TITLE: Induction of Senescence using Dexamethasone to Re-sensitize NSCLC to Anti-PD1 Therapy.

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SUMMARY Of CHANGES

Section	**Description of Change**
Title Page	• Version was updated • Date of version was updated • List of amendments was updated and reformatted with dates
Section 5.1 Inclusion Criteria	• Changed hemoglobin eligibility criteria from 9 to 8.0 g/dL • Changed coagulation screening requirements to only required if clinically indicated or on anticoagulants
Section 5.2 Exclusion Criteria	• Changed exclusion criteria #5 for history of non-infectious pneumonitis to history of non-infectious pneumonitis within the past 12 months
Section 7.2 Treatment Calendars	• Added coagulation screening requirements to Cohort 1, 2, and 3 Schedules of Events to accurately reflect screening activities • Added footnote to Cohort 1, 2, and 3 Schedules of Events to reflect changed coagulation screening requirements to only required if clinically indicated or on anticoagulants

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ALK	Anaplastic Lymphoma Kinase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEX	Dexamethasone
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
ECI	Events of Clinical Interest
EGFR	Epidermal Growth Factor Receptor
ERC	Ethics Review Committee
GCP	Good Clinical Practice
H&P	History & Physical Exam
IHC	Immunohistochemistry
IRB	Institutional Review Board
irRECIST	Immune Response RECIST
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression Free Survival
PI	Principal Investigator
PO	per os/by mouth/orally
PR	Partial Response

RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious Adverse Event
SD	Stable Disease
TEAE	Treatment-emergent Adverse Event
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cells

1.0 TRIAL SUMMARY

Abbreviated Title	**Induction of Senescence using Dexamethasone to Re-sensitize NSCLC to Anti-PD1 Therapy**
Trial Phase	II
Trial Type	Interventional
Study Centers	VA Ann Arbor Healthcare System
Hypothesis	Pre-treatment of NSCLC with dexamethasone followed by pembrolizumab will result in induction of senescence with production of SASP and immune activation markers. Senescence will result in improved response to pembrolizumab.
Objectives	Primary: - To determine whether dexamethasone induces senescence in >60% of patients with stage IV NSCLC who have progressed after initial immunotherapy Secondary: - In patients whose NSCLC has progressed on first line immunotherapy, determine the pre-treatment Dexamethasone duration needed to induce ORR to pembrolizumab of >33% - Determine ORR to pembrolizumab assessed by FDG PET - Determine the relationship between sensitivity to Dexamethasone and ORR using pre- and post-FLT PET and FDG PET scans respectively. - To evaluate response based on immune-related RECIST (ir-RECIST) criteria and compare to response rate as evaluated by RECIST v1.1. Exploratory: - Determine SASP and activation of T and NK cells, measured in peripheral blood. - Functional characterization, including activation markers and intracellular cytokine profile, of immune cell subsets will be evaluated by multi-parametric flow cytometry.
Type of control	Historical controls of patients treated with docetaxel treatment whose FLTPET response was 30% and overall response rate was $\leq$7%.
Study drugs: dose and administration	Dexamethasone cohorts, PO, 4mg BID given for 7 or 10 or 13 days (followed by taper over 2-4 days and 3 day wash out) prior to first dose of pembrolizumab, followed by DEX 4mg BID for 7 or 10 or 13 days (followed by taper over 2-4 days and 3 day wash out) days prior to subsequent pembrolizumab x 3 cycles. Cohort 1 & 2: Pembrolizumab, IV, 200mg on day 1 of a 21-day cycle Cohort 3: Pembrolizumab, IV, 200mg on day 1 of a 28-day
Duration of administration	12 weeks
Inclusion Criteria	• Stage IIIA/B following CRT and durvalumab or Stage IV NSCLC whose tumors do not have a mutation in epidermal sensitizing growth factor (EGFR) or BRAF or rearrangements in ALK (anaplastic lymphoma kinase) or ROS-1and have progressed on therapy with PD1 inhibitor

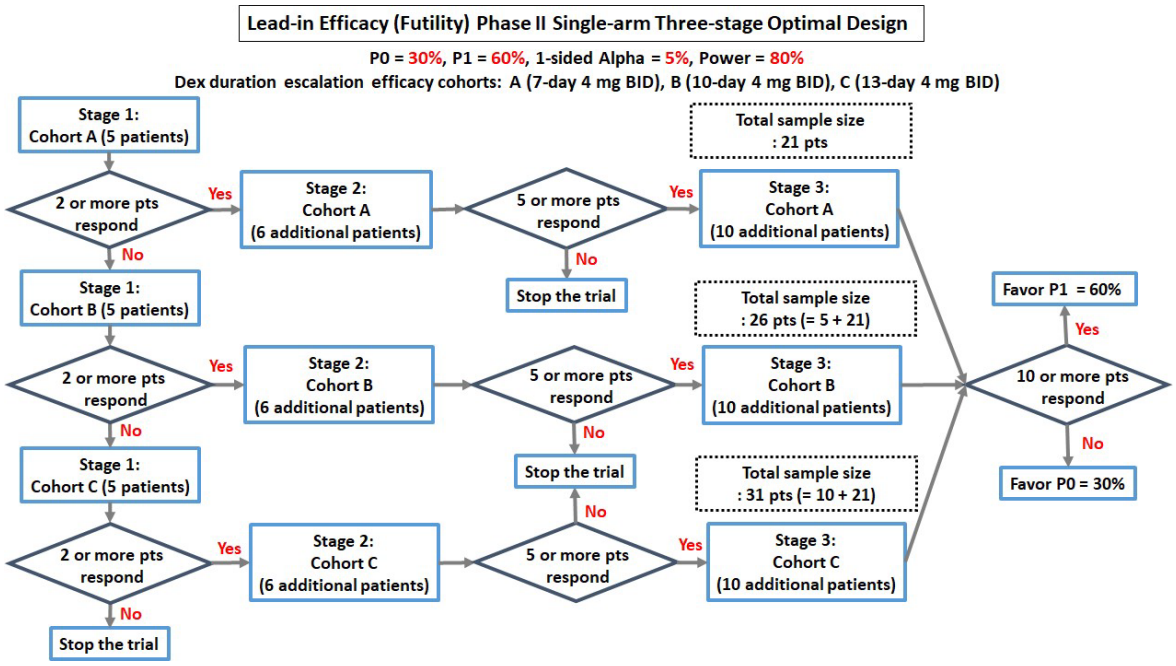
	• Presence of measurable disease according to RECIST v1.1 • ECOG performance status 0-2No significant weight loss; >30% in 90-days • Adequate organ function defined as AST and ALT ≤ 2.5 × ULN, bilirubin ≤ 1.5 × ULN, and creatinine clearance ≥ 40 ml/min • Adequate hematologic parameters • Life expectancy of at least 6 months • Sufficient tissue sample of adequate quality for correlative studies
Exclusion Criteria	• Presence of significant comorbidities precluding participation in a clinical study as determined by investigator • Has active autoimmune disease that has required systemic treatment in the past 2 years • Baseline corticosteroid use at study entry • ECOG performance status 3-4 • Pregnancy or lactation
Number of trial subjects	21 to 39 patients
Statistical design	Simon's optimal design with lead in cohorts.
Estimated duration of trial	2 years from 1st patient in, to last patient out
Estimated average length of treatment per patient	3 months

