CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF MEDICAL ONCOLOGY

TITLE: P53MVA AND PEMBROLIZUMAB IN TREATING PATIENTS WITH RECURRENT OVARIAN, PRIMARY PERITONEAL, OR FALLOPIAN TUBE CANCER

CITY OF HOPE PROTOCOL NUMBER: IRB# 16448 **PROTOCOL DATED:** 02/08/23

COH Amendment	DATE(S) OF AMENDMENT(S)/REVISION(S)	
COH Amendment 01	Protocol Dated 04/18/17 (FDA Amend)	Version 01
COH Amendment 02	Protocol Dated 12/06/17	Version 02
COH Amendment 03	Protocol Dated 01/18/18	Version 03
COH Amendment 04	Protocol Dated 05/14/18 (Merck Amend)	Version 04
COH Amendment 05	Protocol Dated 04/12/19 (Merck Amend)	Version 05
COH Amendment 06	Protocol Dated 04/15/19	Version 06
COH Amendment 07	Protocol Dated 05/09/19 (Merck Amend)	Version 07
COH Amendment 08	Protocol Dated 05/15/19	Version 08
COH Amendment 09	Protocol Dated 07/19/19	Version 09
COH Amendment 10	Protocol Dated 09/10/19	Version 10
COH Amendment 11	Protocol Dated 03/24/20	Version 11
COH Amendment 12	Protocol Dated 11/13/20	Packet 12
COH Amendment 13	Protocol Dated 11/13/20 Title Page	Packet 13
COH Amendment 14	Protocol Dated 03/04/21	Packet 14
COH Amendment 15	Protocol Dated 04/15/21	Packet 15
COH Amendment 16	Protocol Dated 11/02/21	Packet 16
COH Amendment 17 at Continuation	Protocol Dated 11/02/21 (tp)	Packet 17
COH Amendment 18	Protocol Dated 02/08/23	Packet 18

SPONSOR/IND NUMBER: COH/IND 14716
DISEASE SITE:
STAGE (if applicable):
MODALITY: IV and SC

PHASE/TYPE: Phase II

PRINCIPAL INVESTIGATOR:	**Thanh Dellinger, M.D.** Department of Medical Oncology, City of Hope Comprehensive Cancer Center
COLLABORATING INVESTIGATOR(S): Division of Translational Vaccine Research	**Don J Diamond, Ph.D** **Ferdynand Kos, Ph.D** **Michael Tran, M.D.** **Alex Jung, M.D.** Department of Diagnostic Radiology
PARTICIPATING CLINICIANS:	**Vincent Chung, M.D**. Department of Medical Oncology **Christine Wei, M.D.** Department of Pathology
STUDY STATISTICIAN:	**Paul Frankel, Ph.D**. Department of Biostatistics
PARTICIPATING SITES:	City of Hope Comprehensive Cancer Center
STUDY SPONSOR AND MONITOR:	City of Hope
AGENT NSC# AND IND#:	p53MVA: COH-IND 14716 Pembrolizumab (Keytruda): NDC 0006-3029-02
COORDINATING CENTER:	City of Hope

SPONSOR: CITY OF HOPE

TITLE: P53MVA AND PEMBROLIZUMAB IN TREATING PATIENTS WITH RECURRENT OVARIAN, PRIMARY PERIOTONEAL, OR FALLOPIAN TUBE CANCER

IND NUMBER: p53MVA vaccine COH/IND 14716

CONTENTS

1.0 TRIAL SUMMARY

Abbreviated Title	Combined Immunotherapy for Ovarian Cancer
Trial Phase	II
Clinical Indication	Platinum Refractory Ovarian Cancer
Trial Type	Therapeutic
Type of control	Immunotherapy
Route of administration	p53MVA (SC) and Pembrolizumab (IV)
Trial Blinding	Not applicable
Treatment Groups	1
Number of trial participants	16-28
Estimated enrollment period	12 months
Estimated duration of trial	24 months
Duration of Participation	Maximum of 24 months
Estimated average length of treatment per patient	6-12 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase II, single center study enrolling 16-28 patients. Patients will be initially enrolled at a single dose level and dose de-escalation of p53MVA will be employed if necessary.

Single arm: *p53MVA* (dose 5.0 x10^8 pfu) + *pembrolizumab* (anti-PD1 mAb flat dose: 200 mg)

p53MVA and pembrolizumab will be given concurrently in accordance with previous studies that show potential for checkpoint inhibitors in combination with vaccines. The aim is to use pembrolizumab to enhance the activity of the p53MVA vaccine to deliver clinical benefit:

Treatment Schedule:
Week 1 (day 1): p53MVA + pembrolizumab

Week 4: p53MVA + pembrolizumab

Week 7: p53MVA + pembrolizumab

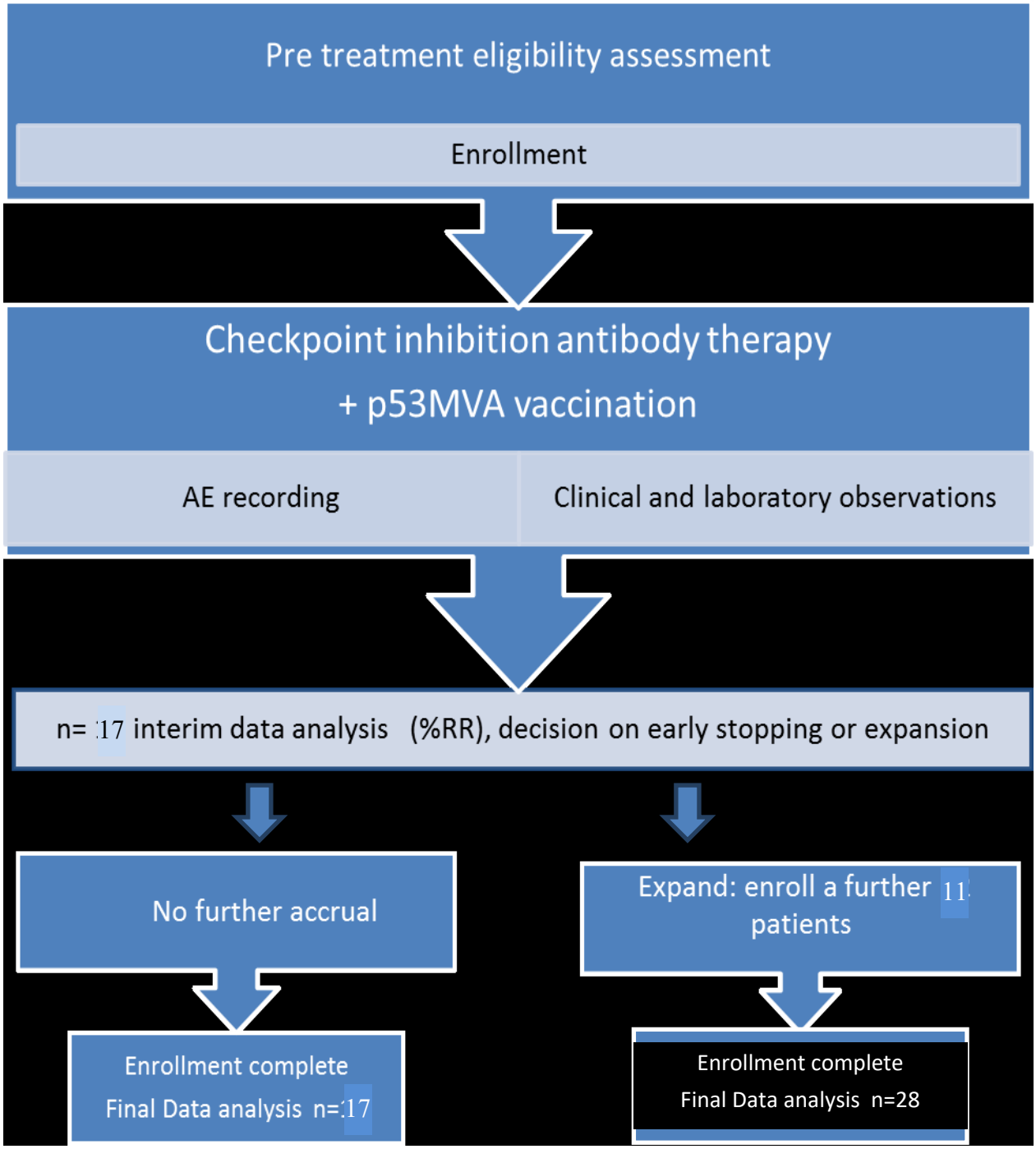
Week 10: pembrolizumab

Week 13: pembrolizumab

Week 16: pembrolizumab continuing every 3 weeks up to 35 cycles (105 weeks)*

(Pembrolizumab treatment may be extended beyond 49 weeks if a second course is indicated, see Section 5.2.3)

2.2 Trial Diagram



3.0 OBJECTIVES &HYPOTHESES

3.1 Primary Objective & Hypothesis

(1) **Objective:** to assess response rate (complete responses and partial responses) after treatment with p53MVA and Pembrolizumab.

Hypothesis: combined treatment with p53MVA and Pembrolizumab will result in a higher response rate than observed with single agent Pembrolizumab in this patient population (8% with acceptable toxicity.

3.2 Secondary Objectives & Hypotheses

(1) **Objective**: Secondary objectives are to assess median PFS, clinical benefit (complete response, partial response lasting >6 months), overall survival (OS), safety and tolerability.

