text{-}DR^{-/low}$ cells.

9.2 Comparable Methods

This study will employ procedures that have been validated previously for clinical use.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

Clinical laboratory analyses will take place at each Participating Organizations' CAP-certified laboratory.

Immunology analyses will take place in the laboratory facilities overseen by Olivera Finn, Ph.D. at the University of Pittsburgh:

E1000-17B Biomedical Science Tower
200 Lothrop Street, Pittsburgh, PA. 15261
Phone: 412-648-8561 or 412-648-9817; Fax: 412-383-8098; Email: mckolani@pitt.edu

10.2 Collection and Handling Procedures

10.2.1 Specimen Kits and Shipping Instructions

Research blood kits will be provided by BAP Kit Building (Biospecimen Accessioning and Processing Core Facility). Collection, handling, and shipping instructions will be included with each kit. Participating Sites may obtain research blood kits by faxing the Supply Order Form to the number provided (found in the Forms Packet). At least two weeks should be allowed to receive the shipping kits. Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. They will not be forwarded by FedEx® rush delivery service unless the participating institution provides their own FedEx® account number. CPN will not cover the cost for rush delivery of kits.

Because charges are incurred for all outgoing kits, a small, but sufficient, supply of specimen collection kits should be ordered prior to participant entry.

- ALL sections of the requisition form and specimen collection labels must be completed and legible.
- Blood specimens should be sent over night via FedEx® on cold packs **Monday - Thursday ONLY**.
- All samples must be shipped to the address provided on the specimen shippers (See Section 10.2.2).

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

10.2.2 Research Blood Specimens

Research blood specimens will be collected according to the table in Section 7.1. Blood specimens for the immune assays must be collected **M-Th only** and shipped overnight for next day analysis. Detailed instructions for collecting, processing, labeling, and shipping the specimens can be found in the instructions provided in each blood specimen kit.

Immune Assays: Heparinized whole blood (4 green-topped tubes) collected at all locations will be shipped to the University Of Pittsburgh School Of Medicine. Trained laboratory personnel will receive

and record the specimens, and will also be responsible for processing the blood into plasma and PBMCs. PBMCs will be frozen at -70 to -80°C in human serum with 20% DMSO and plasma will be frozen at -20°C. Lab personnel will run ELISA assays for anti-MUC1 IgG and FACS analysis of % MDSC. Approximately 50% of plasma and 25% of the live cells will be shipped to the Biorepository at the Mayo Clinic for storage and later release when requested for analyses of MUC1 immune response (T-cells +/- cytokine responses), as well as additional biomarker studies.

Blood specimens for immune assays will be sent to:

Jia Xue, E1000-17B Biomedical Science Tower
200 Lothrop Street, Pittsburgh, PA. 15261
Phone: 412-648-8561 or 412-648-9817; Fax: 412-383-8098; Email: jix11@pitt.edu

For tracking purposes, participating organizations will telephone or email Jia Xue to inform the lab that specimens are being sent to the University of Pittsburgh.

Jia Xue,
Email: jix11@pitt.edu

Mandatory blood specimen for secondary and exploratory endpoints, as well as optional research blood collection (for individuals who consent to providing blood for future unspecified research) will take place at Baseline/Screening and at Week 24. See the table on the following page for details.

BAP kits will be available for this blood collection utilizing the MAY2016-08-01 BAP Kit Supply Order Form. If are questions or problems with the BAP kits, please email: mccc/ncctg@mayo.edu

Biospecimen Summary

Specimen	Timepoints	Processing	Shipping
Mandatory clinical blood specimen for safety/ Toxicity monitoring. Specimen specifications per local lab SOPs.	Baseline/Screening and Weeks 2, 4, 10, 12, and 24	Process according to local lab SOPs	Not applicable
Mandatory clinical urine specimen for cotinine (nicotine and metabolites). Specimen specifications per local lab SOPs.	Baseline/Screening and Weeks 12 and 24.	Process according to local lab SOPs	Not applicable
Mandatory research blood specimen for immune assays: Whole blood, Sodium heparin four (4) green topped tubes	Baseline/Screening, Week 2, Week 4, Week 12, and Week 24	No processing; maintain ambient temperature.	Mayo will ship ambient overnight via FedEx™ **M-Th** to U Pitt. U Pitt will transport ambient on the day of collection to Finn lab.
Mandatory specimen for secondary and exploratory endpoints. • One (1) Gold SST tube will be collected for hsCRP. • All remaining blood tests for secondary and exploratory endpoints will utilize specimens remaining after the immunological assays are complete.	Baseline/Screening and Week 24	Process SST tube into serum and aliquot. Label as serum. Freeze at a minimum of -20ºC.	U Pitt will ship frozen on dry ice overnight via FedEx™ to BAP lab for accessioning and storage at -80ºC. Mayo will transport on dry ice on the day of collection to BAP for accessioning and storage at -80ºC.
Optional blood specimen for future research: One (1) 10-mL EDTA purple-topped tube and one (1) 10-mL red/gold topped tube.	Baseline/Screening and Week 24	Process EDTA purple topped tube into plasma and buffy coat; Process red/gold topped tube into serum. Aliquot, label, and freeze at a minimum of -20ºC. Make sure labels distinguish serum versus plasma versus buffy coat.	U Pitt will ship frozen on dry ice overnight via FedEx™ to BAP lab for accessioning and storage at -80ºC. Mayo will transport on dry ice on the day of collection to BAP for accessioning and storage at -80ºC.

10.3 Shipping Instructions

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations.

10.4 Biospecimen Banking

Optional blood specimens collected at baseline and Week 24, as well as any blood specimens remaining after the analyses for the primary and secondary endpoints are complete will be stored for future research, including analyses for exploratory endpoints and future unspecified research.

At study completion, remaining frozen biologic specimens will be labeled (study number, participant ID number, specimen type, specimen number, date of collection) batched, and shipped (overnight, M-Th only) for short-term storage to:

Biospecimens Accessioning and Processing (BAP) Freezer
ST SL-39, 150 Third Street Southwest, Rochester, MN 55902

NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

Since there is considerable physiologic variability in the Pulmonary Function Tests (PFTs) done at two different time points, to report statistically and clinically relevant AEs related to PFTs done at week 24 the following definitions will be used:

A. For a participant with normal PFTs at baseline (normal PFTs as defined by FEV1 >80% predicted and FEV1/FVC ratio ≥ 0.7)
*Any decline in FEV1 done after vaccination series of **≥ (equal or higher) 12%** and **≥ (equal or higher**) **200cc** as compared to baseline FEV1 would be reportable regardless of its relatedness to the study vaccine.

B. For a participant with abnormal PFTs known previously or determined at the time of baseline testing (abnormal PFTs as defined by FEV1 ≤ (equal or less) 80% and FEV1/FVC ratio < 0.7)
*Any decline in FV1 done after vaccination series of **≥ (equal or higher) 20%** and **≥ (equal or higher) 330cc** as compared to baseline FEV1 would be reportable regardless of its relatedness to the study vaccine.

A list of AEs that have occurred or might occur can be found in §6.2 Reported Adverse Events and Potential Risks, as well as the Investigator Brochures.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

11.1.2 AE Data Elements:

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

All AEs, with the exception of changes in Pulmonary Function Tests (PFT) completed at Week 24, will be assessed according to the grade associated with the CTCAE term. Any AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

Grade	Severity	Description
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.3.2 All AEs related to changes in Pulmonary Function Tests at Week 24 when compared to baseline PFTs will be graded according to the following severity guidelines:

Grade	Severity	Description
1	Mild	Remains asymptomatic or exhibits no changes or minimal changes in pre-existing symptoms, *no new related symptoms*; clinical or diagnostic observation only; no changes in management; no intervention indicated.
2	Moderate	Minimal changes (worsening) in pre-existing symptoms, *mild-to-moderate new related symptoms*; minimal local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL**.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the AE is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, or definite.

If the PFT-related AE at Week 24 (as defined above) is determined to be "not related" or "unlikely," this assessment will be accompanied by a note-to-file with the rationale for such assessment.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) define an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE Report Form or application found at http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia.

11.2.2.2 Contact the DCP Medical Monitor by email (preferable) or phone within 24 hours of knowledge of the event.

Malgorzata (Margaret) Wojtowicz, M.D.
National Institutes of Health, National Cancer Institute, Division of Cancer Prevention
Medical and Scientific Monitor
Lung and Upper Aerodigestive Cancer Research Group
9609 Medical Center Drive, Rm 5E-104, MSC9781
Bethesda, MD 20892 (For FedEx, use Rockville, MD 20850)
Phone: 240-276-7012
Fax: 240-276-7848
Email: wojtowim@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug

Guidance for the process of coding the SAE can be obtained by contacting the NCI MD Help Desk: adeersmd@tech-res.com

11.2.2.3 The Lead Organization and all Participating Organizations will also submit typed SAE reports and follow up reports within 48 hours of learning of the event using the DCP SAE Report Form to all of the following:

- **Margaret Wojtowicz, M.D., DCP Medical Monitor**
  Phone: 240-276-7012
  Email: wojtowim@mail.nih.gov
- **Arjun Pennathur, M.D. Principal Investigator/Study Chair**
  Phone: 412-648-6271
  Email: pennathura@pitt.edu
- **CPN Operations Office**
  Phone: 507-284-2180
  Email: cancerpreventionnetwork@mayo.edu
- **DCP's Regulatory Contractor CCS Associates, Inc.**
  Phone: 650-691-4400
  Email: safety@ccsainc.com

11.2.2.4 The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the CIRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to all of the above, including DCP, as soon as available. All SAEs will be followed according to institutional standards of good clinical practice.