2.0 TRIAL DESIGN

2.1 Trial Design

This study is a small Phase II clinical trial designed as a single-arm two-stage study with Dexamethasone dose escalation cohorts (4mg BID on days 1-7, 1-10 or 1-13). The trial will include FLT-PET and FDG-PET imaging to measure tumor senescence to Dexamethasone and treatment response respectively, and also blood analysis for SASP and markers of immune activation. This study is to assess whether senescence induced by oral dexamethasone resensitizes NSCLC patients to intravenous pembrolizumab.

We will use a single arm phase II two-stage design with 3 Dex cohorts (4 mg bid, on Days 1-7. 1-10 and 1-14) to achieve 80% power at a 1-sided alpha 10% level. Each cohort will consist of 5 patients. On the basis of Simon's optimal design, the first cohort will be accrued in the first stage. If there are 3 or more "responses" occur among this cohort, 7 additional patients will be accrued and treated with the same Dex dose for a total of 12 patients; if 7 or more respond at this dose level, we will add 9 more patients for a total of 21 patients (with 20% drop out, n = 31). If no response is noted on FLTPET, 2nd cohort will open up with a 10 day fixed dose Dex and so on as depicted in Schema.



The secondary objective is to establish that the true ORR of Dex followed by pembrolizumab will be at least 33% (p1 = 0.33) vs. docetaxel treatment (as the historical control) whose ORR is $\leq$ 7% (p0 = 0.07). The ORR will be assessed at a 12 week FDG PET scan. The required sample size for both lead-in FLTPET response and phase 2 studies will range 21 to 31 patients. As secondary objectives, we will explore associations of the change in FLT-PET with ORR assessed by FDG-PET, level of plasma SASP, and immune cell activation. The change in FLT-PET will be compared by ORR using an unpaired t-test and the associations with the level of plasma SASP and immune cell activation will be examined by a correlation analysis. The power is not formally justified because these are exploratory.

The patients will be assessed starting with a standard of care FDG-PET within 28-days of 1st dose of dexamethasone along with FLT-PET at baseline (Day 0) and after the last dose of dexamethasone. Response will be assessed through FDG-PET at 12 weeks and with CT imaging every 3 months thereafter (standard of care) until progression. Blood samples for T/NK cell counts, SASP including cytokines and chemokines, and immune cell subsets will be collected. The study will use Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) for disease evaluation. Adverse event (AE) monitoring will occur prior to each cycle (21 days) and events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Patients will continue on trial until confirmed progression as defined by RECIST v1.1, develops unacceptable toxicity or intercurrent illness that prevents further administration of treatment, withdrawal from study, removal by the investigator, becomes pregnant, demonstrates noncompliance with trial requirements, or has received 24 months of treatment with pembrolizumab. Patients may continue on treatment despite RECIST v1.1-defined progression if the subject is felt to be continuing to derive clinical benefit as determined by the investigator. Additional information including the irRC

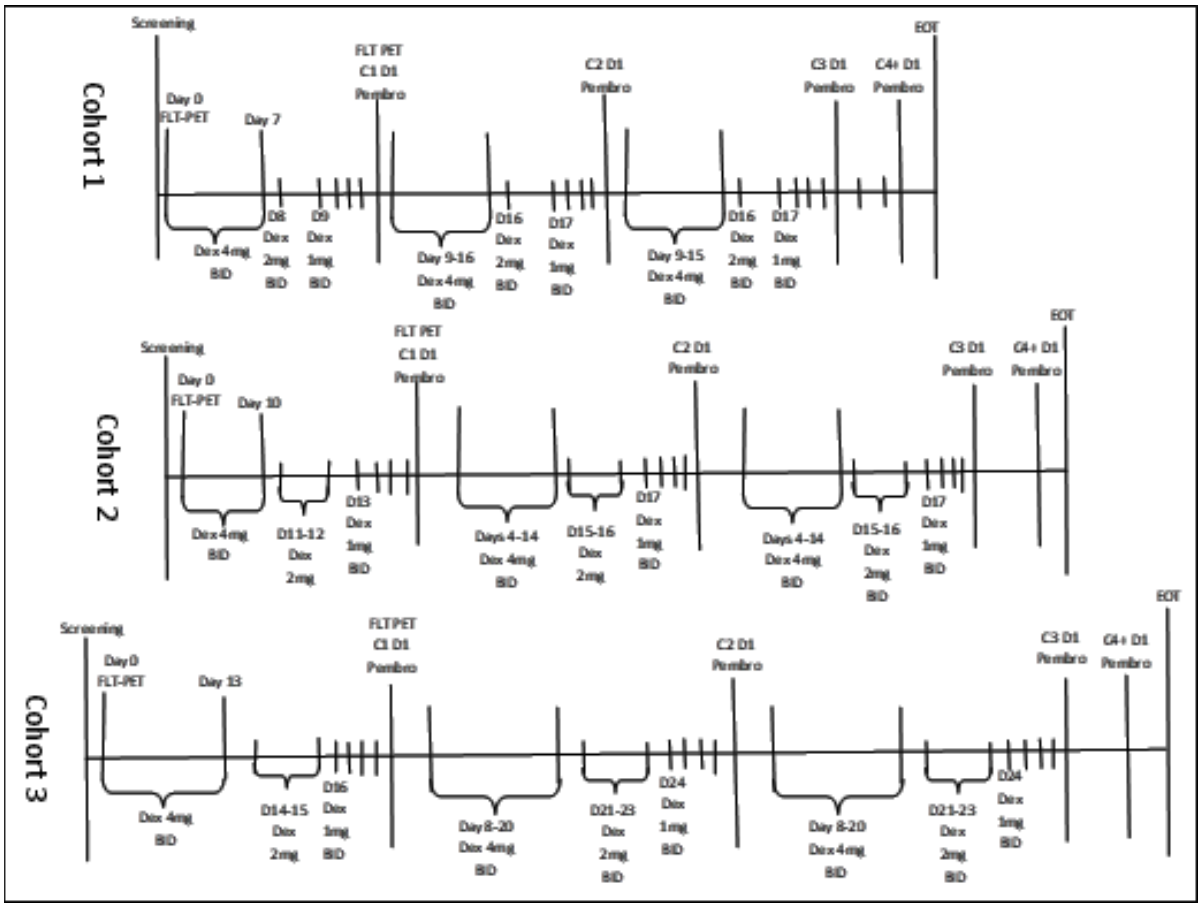
(immune-related response criteria) may be used by the investigator in deciding continuing treatment beyond RECIST v1.1-defined progression.