Hypothesis: median PFS, clinical benefit (complete response, partial response lasting >6 months) and OS will be superior to that reported with single agent Pembrolizumab in this patient population, with acceptable toxicity.

3.3 Exploratory Objective

(1) **Objective:** Biological/immunological correlates which be exploratory in nature. We will evaluate if the $CD8^+$ T cell signal exceeds that detected in the single agent p53MVA trial. In the prior single agent study the p53-reactive $CD8^+$ T cells increased above baseline after the first immunization but did not expand further with subsequent immunization. We hypothesize that the $CD8^+$ T cell response will be enhanced by pembrolizumab, resulting in larger or more durable increases in the $CD8^+$ T cell response.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda®(pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [2, 3].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2)[4, 5].

The structure of murine PD-1 has been resolved [6]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [5, 7-9]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [10, 11]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in platinum resistant ovarian cancer.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Merck Investigator's Brochure for Preclinical and Clinical data on Pembrolizumab.

4.2 Rationale

p53 Immunotherapy: A promising approach to cancer immunotherapy involves the use of vaccines which target defined tumor associated antigens. An ideal and widely expressed target for the cellular immune response is the p53 gene product. The p53 protein maintains normal cell division and about 40-60% of solid tumors have p53 mutations [12]. Mutations of p53, which abrogate its function as a suppresser of cell division, are associated with high intracellular concentration of the

p53 protein. This makes p53 an attractive target for immunotherapy, since the intracellular concentration of wild type p53 in healthy tissue is low. Cells expressing normal p53 at low levels will escape an enhanced immune response to over-expressed mutant p53. In addition, there is considerable evidence that p53 mutation is associated with aggressive disease and metastasis. Antibodies against human p53 are demonstrable in a notable proportion of patients with breast, lung, colorectal, gastric, esophageal, ovarian, pancreatic, and prostate cancer. Furthermore, the presence of T cell responses to p53 has been demonstrated in peripheral blood mononuclear cells (PBMC) from patients with colon [13] and ovarian cancer [14].

It is possible that mutations in the p53 gene give rise to true tumor associated antigens. However, in order to have widespread application, p53 immunotherapy targets the wild type epitopes of p53. Since p53 is a partially tolerized autoantigen, breaking immunological tolerance to p53 is required for successful immunotherapy targeting this antigen. Dr Diamond's group at COH, and others, have generated human CTL *in vitro* capable of lytic activity against human tumor cells overexpressing p53 protein[15-17].

Clinical Trials of p53 Vaccines: Administration of the canarypox virus ALVAC to a group of patients with unresectable colorectal cancer demonstrated that 2 out of 5 patients receiving the highest vaccine dose developed p53 specific responses [18]. Ad-p53 pulsed dendritic cells have been evaluated in Phase I and Phase II clinical trials in cancer patients with advanced malignancies [19]. The majority of patients generated potent p53-specific immunity and evidence of clinical benefit was demonstrated. Leffers *et al* reported that a p53-synthetic long peptide vaccine was well-tolerated and induced p53-specific T cell responses in patients with recurrent ovarian cancer [20]. When the vaccine was combined with cyclophosphamide, a reduction in Tregs was observed and 2/10 patients showed stable disease [21]. This was followed by a Phase 1/2 study combining gemcitabine, Pegintron and p53 SLP vaccine in patients with platinum-resistant ovarian cancer. The combination of gemcitabine and Pegintron stimulated higher frequencies of circulating proliferating CD4+ and CD8+ T-cells but not regulatory T-cells. All vaccinated patients showed strong vaccine-induced p53-specific T-cell response, but clinical responses were disappointing [22]. No autoimmunity or serious adverse events were reported in these trials. p53MVA has advantages over vaccines comprised of selected epitopes, since a wider range of $CD4^+$ and $CD8^+$ T cells epitopes can be generated by antigen processing of the entire p53 protein.

However, p53 clinical vaccines tested to date are limited to patients with certain tissue types, or require individual manufacturing for each patient thus making it costly and laborious to produce. City of Hope (COH) has developed a strategy using the genetically engineered virus MVA (modified vaccinia Ankara) to immunize patients with the wild type p53 antigen.

The p53MVA vector expresses the full-length wild type human p53 gene. This vaccine was well-tolerated in a first-in-human study conducted at City of Hope. This first-in-human study of p53MVA as a single agent in a cohort of 12 patients was found to be well-tolerated and immunogenic but clinical responses were not observed[23].

MVA Vectors: Attenuated poxviruses are being developed as vaccines in numerous diseases, including influenza, HIV, malaria and tuberculosis. Modified Vaccinia virus Ankara (MVA) is an attenuated, replication deficient vaccinia virus strain which is highly immunogenic. The lack of productive viral replication gives MVA a good safety profile, due to minimal potential for

reversion to virulent forms, even when used in immunocompromised individuals. Despite its inability to replicate in most mammalian cells, MVA can still efficiently express viral and recombinant genes making it a potent antigen delivery platform. Furthermore, due to the inactivation of immune evasion genes, MVA vectors demonstrate useful adjuvant properties [24]. MVA vectors are taken up by antigen presenting cells such as dendritic cells, allowing cross presentation of transgene encoded antigens and priming of specific T cell responses [24].

MVA has a superlative safety record, being used in numerous clinical trials with only mild side-effects. MVA was administered as a smallpox vaccine to over 120,000 individuals in Europe during the 1970s. No serious adverse events were reported, and no reports of systemic infection occurred. Recombinant MVA vaccines have been evaluated in over 15 clinical trials in the United States and Europe and no serious adverse events have been reported. Minor adverse events include mild injection site discomfort and erythema and transient influenza like symptoms. In patients with cancer, administration of 5 x 10^8 pfu of recombinant MVA was well tolerated and resulted in recombinant protein specific immunogenicity and evidence of clinical cancer response [25, 26].

Multiple phase 2 studies of single-agent immune checkpoint blockade in epithelial ovarian cancer have been reported [27-29]. These studies varied in terms of patient population, PD-L1 requirement and assays for defining PD-L1 positivity.

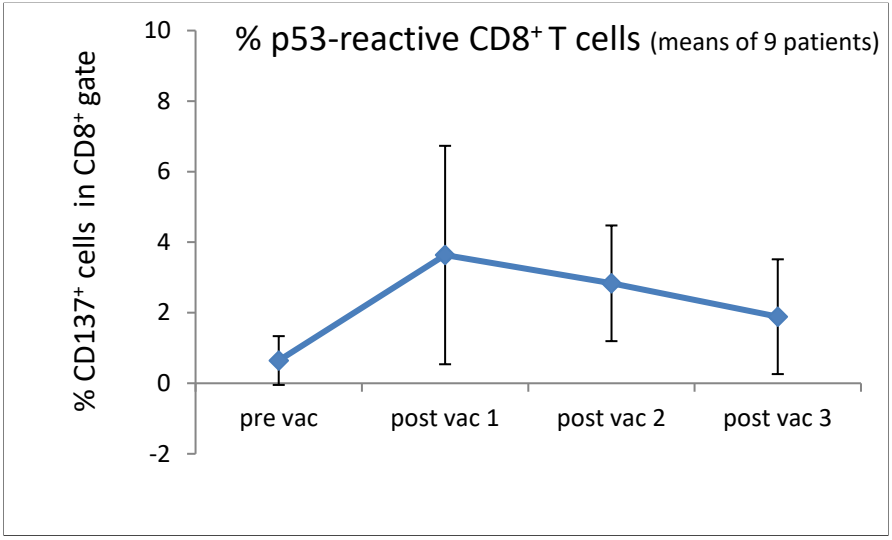
In ovarian cancer, the link between PD-L1 expression and response to check point inhibitors, remains controversial, with mixed correlations in clinical reports. In a large study of avelumab, conducted in ovarian cancer, the ORR was 12.3% for PD-L1 positive cancers (i.e. >1% threshold in tumor cells) versus 5.9% of PD-L1negative cancers. However, the ORR difference, the median PFS and median OS, were not statistically significant [27]. KEYNOTE-100, a phase 2 study that evaluated the activity and safety of pembrolizumab in recurrent ovarian cancer, is the largest study to date of single-agent immune checkpoint in this disease [30]. In this study, PD-L1 expression was measured as combined positive score (CPS) and higher PD-L1 expression CPS of ≥10 resulted in a higher ORR compared to a CPS score of ≥1 or <1.

Combined p53MVA Vaccine and PD-1 Blockade: By immunizing mice with an MVA vaccine expressing p53, it has been possible to generate wild type (wt) p53 specific cytotoxic T lymphocytes (CTL) capable of lysing p53 overexpressing tumor cells. In addition, p53MVA vaccination of mice resulted in rejection of established tumors and lasting systemic anti-tumor immunity [31]. This effect was potentiated by depletion of Tregs, resulting in enhanced antigen specific immunity and tumor rejection in two different strains of mice [32]. In other studies, conducted at City of Hope, PBMC from patients with a variety of solid tumors were stimulated *in vitro* with p53MVA infected antigen presenting cells. The majority of cancer patients evaluated developed p53 specific CTL responses directed against a variety of p53 derived epitopes [33].