12. STUDY MONITORING

12.1 Data Management

The Mayo Clinic Cancer Center database will be the database of record for the protocol and subject to NCI and FDA audit. Minimum Data Sets will be submitted to DCP per contract requirements. Please see the DCP-approved CPN Master Data Management Plan.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF) utilizing NCI-approved Common Data Elements (CDEs). The approved CRFs will be used to create the electronic CRF (e-CRF) screens for data entry into the Mayo Clinic Cancer Center database. Amended CRFs will be submitted to the DCP Protocol Information Office for review and approval.

12.3 Source Documents

A source document is any document, form, or record where *specific participants'* data are first recorded. FDA [21 CFR 312.62 (b)] requires that the investigator "...prepare and maintain accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational agent or employed as a control in the investigation." Among other

items, source documents include:

- Inpatient and outpatient medical records
- Progress notes
- Consults
- Nursing notes
- Pathology reports
- Radiology reports
- Medicine/radiation administration records
- Surgical reports
- Laboratory reports
- Admission forms
- Flow sheets that are signed and dated
- Protocol or study road maps
- Appointment books
- Participant diaries/calendars
- Participant-completed symptom diary/report card

12.4 Data and Safety Monitoring Plan

The DCP-approved Master DSMP, applicable to all studies within the CPN Consortium provides detailed information regarding data and safety monitoring for this study. The trial will be monitored closely for occurrence of adverse events by the study team and by the Mayo Clinic Cancer Center Data Safety Monitoring Board (DSMB). The DSMB will be consulted regarding whether or not accrual should be suspended to allow for investigation in the occurrence of severe adverse events, particularly for those that are possibly, probably, or definitely related to the study agent.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as CIRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

Not applicable.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

This pilot study is designed to evaluate the preliminary immunogenicity of the MUC1 vaccine (as assessed at 12 weeks) and safety (up to 24 weeks of study duration) in individuals at high risk for developing lung cancer.

There are limited Quality of Life (QOL) data on participants who participate in chemoprevention trials and we intend to create a databank of QOL information by administering the "Was It Worth It" (WIWI) questionnaire at trial completion across multiple trials. We will seek to evaluate participant perception of their experience in trial participation once we have a reasonable amount of information (large enough sample size). Since participants who participate in these chemoprevention trials are high risk but otherwise healthy, the WIWI tool would help answer simple questions about participants' assessment of whether or not participation in this trial was "worth it."

13.2 Randomization/Stratification

Not applicable

13.3 Accrual and Feasibility

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	6	9	0	0	15
White	8	20	2	3	33
More Than One Race	0	0	0	0	0
Total	15	30	2	3	50

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0

Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	0	0	0	0	0

The study design requires a total of up to 85 participants for screening evaluation with approximately 50 moving forward to registration and intervention due to anticipated screen failures of41%. We further expect up to 20% of participants to drop out or otherwise become non-evaluable by 12 weeks such that approximately 40 participants should be evaluable for the primary endpoint. We expect to enroll an average of 2-3 participants per month. With a 6-month ramp up period for participating organizations and this accrual rate, we plan to complete accrual in about 2.5 years, which includes 2 months for planned slowing of enrollment due to holidays, as well as a temporary closure in 2020 due to the COVID-19 pandemic. Accounting for participant follow-up, data entry, and analysis, the study should be completed within approximately 3.5 years.

13.4 Primary Objective, Endpoint(s), Analysis Plan

This pilot study is designed to evaluate the preliminary immunogenicity of the MUC1 vaccine (as assessed at Week 12) and the safety (assessed continually through Week 24) in individuals at high risk for developing lung cancer. The immune response to the vaccine will be evaluated by monitoring changes in IgG anti-MUC1 antibody titer ratio; defined as t12/t0, where t0 is the "initial titer" measured prior to vaccination, and t12 is the "final titer" drawn at 12 weeks. A titer ratio of ≥2 will be considered a positive response.

Immunogenicity of the MUC1 vaccine primary endpoint: The primary endpoint is the 12-week immunogenicity response where a response would be an antibody titer that is ≥2 fold higher at 12 weeks compared to baseline. The polyp trial showed a 44% response rate at week 12 compared to baseline. However, in this current study of individuals at high risk for lung cancer, we will enroll current and former smokers; thus, the population would be heterogeneous with potentially different immune response profiles. It is also likely that some spontaneous immunogenicity is generated. However, without a placebo arm, this is hard to estimate. We therefore hypothesize that around 40% of vaccinated participants will demonstrate a 2-fold or more increase in MUC1 titer at week 12 compared to pre-vaccination. A sample size of 40 evaluable participants will provide 96% power to detect an immunogenicity response rate of 15% versus 40% using a 2-sided test of proportions with a type I error rate of 0.05. With that same sample size of 40 evaluable participants, we also have sufficient power (83%) to detect an immunogenicity response rate of 20% versus 40% using a 2-sided test of proportions with a type I error rate of 0.05.

If the projected rates of screen failures and dropouts are overly optimistic, with 30 evaluable participants, we'd still have sufficient power for the primary endpoint. Specifically, a sample size of 30 evaluable participants will provide 90% power to detect an immunogenicity response rate of 15% versus 40% using a one-sided test of proportions with a type I error rate of 0.025. The primary analysis will be on all participants, without consideration of their baseline smoking status or MUC1 expression.

Safety primary endpoint: AEs and toxicities will be closely monitored for up to 24 weeks after participants receive the first dose of the MUC1 vaccine. All registered and treated participants will be evaluable for adverse events (AEs) from the time of their first dose of the vaccine. To evaluate the AE profile for this treatment, the maximum grade for each type of adverse event will be recorded for each participant and frequency tables will be reviewed to determine the overall patterns. In addition, the number and severity of adverse events will be tabulated and summarized across all grades. Grade 2+ adverse events will be similarly described and summarized separately. As per NCI CTC Version 4.0, toxicities are defined as adverse events that are classified as either possibly, probably, or definitely related to the interventional agent. Overall toxicity incidence, as well as toxicity profiles will be explored and summarized. Frequency distributions, graphical techniques, and other descriptive measures will form the basis of these analyses. In addition, we will review all adverse event data that are graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related" to the study intervention in the event of an actual relationship developing.

13.5 Secondary Objectives, Endpoints, Analysis Plans

- To explore potential differences, if any, in the immunogenicity of the vaccine (as assessed at weeks 12 and 24 by the IgG anti-MUC1 antibody titer ratio) in current vs. former smokers. We will thus continuously monitor enrollment to the trial by smoking status. Once 15 participants are enrolled, a breakdown of enrollment by smoking status will be shared with the study team. Based on the smoking status distribution, the study team will make a decision to either continue the study as is, or restrict enrollment to either the current or the former smokers in order to have at least 15 participants each within the former and current smoker categories.
- To evaluate pre-vaccination levels versus post-vaccination (Week 12) levels of circulating myeloid derived suppressor cells (MDSC) and correlate with the ability to respond to the vaccine. For this analysis, we will summarize the data using descriptive statistics and graphical methods (i.e. boxplots, scatter plots, etc.). For continuous MDSC data vs. response data, we will use t-tests or Wilcoxon Rank-Sum tests (for non-normal data). For the associations of 2 continuous variables, we will use linear regression, the correlation coefficient, and scatter plots.

In addition, as exploratory endpoints we will also assess:

- The relationship between COPD status at pre-registration and immune response in current versus former smokers. In individuals with COPD, the severity of airflow obstruction will be measured by the pulmonary function tests as per the GOLD classification
- Whether or not changes in immunogenicity in individuals with COPD corresponds to different circulating MDSC levels
- The impact of the MUC1/Poly-ICLC vaccine on inflammation-related high sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6)
- The ability to successfully vaccinate with MUC1/Poly-ICLC vaccine depending on baseline hsCRP and IL-6 levels.