At the end of treatment, all patients will continue to be followed for a minimum of 30 days for AE monitoring. Subjects will have post-treatment follow-up for disease status, including initiation of non-study cancer therapy until death, withdrawal of consent, or becoming lost to follow-up.

2.2 Trial Diagram

The trial design is depicted below in **Figure 1**.

Figure 1: Trial Design



3.0 OBJECTIVES

3.1 Primary Objective & Hypothesis

(1) **Objective:** To determine the extent of senescence (as measured by change in FLT-Pet of single target lesion) induced by Dexamethasone administered for 7 or 10 or 13 days

- **Hypothesis:** The use of Dexamethasone in NSCLC patients who have progressed after first line immune/chemoimmunotherapy will result in senescence induction in 60% of patients, along with production of senescence associated secretory proteins (SASP) and immune activation.

3.2 Secondary Objectives

(1) **Objective**: Determine the pre-treatment dexamethasone dose and duration needed to induce ORR to pembrolizumab of ≥33% in patients whose NSCLC has progressed on 1st line immunotherapy.

(2) **Objective:** Determine ORR to Pembrolizumab assessed by FDG-PET

(3) **Objective:** Determine the relationship between sensitivity to dexamethasone using pre- and post- FLT PET scans and ORR (by FDG PET).

(4) **Objective:** Determine the relationship between sensitivity to dexamethasone using pre- and post- FLT PET scans and GR expression by IHC.

(5) **Objective:** Evaluate response based on immune-related RECIST (ir-RECIST) criteria and compare to response rate as evaluated by RECIST v1.

3.3 Exploratory Objectives

(1) **Objective:** To induce SASP and activation of T and NK cells, measured in peripheral blood.

(2) **Objective:** Functional characterization, including activation markers and intracellular cytokine profile, of immune cell subsets will be evaluated by multi-parametric flow cytometry.

4.0 BACKGROUND & RATIONALE

4.1 Background

<u>Disease Under Treatment</u>

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-associated mortality worldwide. The prognosis for stage IV NSCLC remains dismal, with a 5-year survival rate of 1-2%. (*1*) In addition to standard first-line platinum-based chemotherapy, other therapeutic options include tyrosine kinase inhibitors for patients with eligible mutations in the EGFR, ALK, or ROS-1 genes, and immune checkpoint inhibitors (ICIs). Currently, both PD-1 (programmed cell death protein 1) and PD-L1 inhibitors are approved for the treatment of advanced NSCLC, irrespective of histology. Multiple phase II/III trials have demonstrated their superiority in terms of response rate and overall survival compared to docetaxel chemotherapy(*2-4*)However, response to these ICIs are about 20% (*5*)with few patients achieving long term durable clinical benefit (16% at 5years) (*6*) . There is an urgent need to identify approaches to prolong durable clinical benefit and thereby further improve long term survival

Study Drugs

Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. It is approved in the United States for the treatment of stage IV NSCLC with PD-L1 ≥50% in the front-line setting or for metastatic disease with PD-L1 ≥1% after progression on platinum-based chemotherapy (*7*). It also recently received accelerated approval by the FDA to be used in conjunction with carboplatin and pemetrexed as upfront therapy followed pembrolizumab +/- pemetrexed maintenance irrespective of PD-L1 expression in non-squamous etiologies (*8*)

Dexamethasone:

Dexamethasone (Dex) is a synthetic glucocorticoid that acts by binding to the glucocorticoid receptor. The effects of dexamethasone are pleiotropic and context dependent. In Lewis lung cancer models, Dex exhibited effective tumor growth inhibition, which was associated with down-regulation of JAK3/STAT, hypoxia inducible factor 1α, vascular endothelial growth factor and IL-6 (*9*)However, long term Dex can also lead to suppression of the immune system, hyperglycemia, psychosis, avascular necrosis, and osteoporosis. We have shown that in the context of lung cancer, a 7-14 day course of Dex treatment leads to senescence with upregulation of p27 (*10*). These effects were most pronounced in lung cancer cells with moderate to high expression of glucocorticoid receptor (GR). Dex induced senescence in turn led to immune cell infiltration including T and NK cells (unpublished data). In the current proposal, we plan to harness this context dependent property of Dex in lung cancer and determine whether senesce will lead to re-sensitization to checkpoint inhibitors.

4.1.1 Limitations of ICI and efforts to improve outcome: As discussed previously, a large proportion of patients do not respond because of primary or acquired resistance (*7, 11, 12*). Accumulating evidence suggests that tumor resistance to ICIs has been attributed to a lack of antigenic stimulation of T cells as well as inadequate infiltration of effector lymphocytes in the tumor (*13*). Cancer cell intrinsic phenomena such as dynamic genomic alterations and

senescence shape the immune microenvironment (*14*). Hence treatments that induce global phenotypic changes in the tumor cells may enhance effector immune cell infiltration and sensitize the tumors to ICI. There are several clinical trials that are attempting to target the tumor to make them more immunogenic. As an example, we and others have proposed the use of hypofractionated radiation to sensitize tumors to ICI (ClinicalTrials.gov Identifier: NCT03035890, NCT03035890). Others are attempting to sensitize cancers to ICI using epigenetic modifiers, oncolytic viruses or by altering the microbiome (*15*) To date, these have led to modest or incremental advances in the field. Therefore, there remains a pressing need to establish new mechanism-based strategies to sensitize or re-sensitize lung adenocarcinoma (AC) to ICIs. This proposal applies a new mechanistic rationale, developed from pre-clinical and clinical data, to sensitize tumors to immunotherapy by first inducing tumor senescence. We will utilize a recently discovered stress response pathway mediated by the glucocorticoid receptor (GR) that is specific to lung AC and induces senescence through a non-canonical mechanism.