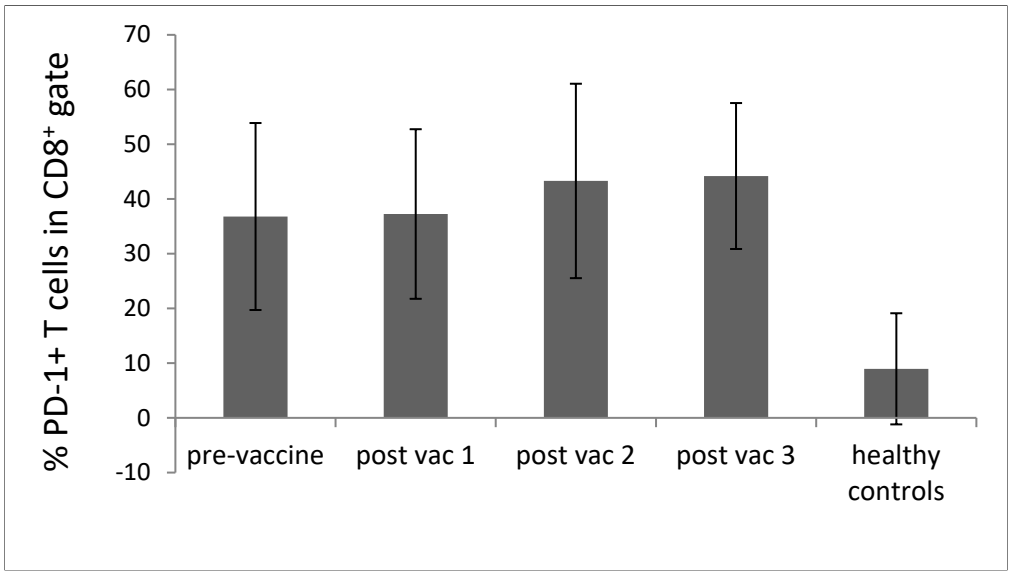
Evidence from murine studies indicate that inhibition of the PD-1/PDL-1 checkpoint pathway with blocking antibodies can enhance the effects of cancer vaccines [34-37]. Our pre-clinical data with a murine equivalent of pembrolizumab has shown dramatic success in a metastatic model of pancreatic cancer that is resistant to the chemotherapy agent Gemzar™ and Abraxane™ combinations. Anti-murine PD1 mAb induced regression in an immunocompetent syngeneic orthotopic murine KPC (Kras and p53 mutant), PD-L1+ pancreatic tumor model. Mice with 13

day established tumors received treatment on days 13 and 20 and showed dramatic regressions of both small and large tumors [38].

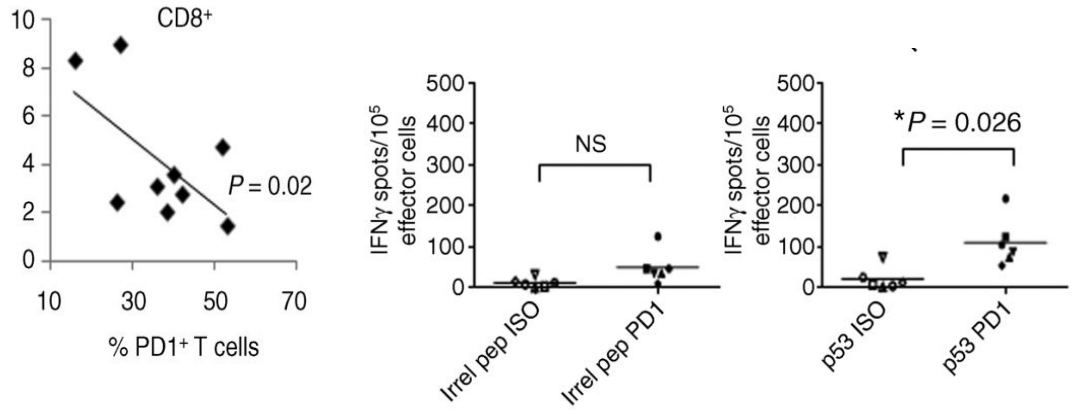
P53MVA and the PD-1/PDL-1 barrier: The first in human Phase I trial of the p53MVA vaccine conducted at COH was well-tolerated at two doses. Three patients were treated with 3 vaccinations of 1 x10^8 pfu and 9 patients were treated with 3 vaccinations of 5.6 x10^8 pfu, with only low grade adverse events reported [23]. Since evidence of strong T cell and neutralizing antibody responses to the MVA backbone were demonstrated [23] it is likely that immune responses are the major mechanism of clearance of p53MVA *in vivo*. p53MVA is well-tolerated and capable of elevating anti-p53 $CD8^+$ T cell responses in patients with advanced, refractory colon and pancreatic cancer. However, despite the detection of immunological responses to the vaccine, clinical responses were not apparent [23]. One possible explanation for this is that the elevation of p53-reactivity was not sustained and expanded by successive vaccination (see below).



Immunosuppression in cancer patients, both systemic and within the tumor microenvironment is now considered a major barrier to effective immunotherapy. This is mediated by suppressive cytokines such as TGF-beta and suppressive cell types including Tregs and MDSC. The ligands for programmed cell death 1 (PD-1), an immuno inhibitory receptor belonging to CD28/cytotoxic T lymphocyte antigen 4 family, are PD-1 ligand 1 and 2 (PD-Ls). Recent reports suggest that the aberrant expression of PD-Ls on tumor cells impairs antitumor immunity, resulting in the immune evasion of the tumor cells. *in vitro* studies with human PBMC have shown that PD-1ligation dramatically shifts the dose-response curve, making T cells less sensitive to T-cell receptor-generated signals. Hence, even low levels of PD-1 expression can inhibit functions such as cytokine release and T cell expansion [39].



High frequencies of PD-1$^+$ T cells were detected in participants of the first-in human, single agent p53MVA trial when compared to healthy donors [40]. Therefore, it was not surprising to find a significant inverse correlation relationship between the frequency of PD1$^+$ T cells and anti-p53 CD8$^+$ T cell response in the trial participants. Further investigation showed that antibody blockade of PD-1 *in vitro* increased the p53 immune responses detected after the second or third immunizations (shown below).



These findings suggested that combination treatment with p53MVA and PD-1 blockade could help sustain the anti-p53 immune response and lead to enhanced clinical benefit. Thus, we believe that a logical strategy is to combine the p53MVA vaccine with checkpoint inhibition therapy.

Published reports of trials combing cancer vaccines and PD-1 blockade are limited to date. A multi peptide vaccine administered in combination with Nivolumab showed immunologic activity and

promising survival in high-risk resected melanoma [41]. Currently there are 12 clinical trials listed on ClinicalTrials.Gov combining peptide or cell based cancer vaccines with nivolumab or pembrolizumab.

4.2.1 Rationale for the Trial and Selected Population

Ovarian cancer is an aggressive malignancy with a very poor prognosis due to intrinsic and acquired chemotherapy resistance. Around 60-80% of patients initially respond to platinum-based chemotherapy (cisplatin/carboplatin) in combination with paclitaxel, however the vast majority later relapse with chemoresistant disease. Hence, new treatments such as immunotherapy are being actively pursued. However, myeloid derived suppressor cells (MDSC) and T regulatory cells (Tregs) are known to accumulate in the ovarian cancer microenvironment [42-46] and are a major barrier to effective immunotherapy.

Ovarian Cancer patients with higher expression of PD-L1 have been shown to have a significantly poorer prognosis than patients with lower expression. Although patients with higher expression of PD-L 2, also had a poorer prognosis, the difference was not statistically significant. In addition, a significant inverse correlation was observed between PD-L1 expression and the intraepithelial CD8+ T lymphocyte count, suggesting that PD-L1 on tumor cells directly suppresses antitumor CD8(+) T cells. Multivariate analysis showed the expression of PD-L1 on tumor cells and intraepithelial CD8(+) T lymphocyte count are independent prognostic factors. Hence it follows that the PD-1/PD-L pathway is a good target for restoring antitumor immunity in ovarian cancer [47].

In a trial of a high-affinity, fully human monoclonal anti-PDL-1 antibody (BMS-936559), in patients with selected advanced cancers, only one of 17 patients with ovarian cancer showed an objective clinical response, compared to 9 of 52 melanoma patients treated [48]. The largest study conducted to date of anti-PDL-1 antibody (Avelumab), reported 123 ovarian cancer patients treated as of October 2015. ORR was 9.7% based on 12 partial responses, of which 6 were ongoing. Stable disease was observed in 55 patients (44%), and the disease control rate was 54.0%. Median OS was 10.8 months [49].

More encouraging results were achieved with the anti-PD-1 antibody, Nivolumab. Twenty patients with platinum-resistant ovarian cancer were treated with an intravenous infusion of nivolumab every 2 weeks at a dose of 1 or 3 mg/kg. The best overall response was 15%, which included two patients with durable complete responses (in the 3-mg/kg cohort). The disease control rate in all 20 patients was 45%, median PFS was 3.5 months (95% CI, 1.7 to 3.9 months) and median OS was 20.0 months (95% CI, 7.0 months to not reached) at study termination. However, grade 3 and higher AEs were observed in around 40% of patients [28].

Another ongoing study of PD-1 blockade in ovarian cancer combines Pembrolizumab with weekly paclitaxel (NCT02440425). Paclitaxel induces proinflammatory cytokine secretion and immune cell activation[50]. Another study of Pembrolizumab in ovarian cancer (NCT02054806) reported the following at ASCO 2015: of 26 patients treated, there was one complete response, 2 partial responses and 6 patients with stable disease[51].

This study will evaluate the p53MVA vaccine in combination with a checkpoint inhibitor, pembrolizumab. Subjects must have recurrent, platinum refractory ovarian cancer, with evidence of p53 over expression to be eligible. Patients will receive injections of p53MVA vaccine, for a total of three injections. Patients will be evaluated for toxicity through the first cycle of therapy.