13.6 Reporting and Exclusions

All registered participants who start treatment and complete both the baseline and 12-week post-baseline evaluation will be evaluable for the 12-week immunogenicity response primary endpoint using the modified intent-to-treat principle, as long as they received the Week 0, Week 2, and Week 10

injections (See Section 5.6 for delays in vaccine administration that are considered allowable and will not impact evaluability for the primary endpoint). We plan to over-accrue by about 20% overall to ensure an adequate sample size in the primary analysis cohort. There will be no imputation for missing data. A summary and listing of all major protocol violations will be provided. All details will be given in the final study report and/or manuscript. Participants lost to follow-up will be censored on the last date of assessment (or contact) and as appropriate for analyses that are dependent upon length of study participation. All eligible participants who start treatment will be evaluable for the safety

13.7 Adverse Event Stopping Rule

The trial will be monitored closely for occurrence of adverse events by the study team and by the Mayo Clinic Cancer Center Data Safety and Monitoring Board (DSMB) using the adverse event (AE) stopping rule specified below:

Adverse Event Stopping Rule: The stopping rule specified below is 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 after any temporary suspension 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 in consultation with the Mayo DSMB may also 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 any of the following criteria for each arm separately:

- If at any time 2 of the initial 10 treated participants or 20% of all participants (i.e. when accrual is greater than 10 participants) have experienced a grade 3 or higher adverse event.)
- Each grade 5 event will be reviewed on a case by case basis in a real time fashion to determine whether study accrual should be suspended. We will also review all grade 4 adverse events regardless of attribution to monitor the emergence of any previously unrecognized treatment related adverse event.

13.8 Evaluation of Response

All registered participants who start treatment and complete both the baseline and 12-week post-baseline evaluation will be evaluable for the 12-week immunogenicity response primary endpoint using the modified intent-to-treat principle, as long as they received the Week 0, Week 2, and Week 10 injections. All conclusions regarding efficacy will be based on all participants who completed both week 0 and week 12 and have immunogenicity response values from those time points as well. Participants with undetectable titers at baseline will be included in evaluation and their positive response to the vaccine will be defined as an increase in titer to at least two times the lower limit of detection of the assay.

Subanalyses may be performed on the subsets of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of

intervention, major protocol violations, etc.). However, sub-analyses may not serve as the basis for drawing conclusions concerning efficacy, and the reasons for excluding participants from the analysis should be clearly reported. For all measurements of response (i.e. the primary endpoint), the 95% confidence intervals will also be provided.

13.9 Interim Analysis

There are no formal interim efficacy/futility analyses planned for the immune response endpoint.

13.10 Ancillary Studies

Laboratory measures will be correlated with participant outcome (i.e., adverse events, immunogenicity response, COPD status, smoking status, etc.) and with each other as well. Cut-points will be determined based on previously defined and accepted standards. Descriptive statistics and simple scatter plots will be generated to review the continuous biomarker data. In addition, for continuous biomarker values, the actual and % change in the level of each of the biomarkers from baseline to post-baseline time points will be explored. All categorical variables will be analyzed using chi-square tests or Fisher's exact test. For all translational endpoints, any notable statistical result will be viewed as an impetus for further study rather than as a definitive finding in and of itself.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.2.4 Documentation of training in "Good Clinical Practice" for all study personnel listed on the FDA Form 1572 and documentation of training in "Human Research Subjects Protection" for all study personnel listed on the Delegation of Tasks form for the Lead Organization and all Participating Organizations

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Central Institutional Review Board (CIRB) Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the appropriate CIRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the CIRB prior to implementation

14.4 Informed Consent

All potential study participants will be given a copy of the CIRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Participants who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the CIRB for each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, and the CIRB prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to DCP's Regulatory Contractor:

Paper Document/CD-ROM Submissions:

Regulatory Affairs Department, CCS Associates, Inc.
2001 Gateway Place, Suite 350 West
San Jose, CA 95110
Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions: regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to DCP's Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

No expenses solely associated with this clinical trial will be incurred by the study participant and/or their insurance carrier. However, participants and/or their insurance carriers will be billed for tests and procedures that are considered standard-of-care. In the event of an injury or illness, the study participant and/or their insurance carrier will be responsible for all expenses related to the injury or illness. Participants will be provided with payments of up to a total of $270 to cover expenses related to their participation in the study.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians 2017;67:7-30.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians 2015;65:87-108.
3. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e1S-29S.
4. Peto R, Lopez AD, Boreham J, Thun M, Heath C, Jr., Doll R. Mortality from smoking worldwide. British medical bulletin 1996;52:12-21.
5. Tong L, Spitz MR, Fueger JJ, Amos CA. Lung carcinoma in former smokers. Cancer 1996;78:1004-10.
6. Halpern MT, Gillespie BW, Warner KE. Patterns of absolute risk of lung cancer mortality in former smokers. Journal of the National Cancer Institute 1993;85:457-64.
7. Szabo E, Mao JT, Lam S, Reid ME, Keith RL. Chemoprevention of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e40S-60S.
8. Keith RL, Blatchford PJ, Kittelson J, Minna JD, Kelly K, Massion PP, Franklin WA, Mao J, Wilson DO, Merrick DT, Hirsch FR, Kennedy TC, Bunn PA, Jr., Geraci MW, Miller YE. Oral iloprost

improves endobronchial dysplasia in former smokers. Cancer prevention research 2011;4:793-802.
9. Finn OJ, Beatty PL. Cancer immunoprevention. Current opinion in immunology 2016;39:52-8.
10. Adams S, Gray RJ, Demaria S, Goldstein L, Perez EA, Shulman LN, Martino S, Wang M, Jones VE, Saphner TJ, Wolff AC, Wood WC, Davidson NE, Sledge GW, Sparano JA, Badve SS. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014;32:2959-66.
11. Azimi F, Scolyer RA, Rumcheva P, Moncrieff M, Murali R, McCarthy SW, Saw RP, Thompson JF. Tumor-infiltrating lymphocyte grade is an independent predictor of sentinel lymph node status and survival in patients with cutaneous melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:2678-83.
12. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pages C, Tosolini M, Camus M, Berger A, Wind P, Zinzindohoue F, Bruneval P, Cugnenc PH, Trajanoski Z, Fridman WH, Pages F. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.
13. Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, Kellokumpu-Lehtinen PL, Bono P, Kataja V, Desmedt C, Piccart MJ, Loibl S, Denkert C, Smyth MJ, Joensuu H, Sotiriou C. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2014;25:1544-50.
14. Kilic A, Landreneau RJ, Luketich JD, Pennathur A, Schuchert MJ. Density of tumor-infiltrating lymphocytes correlates with disease recurrence and survival in patients with large non-small-cell lung cancer tumors. The Journal of surgical research 2011;167:207-10.
15. Vlad AM, Kettel JC, Alajez NM, Carlos CA, Finn OJ. MUC1 immunobiology: from discovery to clinical applications. Advances in immunology 2004;82:249-93.
16. Kimura T, McKolanis JR, Dzubinski LA, Islam K, Potter DM, Salazar AM, Schoen RE, Finn OJ. MUC1 vaccine for individuals with advanced adenoma of the colon: a cancer immunoprevention feasibility study. Cancer prevention research 2013;6:18-26.
17. Cheever MA, Allison JP, Ferris AS, Finn OJ, Hastings BM, Hecht TT, Mellman I, Prindiville SA, Viner JL, Weiner LM, Matrisian LM. The prioritization of cancer antigens: a national cancer institute pilot project for the acceleration of translational research. Clinical cancer research : an official journal of the American Association for Cancer Research 2009;15:5323-37.
18. Kimura T, Finn OJ. MUC1 immunotherapy is here to stay. Expert opinion on biological therapy 2013;13:35-49.
19. Farkas AM, Finn OJ. Novel mechanisms underlying the immediate and transient global tolerization of splenic dendritic cells after vaccination with a self-antigen. Journal of immunology 2014;192:658-65.
20. Ramanathan RK, Lee KM, McKolanis J, Hitbold E, Schraut W, Moser AJ, Warnick E, Whiteside T, Osborne J, Kim H, Day R, Troetschel M, Finn OJ. Phase I study of a MUC1 vaccine composed of different doses of MUC1 peptide with SB-AS2 adjuvant in resected and locally advanced pancreatic cancer. Cancer immunology, immunotherapy : CII 2005;54:254-64.
21. Lepisto AJ, Moser AJ, Zeh H, Lee K, Bartlett D, McKolanis JR, Geller BA, Schmotzer A, Potter DP, Whiteside T, Finn OJ, Ramanathan RK. A phase I/II study of a MUC1 peptide pulsed autologous dendritic cell vaccine as adjuvant therapy in patients with resected pancreatic and biliary tumors. Cancer therapy 2008;6:955-964.
22. Xia W, Wang J, Xu Y, Jiang F, Xu L. L-BLP25 as a peptide vaccine therapy in non-small cell lung