4.1.2 Preclinical and Clinical Trial Data

Tumor resistance to PD1/PDL1 inhibitors has been attributed to a lack of antigenic stimulation of T cells and inadequate infiltration of effector lymphocytes in the tumor (*14*). Cancer cell intrinsic phenomena such as genomic alterations and senescence shape the immune microenvironment (*16*). Hence treatments that induce global phenotypic changes in the tumor cells may enhance effector immune cell infiltration and sensitize the tumors to immune checkpoint inhibition. Depending on the tumor cell context, when malignant cells become senescent, the tumors can evoke an anti-tumor immune response primarily mediated by infiltration of monocytes, T-cells and NK cells in response to senescence associated secretory proteins (SASP) produced by the tumor (*13, 17, 18*). Indeed, attempts have been made to find small molecules that induce senescence in various cancer cells using short-term high throughput screening assays (*19, 20*). We have arrived at a rational approach to inducing senescence in lung AC cells based on previous published observations. We have reported that treatment with dexamethasone (Dex), which is used to alleviate side effects of pemetrexed chemotherapy, causes glucocorticoid receptor (GR) status-dependent reversible G1 arrest, attenuating the cytotoxicity of pemetrexed (*21*). The effect of Dex was also evident from FLT-PET imaging of 4 patients that demonstrated that within 24h of treatment with Dex (4 mg b.i.d.), 3/4 patients showed S-phase suppression in all or some of their tumor lesions (*22*). As steady state G1 arrest cannot be maintained indefinitely, we examined the effect of extended exposure to Dex (*10*). We discovered that in various lung AC cell lines and recombinant isogenic cell models with moderate to high GR that was within the clinical spectrum of tumor GR expression, treatment with Dex led to a senescence phenotype within 7 days as well as progressive irreversible cell cycle blockade. These effects of exposure to Dex were due to a gradual accumulation of P27 through transcriptional activation by Dex. This direct effect of Dex on the tumor cells could explain recent findings from a large retrospective study that perioperative treatment of patients with lung adenocarcinoma, but not ovarian or colon cancer, increased survival, leading to a current open trial to confirm this effect (NCT03172988).

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Further studies (unpublished) showed that following withdrawal of Dex, secretory factors from the senescent cells 1. very strongly attracted T-cells and NK cells, the two immune cell types that have been principally implicated in anti-tumor response during PD1-targeted immunotherapy, 2. induced expansion and activation of NK cells, 3. modestly reduced MHC class I in some tumor cells, but made the cells vulnerable to NK cell cytolysis via induction of NKG2D ligand MIC-A/B, 4. enhanced the expression of PD1 in both T cells and NK cells and 5. did not increase PDL1 expression in tumor cells. These findings set the stage for "jump starting" a renewed response to PD1 inhibitors in patients whose lung ACs have progressed on initial PD1 inhibitor therapy by pre-treating tumors with Dex. Based on our FLT-PET studies and lung AC GR expression and distribution, we expect 33-50% of patients to respond to this approach using Dex.

A natural concern related to the use of Dex to sensitize tumors to immunotherapy is the known effect of Dex in suppressing lymphocytes, although the current standard of care front line combination pembrolizumab + chemotherapy treatment for lung AC does include Dex administered at doses of 4 mg b.i.d. for 3 days spanning chemo-immunotherapy. This question is easily addressed, based on literature data and the treatment design. First, the moderate dose range of Dex used (4 mg b.i.d.) in this study may be expected to cause only a modest decrease in lymphocyte counts (*23*). Second, the effect of glucocorticoids on lymphocyte count is rapidly reversible (*24*) whereas Dex will be withdrawn for 3 days following induction of the senescence phenotype in the tumor cells, prior to immunotherapy. Finally, the preliminary data strongly support an immune sensitizing role for SASP from Dex treated lung AC cells.

Veteran Population: Lung cancer is a devastating disease that affects American War Veterans disproportionately and is the most common cause of cancer related death (*25*). Specifically, Veterans diagnosed with lung adenocarcinoma (AC) are more likely to present with advanced, metastatic disease that is associated with a median survival of 8.2 months. Compared to the general population, fewer Veterans present a driver mutant lung AC genotype that can be treated with targeted therapies. In this group of patients, immunotherapy has emerged as a promising therapeutic strategy that aims to harness the immune system to fight cancer. One such approach involves immune checkpoint inhibitors (ICI), specifically targeting the programmed death receptor or ligand (PD1/PDL1). However, response rates to ICI are modest (15-20%) with a modest prolongation of median survival to 13-15 months (*26*). The vast majority of Veterans (80%) either fail to respond (primary resistance) to initial ICI based therapy or progress (acquired resistance) after initial response. Following initial chemo-immunotherapy or immunotherapy, the cancer progresses and second line salvage chemotherapy options such as docetaxel have very poor response rates of ~ 7%. As such, survival is often less than 6 months in these patients. There is an unmet, urgent need for effective therapies in this group.

4.2.2 Rationale for Dose Selection/Regimen

<u>Pembrolizumab</u>

An open-label Phase I trial (KEYNOTE-001) has been conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (*27*). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provided the scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab as shown in the melanoma indication. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab (*28*)showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

Dexamethasone
Rationale for dose and duration:

Based on our preclinical data, the concentration of DEX required to cause senescence in lung cancer cells was about 100nM (*10*). This concentration can be achieved using the dose of DEX at 4mg BID for 7-13 days. The effects on senescence by DEX was also directly proportional to the intensity of GR expression Given intratumor heterogeneity and the problems of using archival tissue to test this biomarker, we are not pre-selecting patients in this initial study. Instead, we will vary the duration of pre-treatment DEX to 7, 10 or 13 days for the run in part of the study, prior to initial dose of pembrolizumab.

There has been no phase I data that has specifically evaluated pre-treatment with dexamethasone prior to pembrolizumab. There is however data that suggest that the 2 should not be administered concurrently (*29*). We are therefore proposing a wash out period of at least 3 days (t ½ 36-54h) before administration of pembrolizumab. There are not any serious adverse events that appear to overlap between the two agents based on review of published phase I/II/III and data.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary endpoint of this study is a biomarker endpoint. There is a need to probe for mechanism given the degree of heterogeneity in humans at the molecular level and then see if there is any relationship between a clinical outcome and putative mechanism. We therefore chose induction of senescence as the primary endpoint. Based on our preliminary data, at least 50% of pts had a >30% change in FLT-PET in their target lesion post DEX. We will therefore use this as our primary endpoint.

Secondary endpoints will include ORR as we are studying the impact of senescence on jump starting response to failed immunotherapy. Response rate in this setting would therefore be an appropriate endpoint as these patients go onto salvage chemotherapy as standard of care with poor response rates of 7 %.