Pembrolizumab will be administered at a standard dose of 200 mg every 3 weeks, for approximately two years (35 cycles). In the case of grade 3 vaccine related toxicity, the dose of p53MVA will be decreased. In the case of pembrolizumab induced immune-mediated adverse events, treatment will be held or permanently discontinued according to the package insert. Pembrolizumab treatment may be extended beyond 49 weeks (17 cycles) if a second course is indicated (see Section 5.2.3). This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

4.2.2 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated

saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.2.3 Rationale for Endpoints

A phase I trial of p53MVA was completed in patients with colorectal or pancreatic cancer. Patients with unresectable and chemotherapy resistant disease with over expression of p53 were eligible. The highest dose tested (5.6 x10^8 pfu) was well tolerated. A robust $CD8^+$ T cell responses against p53 were detected in the majority of patients after vaccination, but no clinical responses were apparent. We characterized patient peripheral blood T cells for expression of the Programmed Death 1(PD-1) receptor and found frequencies significantly higher than healthy controls. Furthermore, the percentage of $PD1^+$ T cells and peak p53 response showed an inverse, statistically significant correlation in the $CD8^+$ compartment. In light of our findings regarding PD-1 expression, *in vitro* blockade and p53 response, we believe that combining the vaccine with pembrolizumab is the logical next step in the optimization of p53MVA therapy for cancer. We therefore propose a phase II study to evaluate the efficacy and safety of pembrolizumab combined with the p53MVA vaccine in advanced ovarian cancer patients. The primary endpoint in this trial will be response rate (CR+PR). Secondary endpoints include median PFS, clinical benefit (CR+PR+SD>6 months), overall survival, safety and tolerability, and biological correlates which remain exploratory in nature

4.2.3.1 Efficacy Endpoints

Measurement of efficacy (primary endpoint) in this trial will be response rate (CR+PR).

Secondary endpoints will include median PFS, median OS and clinical benefit (CR+PR+SD lasting >6 months) and safety and tolerability. CR, PR and SD will be assessed according to irRECIST criteria (see Section 7.1.2.5)

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Female participants who are at least 18 years of age on the day of signing informed consent with histologically or cytologically confirmed diagnosis of epithelial ovarian, primary peritoneal or fallopian tube cancer will be enrolled in this study. Patients must have experienced recurrence or progression within 6 months after completion of platinum based chemotherapy (by RECIST 1.1 criteria).

2. A patient is eligible to participate if she is not pregnant (see Appendix 3), not breast-feeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3 OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 30 days after the last dose of study treatment.

3. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

4. Have measurable disease based on RECIST 1.1, or detectable disease. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

   a) Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be greater than or equal to 10 mm when measured by CT, PET/CT or MRI. Lymph nodes must be greater than or equal to 15 mm in short axis when measured by CT, PET/CT or MRI.
   -Detectable disease in a patient is defined as one who does not have measurable disease, but has at least one of the following conditions:
   * Baseline values of CA-125 at least 2 X ULN
   * Ascites and/ or pleural effusion attributed to tumor
   * Solid and/ or cystic abnormalities on radiographic imaging that do not meet modified RECIST criteria, immune-related response criteria (irRC) for target lesions.

   b) Platinum Resistance
   - Patients whose ovarian cancer recurs/progresses within 0-6 months following platinum-based chemotherapy have platinum resistant or refractory disease. These patients are not considered to benefit from additional platinum-based therapy and are treated with other sequential single agents. **Such patients are eligible for this trial.**
   - Patients with documented disease recurrence/progression within 6-12 months of completing platinum-based therapy, are considered to have ‘borderline' platinum sensitivity. **These patients will not be eligible for this trial.**

- Patients who relapse more than 12 months after completion of platinum-based treatment are considered 'platinum sensitive' and **will not be eligible for this trial**, since they have a favorable (33-59%) chance of responding to further rounds of platinum based chemotherapy.

5. Patients with confirmed p53 mutation by molecular analysis and/or evidence of p53 overexpression by immunohistochemistry (≥10% of cells within the tumor staining positive) will be eligible. This will be assessed semi-quantitatively by a CLIA approved Pathology Core Pathologist, using CLIA approved mutational analysis or immuno-histochemistry techniques on formalin-fixed paraffin-embedded tissue. In the case of equivocal IHC results, p53 involvement may be confirmed by detection of p53 molecular analysis on tumor DNA. Patients on whom molecular analysis of p53 mutations is already available, will not require ICH analysis. Molecular analysis may be performed as an additional research procedure at the end of the study (distinct from eligibility determination) if the PI deems it of scientific value and research funding is available to cover the cost. Patients are not required to have PD-L1 positive ovarian tumors and PD-L1 testing is not mandatory on this study. However, we will collect the data on PD-L1 testing when available.

6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 (Karnofsky ≥60%) and a life expectancy of at least 3 months.

7. Up to 4 prior chemotherapy regimens for recurrent disease are allowed. Adjuvant chemotherapy and maintenance Taxol after completion of six cycles of adjuvant Carboplatin – Taxol will not be counted as a "prior chemotherapy regimen" for the purpose of this study. Treatment with targeted agents or hormones would not be considered as a systemic chemotherapy regimen. Eligible Patients are those with documented disease recurrence/progression within 0-6 months of completing platinum-based chemotherapy. Patients should not have received any non-oncology, viral vaccines within 30 days prior to starting protocol treatment.

8. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 14 days prior to the start of study treatment.

Table 1 Adequate Organ Function Values

System	Adequate Organ Function (Laboratory Value)
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥50 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Cardiac	
left ventricle ejection fraction (LVEF)	≥55%

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to study treatment start (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

3. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to treatment start.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

4. Has received prior radiotherapy within 3 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

5. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

6. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

7. Has a diagnosis of immunodeficiency (including organ grafts and HIV), or is receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug (exceptions: nasal corticosteroids, inhaled steroids, adrenal replacement steroids and steroid creams are allowed).

8. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer or any carcinoma in situ (e.g. breast

carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

9. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

10. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

11. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

12. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

13. Has an active infection requiring systemic therapy.

14. Has a known history of Human Immunodeficiency Virus (HIV).

15. Has active infection with Hepatitis A (as determined by an acute hepatitis panel), a known history of Hepatitis B (Hepatitis B surface Ag reactive), or active Hepatitis C virus (qualitative HCV RNA detectable).

16. Active TB (Bacillus Tuberculosis) infection (as determined by Quantiferron Test).

17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

18. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

19. Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

20. Patients with a history of cardiac disease are excluded: myocardial infarction or arterial thromboembolic events within 6 months prior to baseline, severe or unstable angina, New York Heart Association Class III or IV disease, QTCB (corrected according to Bazett's formula) interval >470 msec, serious uncontrolled hypertension (systolic >150 and/or

diastolic >100 mm Hg).Baseline electrocardiography, echocardiography and assessment of serum troponin (I) are included in the screening exams. Subjects in whom these assays are abnormal (EKG excluding 1st degree branch block, sinus brachycardia, sinus tachycardia or non-specific T wave changes, serum troponin ≥ grade 2) are ineligible.

21. Patients with a family history or Li-Fraumeni syndrome will not be eligible.

22. History of severe environmental allergies or allergy to egg proteins.

5.1.3 Lifestyle Restrictions

5.1.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

5.1.4 Pregnancy

5.1.4.1 Female participants:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring after the participant receives the first dose of protocol therapy up to 120 days post-last dose of pembrolizumab are considered immediately reportable events or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. **Protocol therapy is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Study PI and the DCC immediately within 24 hours of awareness**. The female subject may be referred to an obstetrician-gynecologist (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator should make every effort to follow the female participant until completion of the pregnancy per institutional policies, and should notify the Study PI.

Abnormal pregnancy outcomes and neonatal deaths that occur within 28 days of birth should be reported as an SAE per expedited reporting guidelines.

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study

Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck.

5.1.4.1.1 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment. The Sponsor must report any potential infant exposure through lactation within 10 calendar days of sponsor's awareness to Merck.

5.1.4.2 Male participants:

If a female partner of a male participant becomes pregnant within 120 days post last dose of pembrolizumab, the male participant should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

The Investigator should make every effort to follow the outcome of the pregnancy per institutional policies and should notify the Study PI.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.

Table 1 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
p53MVA	5.0×10^8 pfu	Q3W	injection into subcutaneous tissue of the upper arm (over deltoid muscle)	every 3 weeks for a total of 3 vaccinations	Experimental

5.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 5 days before or after the scheduled Day 1 of each cycle due to administrative reasons. All trial treatments will be administered on an outpatient basis. Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of

infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The Merck Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. Section 9.0 of this protocol contains instructions for preparation and handling of the p53MVA vaccine.