cancer: a review. Journal of thoracic disease 2014;6:1513-20.
23. Mitchell P, Thatcher N, Socinski MA, Wasilewska-Tesluk E, Horwood K, Szczesna A, Martin C, Ragulin Y, Zukin M, Helwig C, Falk M, Butts C, Shepherd FA. Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: updated overall survival and biomarker analyses. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2015;26:1134-42.
24. Gulley JL, Arlen PM, Tsang KY, Yokokawa J, Palena C, Poole DJ, Remondo C, Cereda V, Jones JL, Pazdur MP, Higgins JP, Hodge JW, Steinberg SM, Kotz H, Dahut WL, Schlom J. Pilot study of vaccination with recombinant CEA-MUC-1-TRICOM poxviral-based vaccines in patients with metastatic carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research 2008;14:3060-9.
25. Rotonda C, Anota A, Mercier M, Bastien B, Lacoste G, Limacher JM, Quoix E, Bonnetain F. Impact of TG4010 Vaccine on Health-Related Quality of Life in Advanced Non-Small-Cell Lung Cancer: Results of a Phase IIB Clinical Trial. PloS one 2015;10:e0132568.
26. Quoix E, Lena H, Losonczy G, Forget F, Chouaid C, Papai Z, Gervais R, Ottensmeier C, Szczesna A, Kazarnowicz A, Beck JT, Westeel V, Felip E, Debieuvre D, Madroszyk A, Adam J, Lacoste G, Tavernaro A, Bastien B, Halluard C, Palanche T, Limacher JM. TG4010 immunotherapy and first-line chemotherapy for advanced non-small-cell lung cancer (TIME): results from the phase 2b part of a randomised, double-blind, placebo-controlled, phase 2b/3 trial. The Lancet. Oncology 2016;17:212-23.
27. Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine 2014;160:330-8.
28. Ye Z, Li Z, Jin H, Qian Q. Therapeutic Cancer Vaccines. Advances in experimental medicine and biology 2016;909:139-67.
29. Pitt JM, Marabelle A, Eggermont A, Soria JC, Kroemer G, Zitvogel L. Targeting the tumor microenvironment: removing obstruction to anticancer immune responses and immunotherapy. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2016;27:1482-92.
30. Baghdadi M, Wada H, Nakanishi S, Abe H, Han N, Putra WE, Endo D, Watari H, Sakuragi N, Hida Y, Kaga K, Miyagi Y, Yokose T, Takano A, Daigo Y, Seino KI. Chemotherapy-Induced IL34 Enhances Immunosuppression by Tumor-Associated Macrophages and Mediates Survival of Chemoresistant Lung Cancer Cells. Cancer research 2016.
31. Finn OJ. Premalignant lesions as targets for cancer vaccines. The Journal of experimental medicine 2003;198:1623-6.
32. Finn OJ. Vaccines for cancer prevention: a practical and feasible approach to the cancer epidemic. Cancer immunology research 2014;2:708-13.
33. Lakshmanan I, Ponnusamy MP, Macha MA, Haridas D, Majhi PD, Kaur S, Jain M, Batra SK, Ganti AK. Mucins in lung cancer: diagnostic, prognostic, and therapeutic implications. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 2015;10:19-27.
34. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
35. Siemes C, Visser LE, Coebergh JW, Splinter TA, Witteman JC, Uitterlinden AG, Hofman A, Pols HA, Stricker BH. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24:5216-22.
36. Allin KH, Bojesen SE, Nordestgaard BG. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. Journal of clinical oncology : official journal of the

American Society of Clinical Oncology 2009;27:2217-24.

37. Chaturvedi AK, Caporaso NE, Katki HA, Wong HL, Chatterjee N, Pine SR, Chanock SJ, Goedert JJ, Engels EA. C-reactive protein and risk of lung cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28:2719-26.
38. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ. Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet 2017.
39. Scrimini S, Pons J, Agusti A, Clemente A, Sallan MC, Bauca JM, Soriano JB, Cosio BG, Lopez M, Crespi C, Sauleda J. Expansion of myeloid-derived suppressor cells in chronic obstructive pulmonary disease and lung cancer: potential link between inflammation and cancer. Cancer immunology, immunotherapy : CII 2015;64:1261-70.
40. Martins KA, Bavari S, Salazar AM. Vaccine adjuvant uses of poly-IC and derivatives. Expert review of vaccines 2015;14:447-59.
41. Goydos JS, Elder E, Whiteside TL, Finn OJ, Lotze MT. A phase I trial of a synthetic mucin peptide vaccine. Induction of specific immune reactivity in patients with adenocarcinoma. The Journal of surgical research 1996;63:298-304.

Summary of Changes – Informed Consent Form

NCI Protocol #: MAY2016-08-01
Local Protocol #: MAY2016-08-01
Protocol Version Date: January 25, 2021

Protocol Title: A Pilot Study of MUC1 Vaccine in Current and Former Smokers at High Risk for Lung Cancer

Informed Consent Version Date: January 25, 2021

Please note that the page numbers in the table below refer to the Word version of the Informed Consent Form that will be submitted to the CIRB.

#	Section	Page(s)	Change
1.	There are no changes in the informed consent form other than the version number and date.		

Consent Form

Study Title for Study Participants: MUC1 Vaccine to Reduce Risk for Lung Cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A Pilot Study of MUC1 Vaccine in Current and Former Smokers at High Risk for Lung Cancer

Introduction

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part in the research. Please take your time to make your decision about volunteering. You may discuss your decision with your friends and family. You can also discuss this study with your health care team. If you have any questions, you can ask your study doctor for more of an explanation. You should only agree to participate in this study when you are comfortable enough with the information so that you can make an informed decision about joining.

What is the usual approach to my risk for lung cancer?

You are being asked to take part in this study because you are a smoker or former smoker at increased risk for lung cancer. People who are at increased risk and choose not to participate in a study are usually followed closely by their doctor to watch for the development of cancer.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above,
- you may choose to take part in a different study, if one is available,
- or you may choose to do nothing.

Why is this study being done?

MUC1 is a natural protein that is changed when a normal cell becomes a cancer cell. The body's immune system can recognize these changes very early in the process of changing from a normal cell to a cancer cell. A vaccine has been developed that consists of a MUC1 protein and

another compound, Poly-ICLC. The Poly-ICLC is believed to make the vaccine more effective. Our goal is to slow or stop the changes from normal to pre-cancer to cancer.

This vaccine has proven to be safe in previous clinical trials in individuals at risk for colon cancer. It also seems to stimulate the body's immune system. The MUC1/Poly-ICLC vaccine is now being tested in persons at high risk for lung cancer due to their smoking history.

The purpose of this study is to test the safety of the vaccine, and to find out what effects, if any, it has on stimulating the body's immune system. There will be about 50 people taking part in this study.

How long will I be in this study?

You will receive 3 doses of the study vaccine over the course of 10 weeks. The vaccine will be given to you in an injection by trained personnel after review of all of your medical history and lab tests. You will receive 0.30 cc (1/20 of a teaspoon) of MUC1/poly-ICLC study vaccine. The injection will be administered under the skin in the upper arm (or upper thigh, if needed) with a thin, tiny needle (like the one used for a tuberculosis test). The site of injection will remain the same for all injections. You will remain at the study visit for about 30 minutes after each injection to watch for side effects.

You will then be watched for a response to the vaccine and any possible side effects for an additional 14 weeks. Even if you do not finish the study, your doctor will continue to watch you for side effects and follow your condition for a total of 24 weeks.

What extra tests and procedures will I have if I take part in this study?

Before you begin the study, you will need to have the following extra tests and procedures to find out if you can be in the study:

- Physical exam with review of vital signs (heart rate, temperature, height, weight, and blood pressure
- Review of your medical and surgical history
- Assessment of your use of alcohol and tobacco
- Review of any medications you are taking
- Review of your CT scan done within the previous 6 months (to make sure you do not have cancer)
- Blood tests, which will require about 3 Tablespoons of blood
- Urine test to evaluate your exposure to tobacco
- Lung function tests
- Pregnancy test, if you are a woman capable of becoming pregnant

Pulmonary Function Tests (PFTs): You will undergo a group of tests called pulmonary function

tests (also called lung function tests) to check how well your lungs work. The tests determine how much air your lungs can hold, how quickly you can move air in and out of your lungs, and how well your lungs put oxygen into and remove carbon dioxide out of your blood. If there are any results that are troublesome, you will be informed and asked if you would like to be referred to an appropriate health care provider for follow-up. The types of PFTs you will undergo in this study are:

> **Spirometry**: You will breathe into a mouthpiece attached to a recording device (spirometer). Spirometry measures how much and how quickly you can move air out of your lungs.
>
> **Lung Diffusion Testing:** You will breathe in air containing a very small amount of carbon monoxide and then hold your breath for 10 seconds. You will then rapidly blow it out. The exhaled (blown out) gas is tested to determine how much of the carbon monoxide was absorbed during the breath and this relates to how well your lungs exchange oxygen and carbon dioxide.

As part of this study you will also be asked to answer questions about your tobacco and alcohol use, both before you begin the study and again at about Week 24. Researchers want to see if tobacco and alcohol use affects the side effects people might get while on this study, or if tobacco and alcohol use modifies the effects of the study agents.

If you agree, an optional blood sample (about 2 Tablespoons) will be collected for possible future research. This is described in more detail in the section entitled "**Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies"** later in this document.

If the exams, tests, and procedures show that you can take part in the study, and you choose to, then you will be scheduled to have your first vaccine injection. A repeat pregnancy test will be performed before the vaccination, if applicable.