Biomarker Research

Blood samples will be collected and analyzed for T/NK cell counts as well as SASP, including various cytokines and chemokines using a multiplex cytokine array. Phenotypic and functional characterization, including activation markers and intracellular cytokine profile, of immune cell subsets will be evaluated by multi-parametric flow cytometry. The change in FLT-PET will be compared by ORR using an unpaired t-test and the associations with the level of plasma SASP and immune cell activation will be examined by a correlation analysis. Any increase in the absolute number, proliferation or activation of T cells and NK cells in the peripheral blood would indicate a positive response to PD1 therapy (*30, 31*). The power is not formally justified because these are exploratory and the comparisons are between pre- and post- treatment samples from individual patients.

Multi-factorial immune profiling. Briefly, plasma and PBMC will be isolated from the peripheral blood following standard percoll-gradient centrifugation. A multiplex Luminex assay (R&D Systems) will simultaneously query 45 different cytokines, chemokines, soluble receptors and growth factors (including, IFN-ϒ, IL-2, IL-2R, IL-6, IL-7, IL-12, IL-15, TNF-α, CCL-2, CCL-4, GRO-α/β, IL-8, IL-10 and VEGF) in the plasma. PBMC will be analyzed via a 12-color flow cytometry to assess:

1. alterations in the absolute number and relative frequency of CD4/CD8 T cells and cytotoxic ($CD56^{low}CD16^{high}$) and regulatory ($CD56^{high}CD16^{low}$) NK cells;
2. Proliferation (Ki67) and activation (NKG2D, Perforin, IFN-gamma) markers as well as
3. PD1 status of T and NK cell subsets.

Immunohistochemistry (IHC): Dr. Murphy, pathologist and co-I at the Ann Arbor VA, will identify and check for quality control for tumor cellularity from biopsy samples. Antibody to GR will be used to assess tumor GR expression. Vecta Elite ABC-HRP Rabbit IgG kit (Vector Labs, Catalog#: PK-4001) will be used to stain slides for GR (Cell signaling, catalog#: 12041S). Antigen retrieval will be performed using Vector Antigen Unmasking solution (Citric Acid Based, Vector Labs, Catalog#: H-3300) using a previously optimized protocol. GR staining will be scored independently by two pathologists, one at the VA (Dr. Murphy) and one at the KCI pathology core (Dr. Fulvio Lonardo). Quantitative expression will also be determined by AQUA.

RNA extraction and measurement of mRNA expression: Retrieval of RNA from formalin-fixed, paraffin-embedded biopsied tissue sections will be performed using the RNeasy FFPE™ Kit from Qiagen. Global degradation/transcript size range will be assessed by analyzing cDNA on agarose gels. RNA quantity and quality will be estimated by spectrophotometry. mRNAs for GRα and GRβ will be measured using specially designed TaqMan RT-PCR probes previously designed and optimized by us.

Measurement of plasma Dex levels: Serum Dex concentrations will be determined at the KCI/WSU Pharmacology Core Service using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) with the linear calibration curve at 5 - 5000 nM Dex in human serum.

5.0 PATIENT ELIGIBILITY

5.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Have a life expectancy of at least 6 months.

4. Have a histologically confirmed diagnosis of stage IV NSCLC (includes patients who have progressed on durvalumab for Stage III NSCLC) and have at least one measurable lesion based on RECIST v1.1.

5. Have disease progression on or after treatment with an anti-PD-L1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. Anti-PD-1/PD-L1 treatment progression is defined by meeting all the following criteria:

    - Most recent treatment with an anti-PD-1/PD-L1 mAb
    - Has received at least 2 doses of an anti-PD-1/PD-L1 mAb
    - Has demonstrated disease progression on or after an anti-PD-1/PD-L1 mAb as defined by RECIST 1.1. OR clinical progression at the investigator's discretion

6. Have a performance status of 0, 1 or 2 on the ECOG Performance Scale (Appendix 15.1).

7. Demonstrate adequate organ function as defined in Table 1; all screening labs should be performed within 28 days of enrollment.

Table 1: Adequate organ function laboratory values

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥8.0 g/dL without transfusion or EPO dependency (within 7 daysof assessment)
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥40 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) (only required if on anticoagulants or clinically indicated) Activated Partial Thromboplastin Time (aPTT) (only required if on anticoagulants or clinically indicated)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

8. Female subject of childbearing potential should have a serum pregnancy within 14 days of enrollment and 72 hours prior to receiving the first dose of study medications.

9. Female subjects of childbearing potential must be willing to use a highly effective method of contraception as outlined in Section 6.3.3 for the course of the study through 180 days after the last dose of study medications.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

10. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 6.3.3, starting with the first dose of study therapy through 180 days after the last dose of study therapy.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

11. Adequate tissue sample for correlative studies. A new sample is not necessary if archival specimen is available and has adequate amount of tumor content (at least 30%). This needs to be determined by a pathologist.

5.2 Exclusion Criteria

The first dose of trial treatment is considered to be first dose of dexamethasone. The subject must be excluded from participating in the trial if the subject:

1. Received palliative radiation within 7 days of enrollment.

2. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to enrollment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior enrollment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

3. Has active autoimmune disease that has required systemic treatment within the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

   Note: Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

4. Subjects requiring daily corticosteroids >10mg of prednisone (or its equivalent) would be excluded from the study.

Note: Subjects with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would NOT be excluded from the study.

5. Has evidence of interstitial lung disease or a history of non-infectious pneumonitis within the past 12 months that required oral or intravenous glucocorticoids to assist with management.

   Note: Lymphangitic spread of the NSCLC is not exclusionary.

6. Has an active infection requiring systemic therapy.

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

8. Subjects with cognitive functioning/impairment based on medical record review ad physician decision.

9. Is pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with informed consent through 180 days after the last dose of trial treatment.

10. Has a diagnosis of immunodeficiency (including Human Immunodeficiency Virus (HIV) or acquired immunodeficiency (AIDS)-related illness) or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to enrollment.

11. Has a known history of active TB (Bacillus Tuberculosis).

12. Has known active Hepatitis B or Hepatitis C.

13. Has received a live vaccine within 30 days of enrollment.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

14. BASELINE CORTICOSTEROID AT STUDY ENTRY - subjects may not be on any steroids (dexamethasone, prednisone, etc) at the time of consent/study start.

6.0 TREATMENT PLAN

6.1 Drug Administration

6.1.1 Treatment

Both dexamethasone and pembrolizumab are standard medications and will be used from commercial standard supply. The first dose of trial treatment is considered to be first dose of dexamethasone. Trial treatment should begin within 14 days of enrollment.

Table 2: Treatment drugs

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle

Dexamethasone will be administered orally, prior to each dose of pembrolizumab for 3 cycles in the following cohorts:

Cohort 1: 4 mg BID for 7 days, followed by taper 2 mg BID for 1 day and 1 mg BID and 3 day wash out.