5.2.2 Dose Modification and toxicity management <u>for immune-related AEs associated with pembrolizumab</u>

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes.
In order to monitor for immune mediated hyperthyroidism and hypothyroidism, patients will be assessed for thyroid function (TSH) at baseline. TSH testing will be repeated during/after the treatment phase if clinical signs and symptoms of thyroid disorders are observed. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

<table>
<tr><td colspan="5">General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.</td></tr>
<tr><th>Immune-related AEs</th><th>Toxicity grade or conditions (CTCAEv5.0)</th><th>Action taken to pembrolizumab</th><th>irAE management with corticosteroid and/or other therapies</th><th>Monitor and follow-up</th></tr>
<tr><td rowspan="2">Pneumonitis</td><td>Grade 2</td><td>Withhold</td><td rowspan="2">• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</td><td rowspan="2">• Monitor participants for signs and symptoms of pneumonitis
• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
• Add prophylactic antibiotics for opportunistic infections</td></tr>
<tr><td>Grade 3 or 4, or recurrent Grade 2</td><td>Permanently discontinue</td></tr>
<tr><td>Diarrhea / Colitis</td><td>Grade 2 or 3</td><td>Withhold</td><td>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</td><td>• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).
• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and</td></tr>
</table>

	Grade 4	Permanently discontinue		performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or	• Monitor for signs and symptoms of thyroid disorders.

			liothyroinine) per standard of care	
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4A Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Precautions and Dose modification and toxicity management of reactions related to p53MVA vaccine

Precautions: All subjects will be monitored for one hour in the clinic after each immunization. Notation will be made of the subject's temperature and of any local reaction at the injection site. The subjects will be contacted by telephone or e-mail approximately 24 and 48 hours after each immunization to evaluate vaccine related complications. If there is any clinical evidence to suggest myopericarditis, patients will receive a full cardiac evaluation, including EKG, serial troponins, echocardiography and consultation by a cardiologist. p53MVA vaccination will be withheld in patients showing ≥Grade 2 hepatitis.

Dose Reductions: In the first-in-human, single agent study, p53MVA vaccination was well-tolerated in 9 patients receiving a dose of 5.6 x 10^8 pfu. The highest level AE recorded was grade 2. Hence, we do not anticipate the need for p53MVA dose reductions. However if required, intra-patient dose reductions will be carried out as follows:

Table 4B p53MVA Vaccine Dose modification and Treatment Guidelines

Toxicity	Management
Grade ≥2 hepatitis related or unrelated to p53MVA Grade ≥3 allergic reactions possibly related to p53MVA	Skip and follow the patient weekly or as needed until the toxicity improves to < Grade 2. May resume p53MVA in the next cycle at 2.8 x 10^8 pfu
Grade 3 non- hematologic toxicity, unrelated to p53MVA	Skip and follow the patient weekly or as needed until the toxicity improves to < Grade 2. Resume p53MVA at 2.8 x 10^8 pfu
Grade 4 non- hematologic toxicity (even if unrelated to p53MVA)	Cease all study agents

5.2.3 Second Course *

All participants who stop study treatment with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
    - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by irRECIST 1.1 after stopping initial treatment, and
    - No new anticancer treatment was administered after the last dose of study treatment, and
    - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
    - The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

**Note: patients must have measurable disease at the start of protocol treatment to be eligible for this provision.*

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.3.2 Prohibited Concomitant Medications/Therapy

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy (radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion).
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.3.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.4 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression, according to irRECIST criteria (outlined in Section 7.1.2.6)
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR), at the PI's discretion. These participants may be eligible for second course treatment described in Section 5.2.3.
- The participant is lost to follow-up
- Completion of 35 treatments with pembrolizumab

  Note: The number of treatments is calculated starting with the first dose. Participants who stop will stop pembrolizumab after receiving 17 doses on study. Patients may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.2.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- Administrative reasons

5.5 Participant Replacement Strategy

5.6 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles**								treatment end
							to be repeated until week 105				Safety Follow-up
Treatment Cycle/Title:	Pre study	screening (Visit 2)	1	2	3	4	5	6	7	8	
Scheduling Window (Days):		-14 to -1		± 5	± 5	± 5	± 5	± 5	± 5	± 5	[d]7-21 days post discon
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Demographics and Medical History	X										
prior/concomitant medication review	X										
Review Adverse Events		X	X	X	X	X	X	X	X	X	X
Physical Examination		X	X	X	X	X----as per standard of care------X					
Vital Signs and Weight		X									
ECOG Performance Status		X									
Pregnancy Test (if indicated)		X									
HIV, active TB and acute hepatitis panel (if indicated)		X									
PT/PTT		X									
CBC with Differential		X	X	X	X	X------as per standard of care----X					
Comprehensive Serum Chemistry Panel		X	X	X	X	X------as per standard of care-----X					
T3, FT4 and TSH		X	X	X	X	X	X	X	X	X	
Cardiac function (EKG/ECG)		X									
Serum Troponin I, BNP		X		X							
Pembrolizumab			X	X	X	X[c]	X	X	X	X	
p53MVA			X	X	X						
Tumor Imaging (CT or PET/CT)	X				X			X--every 9 weeks--X			
CA-125		X	X	X	X	X	X	X	X	X	
Immunologic Blood Collection[b]			X	X	X	X			*X	*X	*X

Study Chart Notes: Baseline evaluations must be conducted no more than 14 days before treatment start, except imaging which are permissible up to 30 days prior to initiation of therapy. All treatments/evaluations during/after the treatment phase may be +/- 5 days. *At the discretion of the PI. [a]Imaging scans must be obtained prior to cycle 4 of therapy +/- 5 days. Subsequent restaging scans will be obtained after every 3 cycles of treatment. +/- 5 days. [b]All blood specimens to be collected prior to administration of study agents. Patients with a hemoglobin (Hgb) level < 9g/dL will not undergo further immunologic phlebotomy until the Hgb level has been documented to rise above 9g/dL. [c]After completion of the three combined doses of p53MVA + PEM, continued administration of PEM as a single agent may continue up to week 49 (first course). [d]Patients completing Week 49 treatment will have an end of study visit, 1-3 weeks after the last dose of PEM. See Section 5.2.3. on 'Second course' of Pembrolizumab.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB approval in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up, according to COH standard practice.

7.1.1.6 Patient Registration

Eligible subjects must be registered with the Clinical Trials Office (CTO) **prior** to start of protocol therapy. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a subject does not receive protocol therapy following registration, the subject's registration on the study may be canceled after discussion with the PI. The CTO should be notified of cancellations as soon as possible.

Once a patient has been identified, the signed informed consent has been obtained, all pretreatment evaluations have been performed, and subject's eligibility has been confirmed, a subject will be registered on study.

To register a subject, the treating physician should contact the protocol nurse or the responsible Clinical Research Coordinator (CRC) in the Clinical Trial Office (CTO) to complete the eligibility checklist.

The protocol nurse or CRC will complete eligibility and enroll patient to trial.

7.1.2 Clinical Assessments

The following laboratory tests will be conducted at baseline and during the treatment phase according to the study chart:

a. Complete blood count with platelet count and differential

b. Comprehensive metabolic panel

c. Urine for pregnancy test where appropriate

d. Blood for immune studies which will be processed and stored by Dr Don Diamond's Lab. PBMC will be separated from heparinized blood by standard density gradient centrifugation and analyzed immediately, or cryopreserved for future analysis.

e. Serum Troponin (I) and B-type natriuretic peptide (BNP)

f. Immuno-histochemistry staining for the primary ligand of PD-1 (PDL-1)

g. CA-125 tumor marker

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee be responsible for determining the event name, assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. Adverse events will be characterized using the descriptions and grading scales found in the most recent version of the NCI CTCAE Version 5.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during the study according to standard of care.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) during eligibility screening.

7.1.2.5 Tumor Imaging and Assessment of Disease

Clinical response will be assessed by modified irRECIST criteria. Conventional RECIST criteria for measuring responses to cytotoxic agents are not optimal for immunotherapies which do not act directly on the tumor, and reductions in disease burden may take many months to occur. Therefore improved overall survival (OS) can result without improved progression free survival/time to progression (PFS/TTP). Hence, we will employ *Immune-related response criteria* (irRECIST, irRC) which are adapted from WHO response criteria are being employed for immunotherapy trials [52], shown below:

New, measurable lesions (i.e., ≥5 × 5 mm)	Incorporated into tumor burden
New, non measurable lesions (i.e., <5 × 5 mm)	Do not define progression (but preclude irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions, 2 consecutive observations, ≥ 4 wks apart
PR	≥50% decrease in tumor burden from baseline, 2 consecutive observations, ≥ 4 wks apart
SD	50% decrease in tumor burden from baseline cannot be established, nor 25% increase compared with nadir
PD	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Decreased tumor volume will be assessed relative to baseline, including measurable lesions >5 × 5 mm. Only index and measurable new lesions are taken into account in irRC (in contrast to conventional WHO criteria which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden).

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment the SPD of the index lesions and of new, measurable lesions (≥5 × 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden: Tumor Burden = SPD index lesions + SPD new, measurable lesions

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis

for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e. the SPD of all index lesions at screening).

Non-Target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or unequivocal progression of each should be noted throughout follow-up.

Metastatic Bone Lesions

Disease progression is considered if a minimum of 2 new lesions is observed on bone scan. New lesions seen by the end of the first response assessment (with the first re-staging bone scan) may represent disease that was not detected on the pre-study scan, and a confirmatory scan will be required at the next scheduled re-staging bone scan unless clinically not indicated. If confirmed, progression should be dated by the initial time when the lesions are first detected. If new lesions are seen after the first assessment, but no additional lesions are seen on confirmatory scans, the scans from post-first assessment would serve as the baseline scan to evaluate for disease progression.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial e.g. palpable lymph nodes.

Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as close as possible to the beginning of treatment. The same method of assessment will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferable unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Duration of Response

The duration of overall response will be measured from the time measurement criteria are met for CR, PR or SD until the first date that recurrent or progressive disease is documented.

Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Overall Survival (OS)

OS will be determined for each patient with time origin at the start of the treatment until death. Every effort will be made to follow patients for survival after they discontinue the study.