During the study:

- Repeat vaccinations at Week 2 and Week 10
- Repeat blood testing at Weeks 2, 4, 10, 12, and 24 to check your response to the vaccine and check for any possible side effects. This will require about 3 Tablespoons of blood.
- Repeat urine testing at Weeks 12 and 24
- Phone calls at Weeks 16 and 20, and possibly 28 to see how you are doing, ask about any side effects, and ask about any new medications you are taking
- Return visit at Week 24 for a repeat physical exam, repeat blood, urine, and lung tests, review of side effects and medications, alcohol and tobacco use follow-up assessments, and completion of the Was It Worth It questionnaire which asks a few questions about your experience on this clinical trial.

A study calendar that shows how often these tests and procedures will be done is attached to the end of this consent form.

What possible risks can I expect from taking part in this study?

If you choose to take part in the study, there is a risk that you may:

- Lose time at work or home and spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions which you normally do not discuss, for example about your alcohol and tobacco use
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or blood relatives could be found during a study.

You will be asked to keep track of any symptoms and possible side effects using a Vaccine Report Card. The study team will provide instructions on how to complete this, and it will be reviewed at each study visit.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common side effects that we know about the MUC1 vaccine, some of which may be serious. There might be other side effects that we do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Common, Some May Be Serious **In 100 people receiving the injection, more than 20 may have:**
• Redness at injection site (erythema) • Pain/soreness at injection site • Painful, red swelling at injection site

- Flu-like symptoms, which may include fever, chills, headache, fatigue, muscle pain, and joint pain
- Night sweats
- Loss of appetite
- Low albumin blood test result (a type of protein in the blood)
- Fever
- Tiredness

The redness and soreness generally go away within a few days to a week. The flu-like symptoms generally resolve within 12-24 hours. Acetaminophen (Tylenol®) generally helps with these symptoms if they occur.

Occasional, Some May Be Serious **In 100 people receiving the injection, 4 to 20 may have:**
• Low white blood cell count (cells that fight infections) • Low platelet count (cells that help the blood clot in order to stop bleeding) • Anemia (which may cause tiredness, or may require blood transfusion) • Abnormal liver function test results

Rare, Some May Be Serious **In 100 people receiving the injection, 3 or fewer may have:**
• Hives, shortness of breath, or an allergic reaction that is life-threatening • Immune reaction to his or her own tissue (autoimmune diseases) or if present, may be made worse.

Risks of the blood tests

Bruising, soreness, or rarely, infection may occur as a result of the needle sticks to obtain blood from your vein.

Risks of the questionnaires

There are some questions on the study questionnaires that may request sensitive information or make you uncomfortable. You are welcome to skip any questions that you do not wish to answer.

Reproductive risks

You should not become pregnant or father a baby while on this study because we do not know the effect that the drugs in this study may have on an unborn baby. Women should not breastfeed a baby while on this study. You should use adequate birth control methods prior to study entry and while on this study if you are at risk for becoming pregnant or impregnating

someone. Check with your study doctor about what kind of birth control methods to use and how long to use them. For more information about risks and side effects, ask your study doctor. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

Effects of other drugs you may be taking

It is important to tell the doctor or study staff if you are taking any prescription medications including prescription steroids, over the counter drugs, or herbal supplements. We will need this information to make sure that there is no interaction with the study agent.

Are there benefits to taking part in the study?

This study may or may not help you because we do not know how the study drugs will compare to the usual approach for your condition. This study may help us learn things that could help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study. The study doctor will tell you about any new information or changes in the study that could affect your health or your willingness to continue in the study.

For the tobacco and alcohol use questions, you can decide to not answer some or all of the questions. Your decision will not affect whether you can participate in the study, and it will not affect your relationship with your doctor or the study staff.

The study doctor may take you out of the study:

- If your health changes.
- If the study is no longer in your best interest.
- If new information becomes available.
- If you do not follow the study rules.
- If the study is stopped early for any reason by the sponsor (National Cancer Institute, Division of Cancer Prevention [DCP]), the Central Institutional Review Board (CIRB), or the United States Food and Drug Administration (FDA).

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal

rights.

For questions about your rights while in this study, call the Central Institutional Review Board (CIRB) at 888-657-3711.

What are the costs of taking part in this study?

The MUC1 vaccine will be supplied at no charge while you take part in this study. The cost of study-specific exams, tests, and any other procedures will be paid for by the study. Some costs associated with your care may be considered standard of care, and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer.

The study will pay for the following:

- MUC1 vaccine
- Physical exams and assessments
- Blood tests
- Urine tests to evaluate your exposure to tobacco
- Lung function tests
- Blood collection for optional research
- Pregnancy tests, if applicable
- Questionnaires and Vaccine Report Cards
- Phone calls to check on side effects and symptoms

You or your insurance company will pay for the following:

- CT scan that is reviewed to confirm the fact that there is no cancer. This will have been completed at a time point that is the same as your usual and routine clinical care

Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

Will I be paid for participating in the study?

If you complete the study, you will receive $270 to cover the costs associated with participation in the study, such as parking, transportation, and child care. This will be paid as follows: $50.00 for completing the screening visit, $50.00 for each vaccine injection, and $70.00 for completion of the post-intervention visit.

The payments will be authorized at the end of each visit, but it will take some time to process the payment and provide the payment to you.

What happens if I am injured or hurt because I took part in this study?

If you feel you have been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor immediately. You will get medical treatment if you are injured or hurt as a result of taking part in this study.

The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance coverage, you would be responsible for any costs. Even though you are in a study, you keep all of your legal rights to receive payment for injury caused by medical errors.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor, NCI Division of Cancer Prevention
- The Central Institutional Review Board, CIRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute.
- **The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.**

Where can I get more information?

You may visit the NCI website at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required

by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

This section is about optional studies you can choose to take part in.

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer or at high risk for cancer in the future.

The results will not be added to your medical records, and you or your study doctor may not know the results. You will not be billed for these optional studies.

You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

As part of the main study, you will be asked to complete the 'Was It Worth It?' questionnaire at Week 24. Your responses will be reviewed as part of the main study. However, you have the option to allow your responses to be included in a central Quality of Life database (along with demographic information) that is accessible to non-study investigators. If you do not wish to include your responses in the central Quality of Life database, your responses will only be reviewed as part of the main study.

Please circle your answer to show whether or not you would like to take part in this option:

I agree to have my responses to the Was It Worth It? Questionnaire included in a central Quality of Life database (along with demographic information) that is accessible to non-study investigators.

YES NO

Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using blood samples from study participants like you. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, a sample of your blood will be collected. The researchers ask your permission to store and use your samples and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking." The Biobank is being run by the Cancer Prevention Network (CPN) at the Mayo Clinic and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) An additional 2 Tablespoons of blood will be collected from a vein in your arm.
2) Your samples and some related information will be stored in the Biobank at the Mayo Clinic along with samples from other people who choose to take part.
3) Your samples will be used for analyses directly related to this study, including additional indicators of immune response.
4) The samples will be stored at the Mayo Clinic until the end of the study, when they may be transferred to the National Institutes of Health. Left-over blood after the main study is complete will also be available for future unspecific research, in addition to the optional blood draw.
5) Qualified researchers can submit a request to use the materials stored in the Biobank. A research committee will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
6) Neither you nor your doctor will be notified if/when research is conducted using your samples.
7) Some of your genetic and health information may be placed in the central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information we have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There are laws against the misuse of genetic information, but they may not give full protection. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name or social security number) will be sent. Samples will be identified by a unique study code only.

2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and Mayo Clinic staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom the Cancer Prevention Network or the National Cancer Institute sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part; however, you may receive some funds to defray some of the cost of participating (*e.g.*, parking, child care). If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, *<name>,* at *<telephone number>* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, *<name>,* at *<telephone number>*

Please circle your answer to show whether or not you would like to take part in each option.

SAMPLES FOR THE OPTIONAL LABORATORY STUDIES:

I agree to have my blood samples collected, and I agree that these samples and related information may be used for the optional laboratory studies described above.

YES NO

I agree that my study doctors, or their representative, may contact me or my physician to see if I wish to learn about results from these optional studies.

YES NO

SAMPLES AND INFORMATION FOR FUTURE RESEARCH STUDIES:

I agree that my blood samples and related information may be collected and kept in a Biobank for use in future health research.

YES NO

I agree that the information from my tobacco and alcohol use assessments may be used in future health research.

YES NO

I agree that my blood samples and related information may be given to researchers at outside institutions

YES NO

I agree that my study doctors, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled "yes."