Cohort 2: 4mg BID for 10 days, followed by 2 mg BID for 2 days, 1 mg BID for 1 day and 3 day wash out.

Cohort 3: 4 mg BID for 13 days, 2mg BID for 3 days, 1 mg BID for 1day and 3 day wash out

Pembrolizumab 200 mg (IV) will be administered per institutional standard of care guidelines.

Subjects will be given a pill diary and instructed to complete for each day of administration of Dexamethasone. Missed and/or vomited doses should be recorded on the diary as such. Subjects will be asked to bring their pill diary to each study visit.

6.2 Pembrolizumab Dose Modification

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**.

For dose modification/management of immune-related adverse events, please see section 7.3 Table 7.

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. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Investigator. The reason for interruption should be documented in the patient's study record.

Table 3: Pembrolizumab infusion reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication and Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
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 subject 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 subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab 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 -Pressers -Corticosteroids -Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. -Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject 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 v4.0.3 (CTCAE) at http://ctep.cancer.gov		

6.3 Dexamethasone dose modification: CBC and Metabolic profile will be monitored once weekly while on DEX. Any Grade III or greater non-hematological side effect will result in holding the DEX with resumption only when AE is Grade 1 or lower, and patient is asymptomatic. If symptomatic, DEX will be permanently discontinued.

6.4 Diet/Activity/Other Considerations: No special considerations. In diabetics, we will encourage stricter adherence to sugar free meals

6.4.1 Contraception and Pregnancy

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab have transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 180 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) highly effective contraception during heterosexual activity.

Highly effective methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of **two** of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill) associated with inhibition of ovulation, contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Patients should be informed that taking the study medications may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 180 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

If a patient inadvertently becomes pregnant while on study, the subject will immediately be removed from the study and the investigator should notify the IRB within 24 hrs of knowledge. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated.

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. If a male subject impregnates his female partner the study personnel must be informed immediately and the pregnancy reported to the IRB within 24 hours of knowledge.

6.4.2 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, subjects who are breast-feeding are not eligible for enrollment. In addition, subjects should not breastfeed for 180 days after the last dose of study medication.

6.5 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.5.

A subject must be discontinued from study treatment for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue treatment with confirmed radiographic progression if clinically stable or clinically improved at thediscretion of the investigators.

- Unacceptable adverse experiences as described in Section 6.2 and 7.3
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7.5.1. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring. Serious adverse events will be collected for 30 days after the end of treatment as described in Section 9.0). End of treatment and survival follow-up procedures are listed in section 7.2. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up

for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed every 6 months through the medical record for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.5.1 Discontinuation of Study Therapy after Complete Response (CR)

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab.

6.6 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 subjects

4. Plans to modify or discontinue the development of the study drug

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

Patient registration for this trial will be managed by VA Ann Arbor Healthcare System as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the site on the Screening and Enrollment Log.

It is the responsibility of the investigator to determine patient eligibility. After patient eligibility has been determined, the **completed** Eligibility Worksheet will be filed in the patientbinder with the signed informed consent form in a locked office and locked cabinets. Electroniccopies will be located on the VA secured T Drive.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them and will not receive study treatment.

The Schedule of Events **Appendix A** summarizes the trial procedures to be performed at each visit. 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 investigator for reasons related to subject 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 subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Informed Consent

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

Consent must be documented by the subject's dated signature or by the subject'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 subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject'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 subject's dated signature or by the subject'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, and applicable laws and regulations.

7.2 Treatment Calendar

SCHEDULE OF EVENTS COHORT 1

Procedure	Screening (within 28 days prior to Day 0)[1]	Baseline Day 0	(C1D1)	Lead In C2 and C3	(C2 and 3D1) (± 3Days)	(C4+) (± 3 Days)	EOT	Follow Up[1]
Informed Consent	X							
Medical History	X							
Physical exam	X		X		X	X	X	
Vital Signs	X		X		X	X	X	
ECOG performance status	X		X		X	X	X	
Adverse Events	X		X		X	X	X	X
Concomitant Medications	X		X		X	X	X	X
CBCPD	X		X		X	X	X	
Comp	X		X		X	X	X	
Coagulation (PT/aPTT)[7]	X							
FDG PET/CT-Chest (VA Ann Arbor)[2]	X					X	X	
CT Abdomen/Pelvis[3]	X							
Research Blood[4]		X	X		X			
FLT PET (University of Michigan)		X	X					
Dexamethasone[5]		X		X	X			
Pembrolizumab[6]			X		X	X		

[1] Follow Up: Phone call 6 weeks after EOT including any new treatments
[2] FDG PET/CT-Chest: C4D1 (±7days), then Every 12 weeks (±7days)
[3] CT-Abdomen/Pelvis: at screening, C4D1 (±7days), then Every 12 weeks (±7days) ***only if disease is present in that area***
[4]Research Blood: T/TK, SAP, cytokines, chemokines, immune cell subsets; Drawn with 1st FLT PET, 2nd FLT PET, C1D1, C2D1, C3D1 only
[5] Dexamethasone given orally. Start immediately after FLT PET Day 0 – Day 9. Lead in Day 9-17
[6]Pembrolizumab given up to 1 year every 21 days
[7]Only required if clinically indicated or on anticoagulants

SCHEDULE OF EVENTS COHORT 2

Procedure	Screening (within 28 days prior to Day 0)[1]	Baseline Day 0	(C1D1)	Lead In C2 and C3	(C2 and 3D1) (± 3Days)	(C4+) (± 3 Days)	EOT	Follow Up[1]
Informed Consent	X							
Medical History	X							
Physical exam	X		X		X	X	X	
Vital Signs	X		X		X	X	X	
ECOG performance status	X		X		X	X	X	
Adverse Events	X		X		X	X	X	X
Concomitant Medications	X		X		X	X	X	X
CBCPD	X		X		X	X	X	
Comp	X		X		X	X	X	
Coagulation (PT/aPTT)[7]	X							
FDG PET/CT-Chest (VA Ann Arbor)[2]	X					X	X	
CT Abdomen/Pelvis[3]	X							
Research Blood[4]		X	X		X			
FLT PET (University of Michigan)		X	X					
Dexamethasone[5]		X		X	X			
Pembrolizumab[6]			X		X	X		

[1] Follow Up: Phone call 6 weeks after EOT including any new treatments
[2] FDG PET/CT-Chest: C4D1 (±7days), then Every 12 weeks (±7days)
[3] CT-Abdomen/Pelvis: at screening, C4D1 (±7days), then Every 12 weeks (±7days) ***only if disease is present in that area***
[4]Research Blood: T/TK, SAP, cytokines, chemokines, immune cell subsets; Drawn with 1st FLT PET, 2nd FLT PET, C1D1, C2D1, C3D1 only
[5] Dexamethasone given orally. Start immediately after FLT PET Day 0 – Day 9. Lead in Day 9-17
[6]Pembrolizumab given up to 1 year every 21 days
[7]Only required if clinically indicated or on anticoagulants