Conventional CT and PET/CT: both CT and PET/CT will be acceptable for measuring baseline and post treatment disease burden.

7.1.2.6 Correlative Studies Blood Sampling

In addition to tolerability and clinical response, immune responses to the vaccine will be determined from *in vitro* analysis of blood draws collected pre-study and during according to the study calendar. All immune correlates will be assessed in a research laboratory rather than in a CLIA-approved laboratory, since they are secondary endpoints. In order to assure reproducibility, SOPs will be followed for all assays. The Department of Experimental Therapeutics at City of Hope has extensive experience using these assays to analyze the immune response of gastric cancer patients on the first-in-human trial of p53MVA as a single agent. We are qualified to conduct the proposed research in compliance with Good Laboratory Practices (GLP) and to comply with all legal and regulatory requirements. Experimental procedures for correlative studies are detailed below:

Correlate	***Assay***	***Methodology***
p53-specific T cell response	*T cell activation assay*	peripheral blood $CD3^+$ T cells are tested for reactivity to a p53 peptide library by flow cytometric detection of the T cell activation marker CD137. This provides a marker of anti p53 reactivity post vaccination i.e. an indicator of p53MVA vaccine activity.
Immuno phenotyping	*Multi color flow cytometry*	The frequency of MDSC, Tregs and checkpoint molecules such as PD-1 and PDL-1 will be quantified using commercially available fluorescently labeled antibodies. Cells are washed and incubated with antibody in the presence of 1 % FBS for 30 mins at room temperature, in the dark. Matched isotype controls are included for each sample. In the case of Treg analysis, a permeabilization step, using the BD Cytofix/Cytoperm kit, is incorporated into the protocol to allow detection of the intracellular marker FOXP-3. Analysis will be carried out using a Gallios cytometer (Beckman Coulter).

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Urine pregnancy test †	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase (ALP)		
Platelet count	Alanine aminotransferase (ALT)		PT/PTT
WBC (total and differential)	Aspartate aminotransferase (AST)		Total thriiodothyronine (T3)
Red Blood Cell Count	Lactate dehydrogenase (LDH)		Free tyroxine (T4)
Absolute Neutrophil Count	Carbon Dioxide ‡		Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*		PK
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 14 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

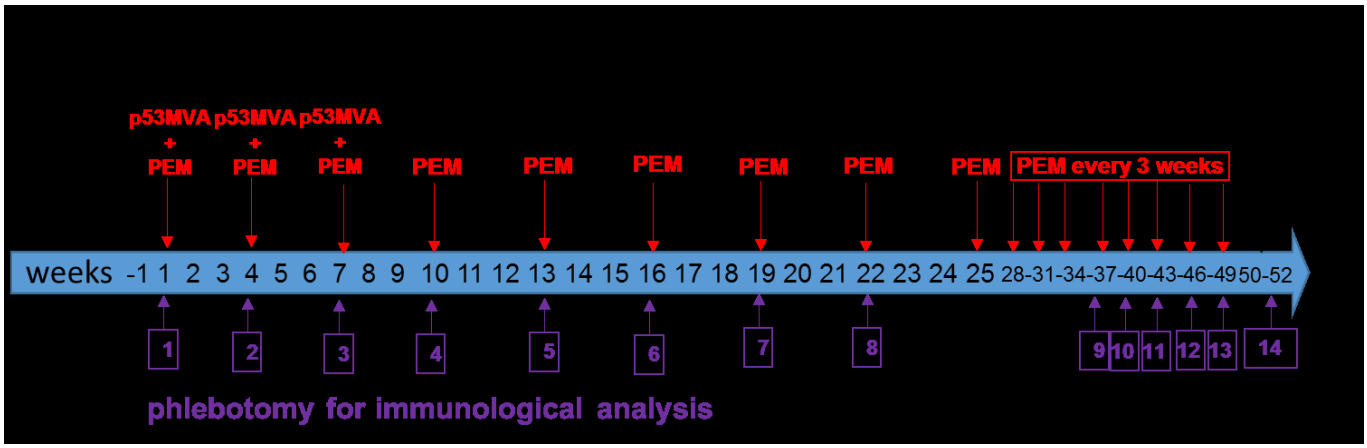
Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained. All clinical laboratory tests and blood draw volumes will be performed at a COH CLIA approved lab for both inpatients and outpatients, and as specified in the Study Flow Chart. All test results and assessments required to establish pre-eligibility of a recipient subject (related or unrelated) must be obtained prior to enrollment. The following "Eligibility Check List" is required at the screening visit:

- Signed ICF/disclosure authorization form
- Medical history
- Physical exam including vital signs, height and weight
- HIV antibody if appropriate
- Acute Hepatitis panel
- Quantiferron test for active TB infection
- Comprehensive metabolic panel (CMP) CBC with differential
- Cardiac function tests: electrocardiography, echocardiography, serum troponin (I) and BNP (B-type natriuretic peptide)
- Pregnancy test if appropriate
- Review of concomitant medications
- Assessment of inclusion/exclusion criteria
- Enrollment

*Complete metabolic panel (CMP) CLIA approved lab, including the following: glucose, BUN (blood urea nitrogen), creatinine, total protein, albumin, calcium, sodium, potassium, chloride, total carbon dioxide, total bilirubin, alkaline phosphatase, ALT (alanine transaminase) and AST (aspartate aminotransferase).

7.1.5.2 Treatment Period

Treatment will be administered on an out-patient basis. At weeks 1, 4 and 7 Pembrolizumab and p53MVA will be administered at the same study visit. Pembrolizumab will be administered first followed by p53MVA at least 30 minutes later.



Patients showing progressive disease by imaging (according to irRECIST criteria) will receive no further study agents.

Patients completing combination therapy (p53MVA+PEM on weeks 1, 4 and 7) may be treated with doses of pembrolizumab (PEM) alone every 3 weeks, up to 35 cycles. The intended function of pembrolizumab in this setting is to enhance the activity of the p53MVA vaccine to clinically beneficial levels. Pembrolizumab treatment may be extended beyond 49 weeks (17 cycles) if a second course is indicated (see Section 5.2.3).

Treatment delays due to adverse events of less than 3 weeks are allowable on this protocol.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 1-3 weeks after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Participants who are eligible for retreatment

with pembrolizumab (as described in Section 5.2.3) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

7.1.5.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (42 ± 7 days) by radiologic imaging to monitor disease status, as per standard of care. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 5.2.3. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 5.2.3 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.5.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.2 City of Hope Data and Safety Monitoring

7.2.1 Risk Determination

This is a high risk study, as defined in the City of Hope Institutional DSMP. This determination was made because the study involves a COH held IND for p53MVA and off label use of a commercially available product, Pembrolizumab. This is a combined immunotherapy study of vaccine and antibody. As p53MVA does not integrate into host DNA, this study is NOT classified as gene therapy. p53MVA has already been tested in 20 human subjects at COH (IRB#10105 and IRB#13373). Pembrolizumab is FDA approved for two indications. A study testing the combination of p53MVA and Pembrolizumab is underway at COH (IRB#15002). This will be the second study testing the two agents in combination.

7.2.2 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

7.2.3 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

7.2.4 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

7.2.5 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigator, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations, and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

7.2.6 Quality Assurance

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Monitoring (OCTM), within City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These documents specify the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring reports to the study team and the COH DSMC.

7.2.7 Adverse Events and Unanticipated Problems

The research team is responsible for classifying adverse events (AE) and unanticipated problems (UP) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

7.2.8 Assessment of Adverse Events

The PI will be responsible for determining the event name, and assessing the severity (i.e. grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0. A copy of the scale can be found at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Definite –** The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

7.2.9 Reporting of Adverse Events

AEs will be collected from the signing of informed consent until ending study participation. Routine AE reporting will occur via data entry into the study eCRF. AEs will be monitored by the Protocol Management Team (PMT). AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

7.2.10 Expedited Reporting Requirements of SAEs and UPs to the COH Regulatory Committees

Adverse events that meet the criteria of serious OR are unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. Reporting of SAEs will begin once the patient undergoes study intervention

and must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator. Follow-up SAE reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

7.2.11 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the Medwatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition, the study PI will submit annually within 60 days (via COH OIDRA) of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

7.2.12 Adherence to the Protocol & Reporting of Protocol Deviations

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the City of Hope Clinical Research Protocol Deviation policy.

7.3 Merck requirements for Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not

necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment starts, must be reported by the investigator if the participant is receiving run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

● All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment start through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment start through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

●Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the

event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

7.3.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

7.3.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breast feeding that occur after the consent form is signed but before treatment must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

Pregnancies and infant exposures during breast feeding that occur from the time of treatment start through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229).

7.3.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.3.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- causes another important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified

in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

All participants with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

7.3.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.4.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.3.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

This Phase II study is based on prior experience of the combination of p53MVA and pembrolizumab, and overlapping toxicities are not expected. However, we will monitor closely for toxicity. If there are more than 2 serious adverse events related to treatment on protocol in the first 9 subjects, the study will hold for toxicity review.

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

CTCAE V5.0 Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days.	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCTPOSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

7.3.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This is a phase II study to evaluate the efficacy and safety of pembrolizumab+p53MVA vaccine in advanced ovarian cancer who have progressed after at least one line of chemotherapy for advanced disease and are resistant to platinum therapy.

The primary endpoint in this trial will be response rate (CR+PR).