Participant's signature **_____**

Date of signature_____

Signature of person(s) conducting the informed consent discussion _____

Date of signature_____

Study Calendar

Time Point/Visit	Tests and Procedures
Screening	• Sign informed consent document • Physical exam with review of vital signs (pulse, blood pressure, height, weight, temperature, and breathing rate) • Review of existing symptoms and medications you are taking • Review of your medical history • Alcohol and tobacco use assessments • Blood and urine tests • Lung function tests • Optional blood collection for research • Pregnancy test, if applicable
Registration/ Day 0	• Receive instructions for completing a Vaccine Report Card • Repeat pregnancy test, if it has been more than 7 days since the previous test • Review vital signs • First vaccine injection
Week 2	• Review your Vaccine Report Card and discuss any side effects, symptoms, and medications you are taking • Review of vital signs • Blood tests for monitoring and to test for a response to the vaccine • Pregnancy test, if applicable • Second vaccine injection
Week 4	• Review your Vaccine Report Card and discuss any side effects, symptoms, and medications you are taking • Review of vital signs • Blood tests for safety monitoring and to test for a response to the vaccine
Week 10	• Review of vital signs • Blood tests for safety monitoring • Pregnancy test, if applicable • Third vaccine injection
Week 12	• Review your Vaccine Report Card and discuss any side effects, symptoms, and medications you are taking • Blood and urine tests for safety monitoring and to test for a response to the vaccine
Weeks 16 and 20	• Phone calls to check on side effects and symptoms you are experiencing and any medications you are taking
Week 24	• Physical exam with review of vital signs (pulse, blood pressure, weight, temperature, and breathing rate)

	• Lung function tests • Review your symptom diary and discuss any side effects, symptoms, and medications you are taking • Alcohol and tobacco use follow-up assessments • Blood and urine tests for safety monitoring and to test the response to the vaccine • Optional blood collection for research • Questionnaire about your experience on this clinical trial: Was It Worth It?
Week 28	• Phone call to see how you are doing might take place, if needed, to ask about side effects and ask about any medications you are taking.

APPENDIX A

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B

GLOSSARY

aa – Amino acid
AA – Advanced adenoma
ADL – Activities of daily living
AE – Adverse events
ADCC – antibody-dependent cell-mediated cytotoxicity
ANA – Antinuclear antibody
BAP – Biospecimens Accessioning and Processing
CACC – Colitis-associate colon cancer
CIRB – Central Institutional Review Board
CPN – Cancer Prevention Network
CRF – Case report form
CTL – Cytotoxic T-lymphocytes
DCP – NCI, Division of Cancer Prevention
dsRNA – double-stranded RNA
FAP – Familial adenomatous polyposis
FDA – Food and Drug Administration
HNPCC – Heritable nonpolyposis colorectal cancer
IBD – Irritable bowel disorder
IFNs – Interferons
IgG – Immunoglobulins
IND – Investigational new drug
IRB – Institutional Review Board
MDSC – Myeloid derived suppressor cells
MUC1 – Mucin 1 (high molecular weight type I transmembrane glycoprotein)
NCI – National Cancer Institute
NK – Natural killer cells
NF-kB – Nuclear factor kappa-light-chain-enhancer of activated B cells
OAS – Oligoadenylate synthetase
PBMC – Peripheral blood mononuclear cells
PO – Participating Organization
PKR – Protein kinase receptor
SAE – Serious adverse events
T12 – Antibody titer at week 12
Th cells – T-helper cells
TLR – Toll like receptor
VNTR – Variable number of tandem repeats
WIWI – Was It Worth It Questionnaire

APPENDIX C

Was It Worth It Questionnaire

Visit type (Time point):* ☐ Week 24 or early termination

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study. Please respond to the following questions as indicated.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

Was it worthwhile for you to participate in this research study? Y N U

If you had to do it over, would you participate in this research study again? Y N U

Would you recommend participating in this research study to others? Y N U

Directions: Circle one response

Overall, did your quality of life change by participating in this research study?

It improved It stayed the same It got worse

Overall, how was your experience of participating in this research study?

Better than I expected The same as I expected Worse than I expected

If there was one thing **that could have been done to improve your experience in this research study, what would it be?**

_____

_____

_____

Would you like to talk to someone about your concerns (circle one response)? Yes No

_____ _____

Signature Date

APPENDIX D

Vaccine Report Card

Dear Study Participant,

Thank you for your willingness to participate in this clinical trial of the MUC1 vaccine. This is one of the first cancer prevention vaccine trials, and we want to carefully document the vaccine experience.

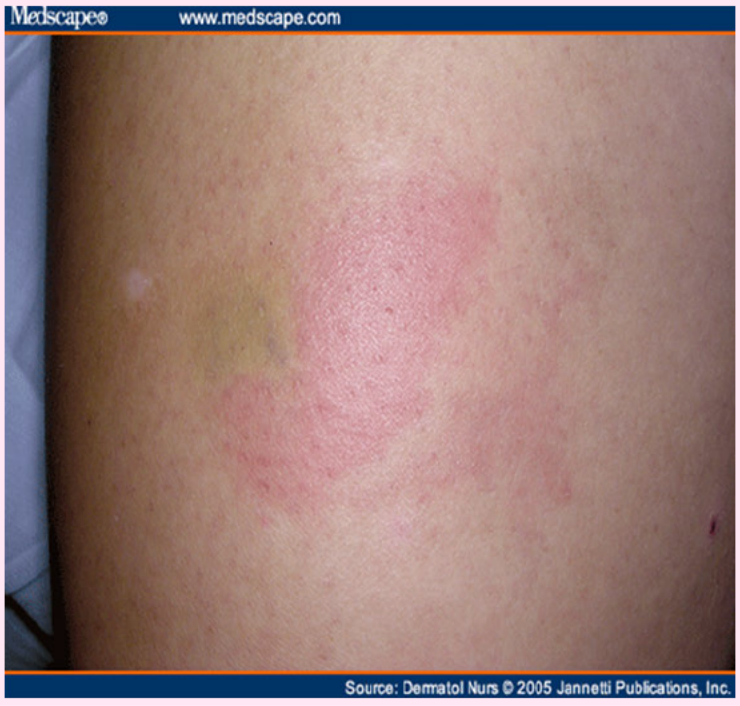
In this booklet you will find a "vaccine report card" to record symptoms. Please review these instructions carefully. If you have any questions about the report card, ask your study team.

When to record symptoms:
The day of your first vaccine injection will be considered Day 0.

- On Day 2, please record symptoms you have experienced since you left your study visit. If you took any medications to relieve symptoms, please write them down. If the symptoms have disappeared, write down the date on the report card in the column labeled "date symptoms disappeared." Once a symptom disappears, you do not need to continue recording anything about that symptom.
- On Day 7, write down all of the symptoms you experience from Day 3 to Day 7.
- On Day 14, write down all of the symptoms you experience from Day 8 to Day 14.
- If you are not scheduled to return for a study visit on or around Day 14, please send this booklet back to the study team by mail, fax, or email. Your study team members will provide a postage-paid envelope, fax number, or email address for you.

What to record:
The previous studies with the MUC1 vaccine have shown us that some, but not all people receiving the vaccine will have reactions such as redness at the injection site, swelling, warmth or itching, and pain or tenderness. Not everyone experiences these symptoms. Some people will have no symptoms.

If there are any other symptoms you experience and want to document, please write them in the text box on the back page of this booklet. If assistance is needed to complete the vaccine report card, please contact your study team.



About Injection Site Reactions

Measuring the size of the redness (erythema):
This picture shows redness of the skin. To measure this, use a tape measure or ruler to measure the maximum distance from one side of the red patch to the other in centimeters. It might be helpful to measure it across the red patch both from side to side and from top to bottom. Record the longest distance.

Pain and Tenderness:
You may experience pain at the injection site. There are two possible types. One is general muscle pain or achiness at the site that is present even when you're not touching the area, such as with movement or even sitting. The other type is tenderness, which is pain when you touch the injection site. Please record these separately.

Swelling or Induration:
Swelling or induration is firmness, like the bump that may be experienced after a mosquito bite. The easiest way to measure it is to use your fingertip to feel the edge of the firmness, and then make a mark with an ink pen at one edge. Make another mark at the opposite edge. It might be helpful to measure and mark the swelling or induration both from side to side and from top to bottom. To measure this, use a tape measure or ruler to measure the maximum distance between the two marks in centimeters. Record the longest distance.

Warmth and itching:
Document when warmth or itching begins and when these symptoms go away.

_____ _____

Your Signature **Date**

_____ _____

Study Coordinator Signature **Date**

MAY2016-08-01,"A Pilot Study of MUC1 Vaccine in Current and Former Smokers at High Risk for Lung Cancer"

Vaccine Report Card

Participant ID _____ **Date of Injection** _____

Instructions: Please complete this "report card" at 2 days, 7 days, and 14 days after your injection. Bring it to your next study visit or return it to the study team by mail, fax, or email. If you have any worrisome symptoms or if you need assistance completing this form, please contact _____ *(insert name of study team member)* at _____ *(insert phone number)*.