SCHEDULE OF EVENTS COHORT 3

Procedure	Screening (within 28 days prior to Day 0)[1]	Baseline Day 0	(C1D1)	Lead In C2 and C3	(C2 and 3D1) (± 3Days)	(C4+) (± 3 Days)	EOT	Follow Up[1]
Informed Consent	X							
Medical History	X							
Physical exam	X		X		X	X	X	
Vital Signs	X		X		X	X	X	
ECOG performance status	X		X		X	X	X	
Adverse Events	X		X		X	X	X	X
Concomitant Medications	X		X		X	X	X	X
CBCPD	X		X		X	X	X	
Comp	X		X		X	X	X	
Coagulation (PT/aPTT)[7]	X							
FDG PET/CT-Chest (VA Ann Arbor)[2]	X					X	X	
CT Abdomen/Pelvis[3]	X							
Research Blood[4]		X	X		X			
FLT PET (University of		X	X					
Dexamethasone[5]		X		X	X			
Pembrolizumab[6]			X		X	X		

[1] Follow Up: Phone call 6 weeks after EOT including any new treatments
[2] FDG PET/CT-Chest: C4D1 (±7days), then Every 12 weeks (±7days)
[3] CT-Abdomen/Pelvis: at screening, C4D1 (±7days), then Every 12 weeks (±7days) ***only if disease is present in that area***
[4]Research Blood: T/TK, SAP, cytokines, chemokines, immune cell subsets; Drawn with 1st FLT PET, 2nd FLT PET, C1D1, C2D1, C3D1 only
[5] Dexamethasone given orally. Start immediately after FLT PET Day 0 – Day 9. Lead in Day 9-17
[6]Pembrolizumab given up to 1 year every 21 days
[7]Only required if clinically indicated or on anticoagulants

7.3 Management of Adverse Events

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 one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial 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. 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 4**.

Table 4: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

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.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		

Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects 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.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin	Please see section 6.2.3 regarding the management of overlapping hepatotoxicity with rucaparib and pembrolizumab.			
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 subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects 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 (e.g. 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 (e.g. 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 1-2mg/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	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		
NOTES: 1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. 2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding 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)				

7.4 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

1. Antineoplastic systemic chemotherapy or biological therapy
2. Immunotherapy not specified in this protocol
3. Chemotherapy not specified in this protocol
4. Investigational agents
5. Radiation therapy
    - **Note:** Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
6. Live vaccines within 30 days prior to enrollment and while participating in thetrial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

7. Daily systemic glucocorticoids with dose >10mg of prednisone (or its equivalent) for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.

   Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

7.5 Withdrawal/Discontinuation

When a subject 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 9.0.

7.5.1 End of Treatment Follow-up Visits

The mandatory Safety Follow-Up Visit should be conducted within 30 +/- 10 days after the last dose of pembrolizumab. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Procedures should be conducted according to the Treatment Calendar in Section 7.2. SAEs that occur within 30 days of the end of treatment should be followed and recorded.

7.5.2 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject will be followed through his/her medical record and assessed for survival status until death or 2 years. Data will be collected every 6 months.

8.0 IMAGING AND MEASUREMENT OF DISEASE

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (*32*)

Immunotherapy drugs can initially cause inflammation in the early stages of treatment. Immune-related RECIST (irRECIST) utilizes RECISTv1.1 but considers an inflammatory response (or "pseudo-progression") as normal. The main difference between RECISTv1.1 and irRECIST is that patients can stay on trial after the first progressive disease (PD) assessment (as per RECISTv1.1) if using immune-related RECIST criteria. This PD per RECISTv1.1 is then re-labeled as immune related stable disease (irSD) per irRECIST (*33*) and requires addition of unidimensional measurements of all new lesions (that meet the definition of target lesion) to be added to the sum of longest diameters (SLD) calculation for response assessment. Importantly, immune-related progression (irPD) must be confirmed by a follow-up scan at

least 4 weeks (within 4-8 weeks) following the initial PD/irSD assessment in order to take the patient off the trial.

Subjects that are deemed to have clinical progression and unstable should not be continued on therapy after PD (per RECISTv1.1) and are therefore not required to have repeat tumor imaging for confirmation as per irPD definition. It is at the discretion of the site investigator whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

Definitions

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least 2 cycle(s) of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

8.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (or MRI) for studies with a slice thickness of ≤5mm, or twice the slice thickness
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Note: Tumor lesions that are situated in a previously irradiated area will only be considered measurable, if they have had subsequent progression by at least 5 mm.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total 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), representative of all involved organs, and those that lend themselves to reproducible repeated measurements. If a non-nodal lesion is either not present or is initially measured with longest diameter <10mm as a non-target then grows to ≥10mm after baseline, this lesion then becomes a new target lesion as per irRECIST criteria. The non-nodal longest diameter is then added to the sum of diameters, and patient response is calculated with the new lesion.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

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 as noted above, 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. If a non-target lymph node grows to >15mm after baseline, this node then becomes a new target lesion as per irRECIST. The nodal short axis is then added to the sum of diameters, and patient response is calculated with the new lesion.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’)

8.2 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before enrollment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and > 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

CT and MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

8.3 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/SD	No	PR	
PR	Non-PD	No	PR	≥4 wks. confirmation
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	
Any	PD*	Yes or No	PD	no prior SD, PR or CR
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects will be permitted to continue study treatment beyond initial RECISTv1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator determined clinical benefit
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
- Tumor markers are stable/improving, if expressed

A radiographic assessment/ scan should be performed within 4-8 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD (termed irPD). The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Study Calendar (see Table 7.2).

For the subjects who continue study therapy beyond progression, further progression is defined as an additional 20% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Study treatment should be discontinued permanently upon documentation of further progression (i.e. irPD).

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival is defined as the duration of time from start of treatment to time of progression.

9.0 ADVERSE EVENTS

Adverse event monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial dose of dexamethasone through 30 days after the last dose of pembrolizumab (whichever is later). Serious adverse events will be collected from the time of the initial dose of dexamethasone through 30 days after the last dose pembrolizumab (whichever is later). Any serious adverse event that occurs more than 30 days after the last dose of pembrolizumab and is considered related to the study must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study drugs for the changes observed;
- The patient is lost to follow-up or withdraws consent; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before enrollment onto study is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 9.1, occurring from the initial dose of dexamethasone through 30 days following the last dose of pembrolizumab must be recorded as an adverse event regardless of frequency, severity (grade) or assessed relationship to the study drugs.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study is also considered an adverse event.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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 the IRB.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject 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 or vital sign which requires protocol treatment to be modified, 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 study drugs, is also an adverse event.