Secondary endpoints include median PFS, median OS and clinical benefit (CR+PR+SD>6 months), safety and tolerability, and biological correlates which remain exploratory in nature. Median PFS and OS will be reported in months. Clinical benefit will be calculated as the % of patients experiencing CR or PR or SD in total. Response rate, clinical benefit, PFS, and OS will also be summarized by PDL-1 expression.

8.2 Statistical Analysis Plan

Sample Size Accrual Rate

Study size is based on our therapeutic target of achieving with acceptable toxicity a considerable improvement in the response rate observed with single agent pembrolizumab in this patient population, previously reported as 8% (KEYNOTE-100). Specifically, we seek to have good power to detect an improvement in the response rate to 25%. To achieve this, Simon's MiniMax two-stage design is employed to have 85% power to detect a true promising response rate of 25%, with a type I error of 8% for declaring a true discouraging response rate of 8% as worthy of further consideration: Initially, 17 patients will be enrolled for the first stage. If 2 or more patients experience a response during the first stage, accrual will continue to 28 patients. With a total of 28 patients, at least 5 responders (18%) is the minimum to determine the combination worthy of further consideration. This design has a 60% chance of early stopping if the true response rate is 8%. Final determination of promise will be based on the totality of the clinical endpoints and consideration of the profile of patients' PDL-1 expression, where a different accrual pattern when compared to KEYNOTE-100 may require a higher or lower threshold for the final decision. Expected accrual rate is approximately one patient every one and ½ months.

Analysis of Biological Correlates

Peripheral blood samples will be collected pre- and post-immunization for assessment of anti-p53 T cell responses and immunophenotyping. Immunosuppresive cell types (MDSC, Tregs) and other selected lymphocyte subsets and markers including PD-1, PDL-1 and PDL-2 will be quantified. Secondary endpoints will be clinical responses and T cell reactivity to p53. These

secondary endpoints are exploratory in nature. We will evaluate if the $CD8^+$ T cell signal exceeds that detected in the single agent p53MVA trial. In the prior single agent study the p53-reactive $CD8^+$ T cells increased above baseline after the first immunization, but did not expand further with subsequent immunization. We hypothesize that the $CD8^+$ T cell response will be enhanced by pembrolizumab, resulting in larger or more durable increases in the $CD8^+$ T cell response. The total area under the curve (AUC) of the $CD8^+$ T cell reactivity over three injections (minus the baseline) provides a metric for this requirement. We have approximately 84% power to detect a 2.1-fold increase in AUC with a type I error of 22%. Empirically, this is associated with a cut-off of a 55% increase in AUC. These estimates use the Wilcoxon rank-sum test, and are based on residual re-sampling simulations based on historical AUC values (subtracting baseline) and a hypothesized increase in that AUC.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Pembrolizumab will be provided by Merck as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

PEMBROLIZUMAB

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

Preparation: Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial (not directly on the lyophilized powder), resulting in a concentration 25 mg/ml. Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial. Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Reconstituted pembrolizumab is a clear to slightly opalescent, colorless to slightly yellow solution. Discard reconstituted vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed. Alternatively, pembrolizumab solution provided at 100mg/4mL (25mg/mL) will be used.

Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be 1 mg/mL - 10 mg/mL and administered IV over 30 minutes, through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.

Storage of Reconstituted and Diluted Solutions: pembrolizumab contains no preservative, hence reconstituted, diluted solutions should not be stored at room temperature for more than 6 hours after preparation. This includes storage of reconstituted vials, storage of infusion solutions in the IV bag and the duration of infusion. Under refrigeration (2°C - 8°C) diluted solutions should not be stored for more than 24 hours from the time of preparation. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not freeze. Caution should be exercised in handling pembrolizumab solutions. The use of gloves and gowns is recommended. If the product comes into contact skin or mucosa, the skin should be washed thoroughly with soap and water and mucosa irrigated with copious amounts of water.

Disposal: Unused and residual drug should be put into a plastic bag and disposed of in a chemical waste container.

p53MVA Vaccine (IND#14716)
p53MVA is a Modified Vaccina Ankara Virus based vaccine expressing the full length, wild type human p53 gene. The p53MVA vaccine was evaluated in an FDA directed toxicology study in mice. p53MVA was administered doses 50 fold higher, in a mg/kg basis, than the proposed starting clinical dose. There was no obvious toxicity seen in the animals in terms of weight, physical appearance, activity level, chemical or hematologic parameters. Histologic evaluation of organs at necropsy revealed no evidence of toxicity. p53MVA was cleared from the skin injection site within 60 days of administration and from all other tissues including blood within 2 weeks of administration. In the first in human study conducted at COH, the

p53MVA vaccine was been well-tolerated at doses of 1 x10^8 pfu and 5.6 x10^8 pfu with only low grade toxicity being reported.

p53MVA has been manufactured using GMP-grade materials at The Center for Biomedicine and Genetics (CBG) at City of Hope. The final product is diluted in PBS with 7.5% lactose and vialed at 1.2ml per vial. The concentration is 4.5 x 10^8 pfu/ml. The vaccine is expected to remain stable at room temperature for a minimum of 4 hours, as determined in recently completed stability study stipulated by the FDA. Patients will receive injections of 1.1ml for dose level 1. In the event of de-escalation to dose level -1, patients will receive an injection volume of 0.5ml, giving a dose of 2.2 x 10^8 pfu.

Preparation: p53MVA will be stored in a -80 C freezer with restricted access. Variations in temperature between -60 C to -90 C will be acceptable and will maintain MVA virus stability. Vaccine preparations will be dispensed by the City of Hope Investigational Drug Service (IDS). Vials will be thawed at room temperature. Administration of the vaccine must occur within 4 hours after vial is removed from freezer. The vial will be vortexed for 60 seconds at the highest setting followed by visual inspection for clumps. If clumps are observed, a further vortex of 60 seconds will be performed. The time at which vortexing is completed will be recorded in the log and the vaccine dispensed, even if clumping is still visible. One dose of vaccine preparation will be drawn into a 3ml sterile syringe (dose level 1) or 1ml sterile syringe (dose level -1), approximately 1.1ml of solution, dose volume not to exceed 1.1ml. After labeling appropriately, the syringe will be placed in a sealable plastic bag and placed on ice for transport to the clinic for administration. The research nurse will attach a needle to the syringe containing the vaccine and the dose of p53MVA will be administered by a single injection into subcutaneous tissue of the upper arm (over deltoid muscle). There is no available data on potential drug interactions of p53MVA in humans.

Caution should be exercised in handling and preparing p53MVA vaccine solution. The use of gloves and gowns is recommended. If vaccine comes into contact with skin or mucosa, skin should be washed thoroughly with soap and water and mucosa irrigated with copious amounts of water. Unused and residual p53MVA should be put into a plastic biohazard bag and disposed of in a biological waste container.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product from Merck will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

All unused (unopened) vials of p53MVA vaccine will be stored at COH IDS, or returned to the CBG, as per the PI direction.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

10.2 Recruitment of Subjects

Individuals who satisfy the inclusion criteria will be identified through the individual practitioners in the Departments of General & Oncologic Surgery and Medical Oncology and Therapeutics Research at COH. Written informed consent will be obtained from the participant.

10.3 Advertisements

A lay summary to be posted on City of Hope's public Clinical Trials On-Line^{SM} website and Clinicaltrials.gov will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

10.4 Study location and Performance Sites

This study will be performed at the City of Hope National Medical Center. All study interventions will be performed at this site by a study nurse under the direction of Dr. Thanh Dellinger or her designee at the Clinical Research Unit (Phase I unit) at COH. The laboratory analysis will take place in the Department of Experimental Therapeutics, Fox South, Room 1002 under the direction of Dr. Don Diamond.

10.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). The study will record individual immunological response to the vaccine and any side effects, and this will be linked to the subject's identity using a coded study number. The principal investigator, co-investigators, and laboratory technicians will have access to this information, but all information will be treated confidentially. No identifiers will be used in any subsequent publication of these results. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA or NIH.

10.6 Financial Obligations and Compensation

The investigational agents, p53MVA and pembrolizumab, will be provided free of charge by COH according to the protocol.

Standard of care drugs and procedures will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study. However, neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope to the injured research participant, however financial compensation will not be available. The research participant will not be paid for taking part in this study.

10.7 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Research subjects will be afforded sufficient time to consider whether or not to participate in the research.

Before signing the study consent form, HIPAA authorization form and the Experimental Subject's Bill of Rights, research subjects will undergo an assessment of their comprehension of the study by the Research Subject Advocate. Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. For those subjects who do comprehend the fundamental aspects of the study, consent will be obtained and documented, followed by eligibility testing. The research team will review the results of eligibility testing and determine if the subject is a candidate for study enrollment.