Possible side effects	Date Symptom Appeared	2 days after injection Date _____	7 days after injection Date _____	14 days after injection Date _____	Date Symptom Disappeared
Redness at the injection site		□ None □ Yes. It measured _____ centimeters	□ None □ Yes. It measured _____ centimeters	□ None □ Yes. It measured _____ centimeters	
Pain at the injection site <u>without</u> touching		□ None □ A little, but it didn't interfere with normal activity □ Some, required OTC* medications for more than 24 hours or limited normal activity □ A lot, required prescription medications, interfered with normal activity □ Required ER visit or hospitalization	□ None □ A little, but it didn't interfere with normal activity □ Some, required OTC* medications for more than 24 hours or limited normal activity □ A lot, required prescription medications, interfered with normal activity □ Required ER visit or hospitalization	□ None □ A little, but it didn't interfere with normal activity □ Some, required OTC* medications for more than 24 hours or limited normal activity □ A lot, required prescription medications, interfered with normal activity □ Required ER visit or hospitalization	

Possible side effects	Date Symptom Appeared	2 days after injection Date _____	7 days after injection Date _____	14 days after injection Date _____	Date Symptom Disappeared
Tenderness (Pain at the injection site <u>with</u> touch)		□ None □ A little, but it didn't interfere with normal activity □ Some, required OTC* medications for more than 24 hours or limited normal activity □ A lot, required prescription medications, interfered with normal activity □ Required ER visit or hospitalization	□ None □ A little, but it didn't interfere with normal activity □ Some, required OTC* medications for more than 24 hours or limited normal activity □ A lot, required prescription medications, interfered with normal activity □ Required ER visit or hospitalization	□ None □ A little, but it didn't interfere with normal activity □ Some, required OTC* medications for more than 24 hours or limited normal activity □ A lot, required prescription medications, interfered with normal activity □ Required ER visit or hospitalization	
Swelling/ Induration**		□ None □ Yes. It measured _____ centimeters	□ None □ Yes. It measured _____ centimeters	□ None □ Yes. It measured _____ centimeters	
Itching at site		□ None □ Yes	□ None □ Yes	□ None □ Yes	
Skin warmth at site		□ None □ Yes	□ None □ Yes	□ None □ Yes	

* OTC – Over the counter medications such as Tylenol® or ibuprofen.

** Firm, raised swelling.

Appendix E. Alcohol Assessment: Baseline

Instructions: For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

1. In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage? *(check one)*
   - ☐ Yes
   - ☐ No **(End)**
   - ☐ Choose not to answer **(End)**
   - ☐ Don't know/Not sure

   (If No or Choose not to answer), stop assessment

2. In the past 12 months, on average, how often did you drink any type of alcoholic beverage? *(Enter the number of days you drank based on the timeframe checked below. Enter 0 if you never drank and skip to Question 6.)* _____
   (If more than 0, check one)
   - ☐ Week
   - ☐ Month
   - ☐ Year
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

3. In the past 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have per day?
   *(Enter the average number of drinks per day)*_____
   (If no answer, check one)
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

4. In the past 12 months, on how many days did you have 5 or more drinks of any alcoholic beverage?
   *(Enter the number of days you had 5 or more drinks, or enter 0 if none.)*_____
   (If no answer, check one)
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

5. Was there ever a time or times in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost every day?
   (check one)
   - ☐ Yes
   - ☐ No
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

6. If you do not currently drink alcoholic beverages, but did in the past, how long has it been since you last drank regularly?
   (check one)
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)
   - ☐ Between 6 and 12 months (6 to 12 months ago)
   - ☐ Between 1 and 5 years (1 to 5 years ago)
   - ☐ Between 5 and 15 years (5 to 15 years ago)
   - ☐ More than 15 years ago
   - ☐ Don't know/Not sure
   - ☐ Never drank regularly
   - ☐ Choose not to answer

Alcohol Assessment: Baseline (continued)

7. At the heaviest point, either now or in the past, on the days when you drank, about how many drinks did you drink a day on the average? *(Enter the number of drinks a day)*_____
(If no answer, check one)
☐ Choose not to answer
☐ Don't know/Not sure

8. How many years have you been drinking (or did drink) regularly? _____ years
(If no answer, check one)
☐ Choose not to answer
☐ Don't know/Not sure

9. At what age did you begin drinking regularly? _____ years of age
(If no answer, check one)
☐ Choose not to answer
☐ Don't know/Not sure

10. What type(s) of alcohol do you drink?

Wine	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer
Liquor	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer
Beer	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer
Wine cooler	*(check one)* ☐ Yes	☐ No	☐ Choose not to answer

_____ _____
Investigator signature Date

Appendix E. Alcohol Assessment: Follow-Up

Instructions: For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

1. During the past 30 days, did you drink any alcoholic beverages? *(check one)*
   - ☐ Yes
   - ☐ No **(End)**
   - ☐ Choose not to answer **(End)**
   - ☐ Don't know/Not sure

   (If No or Choose not to answer, stop assessment)

2. During the past 30 days, how many days per week or per month did you drink any alcoholic beverages, on the average?
   (Enter number of days you drank based on the timeframe checked below. Enter 0 if you did not drink.) _____
   (If more than 0), specify *(check one)*
   - ☐ Week
   - ☐ Month
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

3. On the days when you drank, on average, about how many drinks did you have?
   (Enter the average number of drinks you had per day. Enter 0 if you did not drink.) _____
   (If no answer, check one)
   - ☐ Choose not to answer
   - ☐ Don't know/Not sure

4. In the past 30 days, on how many days did you have 5 or more drinks per day?
   _____ *(Enter the number of days you had 5 or more drinks, or enter 0 if none.)*
   (If no answer, check one.)
   - ☐ None
   - ☐ Choose not to answer
   - ☐ Do not know/Not sure

_____ _____

Investigator signature Date

Appendix E. Tobacco Assessment: Baseline

Section A. Basic Cigarette Use Information

1. Have you smoked at least 100 cigarettes (5 packs = 100 cigarettes) in your entire life?
   - ☐ Yes
   - ☐ Choose not to answer → **Skip to Section B**
   - ☐ No → **Skip to Section B**
   - ☐ Don't know/Not sure → **Skip to Section B**

2. How old were you when you first smoked a cigarette *(even one or two puffs)*? _____ Years old
   (If no answer, check one)
   ☐ Choose not to answer ☐ Don't know/Not sure

3. How old were you when you first began smoking cigarettes regularly? _____ Years old
   (If no answer, check one)
   ☐ Refused ☐ Don't know/Not sure ☐ Check here if you have never smoked cigarettes regularly.

4. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.
   (If you smoked less than one year, write "1.") _____ Years
   ☐ Choose not to answer ☐ Don't know/Not sure

5. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day? *(A pack usually has 20 cigarettes in it).* _____ Number of cigarettes per day
   (If no answer, check one)
   ☐ Choose not to answer ☐ Don't know/Not sure

6. Do you NOW smoke cigarettes? *(check one)*
   - ☐ Everyday
   - ☐ Some days
   - ☐ Choose not to answer → **Skip to question 8**
   - ☐ Not at all → **Skip to question 8**

7. How soon after you wake up do you smoke your first cigarette? *(check one)*
   ☐ Within 30 minutes ☐ After 30 minutes ☐ Choose not to answer

8. How long has it been since you last smoked a cigarette (even one or two puffs)? *First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.*

   I smoked a cigarette today (at least one puff) *(check one)* ☐ Yes ☐ No
   1-7 days *(check one)* ☐ Yes ☐ No
   (If yes), Number of days since last cigarette _____
   Less than 1 month *(check one)* ☐ Yes ☐ No
   (If yes), Number of weeks since last cigarette _____
   Less than 1 year *(check one)* ☐ Yes ☐ No
   (If yes), Number of months since last cigarette _____
   More than 1 year *(check one)* ☐ Yes ☐ No
   (If yes), Number of years since last cigarette _____
   Don't know/Don't remember *(check one)* ☐ Yes ☐ No
   Choose not to answer ☐

Tobacco Assessment: Baseline (continued)

Section B. Use of Other Forms of Tobacco

9. Have you ever used other forms of tobacco, not including cigarettes? *(check one)*
   ☐ Yes ☐ Choose not to answer
   ☐ No → **Skip to Section C**

10. How often do you/did you use other forms of tobacco?
   Every day *(check one)* ☐Yes ☐No *(If yes)*, Number of times per day _____
   Some days *(check one)* ☐Yes ☐No *(If yes)*, Number of days _____
   (If yes), Per *(select one)* ☐ Week ☐ Month ☐Year

11. Which of the following products have you ever used regularly? *(Mark yes, no., or choose not to answer for all choices)*

Cigarettes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Traditional cigars, cigarillos or filtered cigars	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Hookah	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Bidis	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Snus	*(check one)* ☐Yes ☐No ☐ Choose not to answer
E-cigarettes or other electronic nicotine delivery system	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Pipes	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Waterpipe	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Clove cigarettes or kreteks	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Smokeless tobacco *(like dip, chew, or snuff)*	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Paan with tobacco, gutka, zarda, khaini	*(check one)* ☐Yes ☐No ☐ Choose not to answer
Other, please specify:	

12. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly? *(check one)*
   ☐ Within the past month (0 to 1 month ago)
   ☐ Between 1 and 3 months (1 to 3 months ago)
   ☐ Between 3 and 6 months (3 to 6 months ago)
   ☐ Between 6 and 12 months (6 to 12 months ago)
   ☐ Never used other forms of tobacco regularly
   ☐ Between 1 and 5 years (1 to 5 years ago)
   ☐ Between 5 and 15 years (5 to 15 years ago)
   ☐ More than 15 years ago
   ☐ Don't know/Not sure
   ☐ Choose not to answer

Section C. Second-Hand Smoke Exposure

13. Are you currently living with a smoker? *(check one)*
   ☐Yes ☐No ☐ Choose not to answer

14. In the past 30 days, have you lived in a place where other people smoked cigarettes indoors? *(check one)*
   ☐Yes ☐No ☐ Choose not to answer

15. In the past 30 days, have you worked in a place where other people smoked cigarettes indoors? *(check one)*
   ☐Yes ☐No ☐ Choose not to answer

16. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors? *(check one)*
   ☐Yes → In total, for about how many years? _____ If less than 1, write "1."
   ☐No
   ☐ Choose not to answer

17. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors? *(check one)*
   ☐Yes → In total, for about how many years? _____ If less than 1, write "1."
   ☐No
   ☐ Choose not to answer

_____ _____
Investigator signature Date

Appendix E. Tobacco Assessment: Follow-Up

1. Do you NOW smoke cigarettes? *(check one)*
   - ☐ Everyday
   - ☐ Some days
   - ☐ Choose not to answer→ **Skip to Question 3.**
   - ☐ Not at all → **Skip to Question 3.**

2. On average, when you smoked, about how many cigarettes do you (or did you) smoke a day? *(A pack usually has 20 cigarettes in it)*.
   _____ Number of cigarettes per day
   (If no answer, check one)
   ☐Choose not to answer ☐Don't know/Not sure

3. How long has it been since you last smoked a cigarette (even one or two puffs)? *First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.*
   I smoked a cigarette today (at least one puff) *(check one)* ☐Yes ☐No
   1-7 days *(check one)* ☐Yes ☐No
   (If yes), Number of days since last cigarette _____
   Less than 1 month *(check one)* ☐Yes ☐No
   (If yes), Number of weeks since last cigarette _____
   Less than 1 year *(check one)* ☐Yes ☐No
   (If yes), Number of months since last cigarette _____
   More than 1 year *(check one)* ☐Yes ☐No
   (If yes), Number of years since last cigarette _____
   Don't know/Don't remember *(check one)* ☐Yes ☐No
   Choose not to answer ☐

4. Since your last visit, have you used other forms of tobacco, not including cigarettes? *(check one)*
   - ☐ Yes
   - ☐ Choose not to answer **(End)**
   - ☐ No (**End)** *(If no)*, stop assessment

5. How often do you/did you use other forms of tobacco?
   Every day *(check one)* ☐Yes ☐No *(If yes),* Number of times per day _____
   Some days *(check one)* ☐Yes ☐No *(If yes),* Number of days _____
   (If yes), per *(select one)* ☐Week ☐Month ☐Year
   ☐Choose not to answer

6. Since your last visit, which of the following products have you used? *(Mark yes or no for all choices)*

Cigarettes	*(check one)* ☐Yes ☐No ☐Choose not to answer
Traditional cigars, cigarillos or filtered cigars	*(check one)* ☐Yes ☐No ☐Choose not to answer
Hookah	*(check one)* ☐Yes ☐No ☐Choose not to answer
Bidis	*(check one)* ☐Yes ☐No ☐Choose not to answer
Snus	*(check one)* ☐Yes ☐No ☐Choose not to answer
E-cigarettes or other electronic nicotine delivery system	*(check one)* ☐Yes ☐No ☐Choose not to answer
Pipes	*(check one)* ☐Yes ☐No ☐Choose not to answer
Waterpipe	*(check one)* ☐Yes ☐No ☐Choose not to answer
Clove cigarettes or kreteks	*(check one)* ☐Yes ☐No ☐Choose not to answer
Smokeless tobacco *(like dip, chew, or snuff)*	*(check one)* ☐Yes ☐No ☐Choose not to answer
Paan with tobacco, gutka, zarda, khaini	*(check one)* ☐Yes ☐No ☐Choose not to answer
Other, please specify: _____	

Tobacco Assessment: Follow-Up (continued)

7. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly? *(check one)*
   - ☐ Within the past month (0 to 1 month ago)
   - ☐ Between 1 and 3 months (1 to 3 months ago)
   - ☐ Between 3 and 6 months (3 to 6 months ago)
   - ☐ Between 6 and 12 months (6 to 12 months ago)
   - ☐ Between 1 and 5 years (1 to 5 years ago)
   - ☐ Between 5 and 15 years (5 to 15 years ago)
   - ☐ More than 15 years ago
   - ☐ Don't know/Not sure
   - ☐ Choose not to answer
   - ☐ Never used other forms of tobacco regularly

The following instructions pertain to questions 8 -10. During each of the following time frames, please indicate whether you smoked cigarettes every day, some days, or not at all.

8. During study treatment *(check one)*
   - ☐ Smoked every day
   - ☐ Smoked some days
   - ☐ Did not smoke at all
   - ☐ Don't know/not sure
   - ☐ Choose not to answer
   - ☐ Not applicable

9. After the end of study treatment *(check one)*
   - ☐ Smoked every day
   - ☐ Smoked some days
   - ☐ Did not smoke at all
   - ☐ Don't know/not sure
   - ☐ Choose not to answer
   - ☐ Not applicable (I have not completed the study treatment)

10. Since your last visit to this clinic *(check one)*
    - ☐ Smoked every day
    - ☐ Smoked some days
    - ☐ Did not smoke at all
    - ☐ Don't know/not sure
    - ☐ Choose not to answer
    - ☐ Not applicable (This is my first visit to this clinic)

_____ _____

Investigator signature Date

Appendix F. Alcohol and Tobacco Cessation Resources

National and local resources to help with alcohol abuse and alcoholism

NIAAA's online guide ***Treatment for Alcohol Problems: Finding and Getting Help*** is written for individuals, and their family and friends, who are looking for options to address alcohol problems. It is intended as a resource to understand what treatment choices are available and what to consider when selecting among them.
https://pubs.niaaa.nih.gov/publications/treatment/treatment.htm

Other resources:

National Institute on Alcohol Abuse and Alcoholism www.niaaa.nih.gov
301–443–3860

National Institute on Drug Abuse www.nida.nih.gov
301–443–1124

National Clearinghouse for Alcohol and Drug Information www.samhsa.gov
1–800–729–6686

Substance Abuse Treatment Facility Locator www.findtreatment.samhsa.gov
1–800–662–HELP

Alcoholics Anonymous (AA) www.aa.org
212–870–3400 or check your local phone directory under "Alcoholism"

Moderation Management www.moderation.org
212–871–0974

Secular Organizations for Sobriety www.sossobriety.org
323–666–4295

SMART Recovery www.smartrecovery.org
440–951–5357

Women for Sobriety www.womenforsobriety.org
215–536–8026

Al-Anon Family Groups www.al-anon.alateen.org
1–888–425–2666 for meetings

Adult Children of Alcoholics www.adultchildren.org
310–534–1815

National and local resources to help with quitting smoking

NCI's Smokefree.gov offers science-driven tools, information, and support that has helped smokers quit. You will find state and national resources, free materials, and quitting advice from NCI.

Smokefree.gov was established by the Tobacco Control Research Branch of NCI, a component of the National Institutes of Health, in collaboration with the Centers for Disease Control and Prevention and other organizations.

Publications available from the Smokefree.gov Web site include the following:

- Clearing the Air: Quit Smoking Today for smokers interested in quitting.
- Clear Horizons for smokers over age 50.
- Forever Free™ for smokers who have recently quit.
- Forever Free for Baby and Me™, in English and Spanish, for pregnant smokers who have recently quit.
- Pathways to Freedom: Winning the Fight Against Tobacco for African American smokers.

NCI's Smoking Quitline at **1–877–44U–QUIT (1–877–448–7848)** offers a wide range of services, including individualized counseling, printed information, referrals to other resources, and recorded messages. Smoking cessation counselors are available to answer smoking-related questions in English or Spanish, Monday through Friday, 8:00 a.m. to 8:00 p.m., Eastern Time. Smoking cessation counselors are also available through LiveHelp, an online instant messaging service. LiveHelp is available Monday through Friday, 8:00 a.m. to 11:00 p.m., Eastern Time.

Your state has a toll-free telephone quitline. Call **1–800–QUIT–NOW (1–800–784–8669)** to get one-on-one help with quitting, support and coping strategies, and referrals to resources and local cessation programs. The toll-free number routes callers to state-run quitlines, which provide free cessation assistance and resource information to all tobacco users in the United States. This initiative was created by the Department of Health and Human Services. For more information about quitlines, speak to an expert on the Smokefree.gov Web site.