11.0 REFERENCES

1. Disis, M.L., *Immune regulation of cancer.* J Clin Oncol, 2010. **28**(29): p. 4531-8.
2. Dudley, M.E., et al., *Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma.* J Clin Oncol, 2005. **23**(10): p. 2346-57.
3. Hunder, N.N., et al., *Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1.* N Engl J Med, 2008. **358**(25): p. 2698-703.
4. Greenwald, R.J., G.J. Freeman, and A.H. Sharpe, *The B7 family revisited.* Annu Rev Immunol, 2005. **23**: p. 515-48.
5. Okazaki, T., et al., *PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine.* Proc Natl Acad Sci U S A, 2001. **98**(24): p. 13866-71.
6. Zhang, X., et al., *Structural and functional analysis of the costimulatory receptor programmed death-1.* Immunity, 2004. **20**(3): p. 337-47.
7. Chemnitz, J.M., et al., *SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation.* J Immunol, 2004. **173**(2): p. 945-54.
8. Sheppard, K.A., et al., *PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta.* FEBS Lett, 2004. **574**(1-3): p. 37-41.
9. Riley, J.L., *PD-1 signaling in primary T cells.* Immunol Rev, 2009. **229**(1): p. 114-25.
10. Parry, R.V., et al., *CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms.* Mol Cell Biol, 2005. **25**(21): p. 9543-53.
11. Francisco, L.M., P.T. Sage, and A.H. Sharpe, *The PD-1 pathway in tolerance and autoimmunity.* Immunol Rev, 2010. **236**: p. 219-42.
12. Hainaut, P. and M. Hollstein, *p53 and human cancer: the first ten thousand mutations.* Adv Cancer Res, 2000. **77**: p. 81-137.
13. Benson, D.M., Jr., et al., *The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody.* Blood, 2010. **116**(13): p. 2286-94.
14. Lambeck, A., et al., *P53-specific T cell responses in patients with malignant and benign ovarian tumors: implications for p53 based immunotherapy.* Int J Cancer, 2007. **121**(3): p. 606-14.
15. Nikitina, E.Y., et al., *Dendritic cells transduced with full-length wild-type p53 generate antitumor cytotoxic T lymphocytes from peripheral blood of cancer patients.* Clin Cancer Res, 2001. **7**(1): p. 127-35.
16. Ropke, M., et al., *Spontaneous human squamous cell carcinomas are killed by a human cytotoxic T lymphocyte clone recognizing a wild-type p53-derived peptide.* Proc Natl Acad Sci U S A, 1996. **93**(25): p. 14704-7.
17. Chikamatsu, K., et al., *Generation of anti-p53 cytotoxic T lymphocytes from human peripheral blood using autologous dendritic cells.* Clin Cancer Res, 1999. **5**(6): p. 1281-8.
18. van der Burg, S.H., et al., *Induction of p53-specific immune responses in colorectal cancer patients receiving a recombinant ALVAC-p53 candidate vaccine.* Clin Cancer Res, 2002. **8**(5): p. 1019-27.

19. Antonia, S.J., et al., *Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer.* Clin Cancer Res, 2006. **12**(3 Pt 1): p. 878-87.
20. Leffers, N., et al., *Immunization with a P53 synthetic long peptide vaccine induces P53-specific immune responses in ovarian cancer patients, a phase II trial.* Int J Cancer, 2009. **125**(9): p. 2104-13.
21. Vermeij, R., et al., *Potentiation of a p53-SLP vaccine by cyclophosphamide in ovarian cancer: A single-arm phase II study.* Int J Cancer, 2011.
22. Dijkgraaf, E.M., et al., *A phase 1/2 study combining gemcitabine, Pegintron and p53 SLP vaccine in patients with platinum-resistant ovarian cancer.* Oncotarget, 2015. **6**(31): p. 32228-43.
23. Hardwick N R, M.C., Teodora Kaltcheva, Dajun Qian, Dean Lim, Lucille Leong, Peiguo Chu, Joseph Kim, Joseph Chao, Marwan Fakih, Yun Yen, Jonathan Espenschied, Joshua D I Ellenhorn, Don J Diamond, Vincent Chung, *p53MVA therapy in patients with refractory gastrointestinal malignancies elevates p53-specfic CD8+ T cell responses.* Clin Cancer Res, 2014.
24. Antoine, G., et al., *The complete genomic sequence of the modified vaccinia Ankara strain: comparison with other orthopoxviruses.* Virology, 1998. **244**(2): p. 365-96.
25. Meyer, R.G., et al., *A phase I vaccination study with tyrosinase in patients with stage II melanoma using recombinant modified vaccinia virus Ankara (MVA-hTyr).* Cancer Immunol Immunother, 2005. **54**(5): p. 453-67.
26. Harrop, R., et al., *Vaccination of colorectal cancer patients with modified vaccinia ankara encoding the tumor antigen 5T4 (TroVax) given alongside chemotherapy induces potent immune responses.* Clin Cancer Res, 2007. **13**(15 Pt 1): p. 4487-94.
27. Disis, M.L., et al., *Efficacy and Safety of Avelumab for Patients With Recurrent or Refractory Ovarian Cancer: Phase 1b Results From the JAVELIN Solid Tumor Trial.* JAMA Oncol, 2019.
28. Hamanishi, J., et al., *Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer.* J Clin Oncol, 2015. **33**(34): p. 4015-22.
29. Varga, A., et al., *Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analysis of KEYNOTE-028.* Gynecol Oncol, 2019. **152**(2): p. 243-250.
30. Matulonis, U.A., et al., *Antitumor Activity and Safety of Pembrolizumab in Patients with Advanced Recurrent Ovarian Cancer: Results from the Phase 2 KEYNOTE-100 Study.* Ann Oncol, 2019.
31. Espenschied, J., et al., *CTLA-4 blockade enhances the therapeutic effect of an attenuated poxvirus vaccine targeting p53 in an established murine tumor model.* J Immunol, 2003. **170**(6): p. 3401-7.
32. Daftarian, P., et al., *Two distinct pathways of immuno-modulation improve potency of p53 immunization in rejecting established tumors.* Cancer Res, 2004. **64**(15): p. 5407-14.
33. Song, G.Y., et al., *An MVA vaccine overcomes tolerance to human p53 in mice and humans.* Cancer Immunol Immunother, 2007. **56**(8): p. 1193-205.

34. Pilon-Thomas, S., et al., *Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma.* J Immunol, 2010. **184**(7): p. 3442-9.
35. Song, M.Y., et al., *Enhancement of vaccine-induced primary and memory CD8(+) T-cell responses by soluble PD-1.* J Immunother, 2011. **34**(3): p. 297-306.
36. Karyampudi, L., et al., *Accumulation of memory precursor CD8 T cells in regressing tumors following combination therapy with vaccine and anti-PD-1 antibody.* Cancer Res, 2014. **74**(11): p. 2974-85.
37. Soares, K.C., et al., *PD-1/PD-L1 blockade together with vaccine therapy facilitates effector T-cell infiltration into pancreatic tumors.* J Immunother, 2015. **38**(1): p. 1-11.
38. D'Alincourt Salazar, M., et al., *Evaluation of innate and adaptive immunity contributing to the antitumor effects of PD1 blockade in an orthotopic murine model of pancreatic cancer.* Oncoimmunology, 2016. **5**(6): p. e1160184.
39. Wei, F., et al., *Strength of PD-1 signaling differentially affects T-cell effector functions.* Proc Natl Acad Sci U S A, 2013. **110**(27): p. E2480-9.
40. Hardwick, N.R., et al., *p53MVA therapy in patients with refractory gastrointestinal malignancies elevates p53-specific CD8+ T-cell responses.* Clin Cancer Res, 2014. **20**(17): p. 4459-70.
41. Gibney, G.T., et al., *Safety, correlative markers, and clinical results of adjuvant nivolumab in combination with vaccine in resected high-risk metastatic melanoma.* Clin Cancer Res, 2015. **21**(4): p. 712-20.
42. Obermajer, N., et al., *Positive feedback between PGE2 and COX2 redirects the differentiation of human dendritic cells toward stable myeloid-derived suppressor cells.* Blood, 2011. **118**(20): p. 5498-505.
43. Obermajer, N., et al., *PGE(2)-induced CXCL12 production and CXCR4 expression controls the accumulation of human MDSCs in ovarian cancer environment.* Cancer Res, 2011. **71**(24): p. 7463-70.
44. Fialova, A., et al., *Dynamics of T-cell infiltration during the course of ovarian cancer: the gradual shift from a Th17 effector cell response to a predominant infiltration by regulatory T-cells.* Int J Cancer, 2013. **132**(5): p. 1070-9.
45. Govindaraj, C., et al., *Impaired Th1 immunity in ovarian cancer patients is mediated by TNFR2+ Tregs within the tumor microenvironment.* Clin Immunol, 2013. **149**(1): p. 97-110.
46. Preston, C.C., et al., *The ratios of CD8+ T cells to CD4+CD25+ FOXP3+ and FOXP3- T cells correlate with poor clinical outcome in human serous ovarian cancer.* PLoS One, 2013. **8**(11): p. e80063.
47. Hamanishi, J., et al., *Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer.* Proc Natl Acad Sci U S A, 2007. **104**(9): p. 3360-5.
48. Brahmer, J.R., et al., *Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.* N Engl J Med, 2012. **366**(26): p. 2455-65.
49. Disis, M.L., *Avelumab in patients with recurrent/refractory ovarian cancer from the JAVELIN solid tumor phase 1b trial.* J of Clin Oncology 2016. **34**(Abst 5533).
50. Wenham, R.M., *Phase 2 trial of dose dense (Weekly) Paclitaxel with pembrolizumab (MK-3475) in platinum resistant recurrent ovarian cancer.* J of Clin Oncology, 2016. **ASCO Abstracts 2016**(#TPS5612).

51. Varga, A., *Antitumor activity and safety of pembrolizumab in patients with PD-L1 positive advanced ovarian cancer: interim results from a phase 1b study.* Journal of Clinical Oncology, 2015. **33 suppl**(#5510).
52. Wolchok, J.D., et al., *Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria.* Clin Cancer Res, 2009. **15**(23): p. 7412-20.

12.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
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.
* As published in Am. J. Clin. Oncol.:*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J ClinOncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Appendix 2: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 9 during the treatment phase and for 30 days after cessation of therapy.

Table 9 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen-only contraceptive implant [a] ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test. Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.