Progression of the cancer under study and/or symptoms related to progression of the underlying cancer are not considered an adverse event.

9.1.2 Serious Adverse Event

An adverse event is considered "serious" if, in the view of the investigator it results in any of the following outcomes:

- Death

  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event

  An adverse event is considered 'life-threatening' if, in the view of either the investigator or sponsors, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event: Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

9.1.3 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs, those adverse events are described in the approved Package Insert.

9.1.4 Events Not Qualifying as SAEs

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE. *Progression of the cancer under study and/or symptoms related to progression of the underlying cancer are not considered a serious adverse event unless it resulted in death*.

9.2 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 4.0.3 All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site. (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded.

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

Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.

Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment/intervention

9.3 Reporting of Adverse Events

9.3.1 Reporting procedures for multi-site trials

All adverse events (AEs), serious adverse events (SAEs) and unanticipated problems (UPs),

will be reported to the IRB per current institutional standards.

10.0 CORRELATIVE STUDIES

10.1 FDG-PET: [^{18}F]-fluorodeoxyglucose (FDG) has been used extensively as a glucose analogue to image glycolysis in the body. Its accumulates in many cancers, most notably lung cancer due to their elevated glycolytic rate compared to normal background tissue. This has allowed FDG to be the standard for oncologic staging prior to therapy, and one of the main modalities to monitor recurrent disease/treatment response to therapy. In FDG PET/CT, significant variation in tracer uptake has been suggested to be 30 % for the SUV max using PERCIST criteria (*34*) Although this metric has been suggested, we will also look at normalized SUV max using an internal reference tissue given that tumor burden and hyperglycemia has been shown to effect PERCIST criteria (*35, 36*) Additionally, total lesion glycolysis (the SUV mean of the segmented volume multiplied by the tumor volume) has been shown to be a better estimation of FDG uptake and account for variation of a very "hot tumor" that is small compared to a "warm tumor" that is large (*35*)

10.2 FLT-PET: [^{18}F]-3-fluro-deoxy-thymidine (FLT) is a thymidine analogue as FDG is an analogue to glucose. It is an NIH held IND drug with a current/active RDRC at the University of Michigan. FLT's incorporation into the cell occurs through thymidine kinase within the DNA synthesis machinery. Once in the cell it is phosphorylated and trapped within the cytosol. The degree of uptake correlates to the degree of DNA synthesis/proliferation, analogous to Ki-67. FLT PET/CT imaging will be used both prior to and after DEX treatment (*37*). The initial scan will provide a baseline DNA synthesis rate based on the uptake within the tumor. Following DEX therapy, if there is senescence as predicted and resultant G1 arrest, there will be fewer cells in S phase (DNA synthesis) and a corresponding reduction in FLT uptake in the tumor. The reduction in FLPET is hypothesized to be directly proportional to reduced FDG uptake, denoting response to therapy. FLT PET can eventually be used a biomarker to identify who would benefit from the proposed approach in this study.

10.3 GR expression

A specific cut-off for tumoral GR expression is not a pre-requisite for enrollment onto this protocol. Tumoral GR expression will be determined by immunohistochemistry (IHC) methods. GR expression will be divided as low (<1%), intermediate (1-49%), and high (≥50%).

10.4 SASP

The tumor cells will remain senescent and continue secreting SASP even after Dex washout. The SASP is expected to enhance the frequency and cytolytic functions of T and NK cells in the peripheral blood as well as in the tumor, especially in combination with the checkpoint inhibitor, Pembrolizumab. The SASP will be analyzed by a multiplex cytokine array

10.5 T and NK cells in PBMC

T cells and NK cells are major contributors to cytolytic function against the tumor, which is often blocked by PD1-PDL1 interaction. Although the number of T cells would deplete to some extent during Dex treatment, it is expected to recover quickly during/following the 3-day washout., while a multi-parametric flow cytometric analysis will detect any change in the number and functions of T and NK cells in the peripheral blood.

11.0 STATISTICAL ANALYSIS PLAN

11.1 Statistical Design (see page 10 for Schema)

In the first stage, three DEX escalation cohorts will be evaluated sequentially from Cohort A to Cohort C until two or more patients have the FLT-PET response (i.e., ≥30% reduction in FLT-PET uptake in at least one target lesion) and, otherwise, the trial will be terminated due to futility. When a lead-in cohort has two or more FLT-PET responses, this lead-in cohort will be considered the optimal DEX duration and the primary endpoint will be evaluated in the following second and third stages using this optimal DEX duration. That is, after the optimal DEX duration is decided in the first stage, six additional patients will be enrolled in the second stage with the same DEX duration as the associated cohort. If four or less patients respond among 11 patients, the trial will be terminated. Otherwise, 10 additional patients will be enrolled in the third stage. The null hypothesis ($p0 = 30\%$) will be rejected if 10 or more FLT-PET responses are observed in 21 patients. This design yields a 1-sided type I error rate of 5% and power of 80% when the true FLT-PET response rate is 60% (i.e., $p1 = 60\%$). The minimum sample size will be 11 patients when Cohort A becomes the optimal duration and the trial is terminated at the end of the second stage. The maximum sample size will be 31 patients when Cohort C becomes the optimal duration and the patients are enrolled into the third stage.

We will also explore the associations between the FLT-PET response and the changes in senescence associated secretory proteins (SASP) and lymphocyte, phenotypic and functional markers (LPFM), (ii) monitor the changes and trajectories in SASP and LPFM, and (iii) explore the association between the FLT-PET response and GR expression at cycle 0. The expression levels of SASP and LPFM/GR will be measured using plasma and tissue samples,

respectively. The secondary endpoints are the changes in SASP and LPFM expression levels between cycle 0 and cycle 1 as well as the expression level of GR at cycle 0. The association between the FLT-PET response and the changes in the expression levels of each of SASP and LPFM will be examined using logistic regression models. The expression levels of SASP and LPFM between cycle 0 and cycle 1 will be examined using a paired t-test, if needed, after data transformation (such as log or square root transformation). The association between the FLT-PET response and the GR expression level will be assessed using logistic regression models. The trajectories from cycle 0 to cycle 4 for the expression levels of each of SASP and LPFM will be examined to see if the expression levels increase monotonically across cycles. To do this, linear mixed-effects models will be used, if needed, after data transformation. In addition, in case that either Cohort B or C becomes the optimal duration, we will descriptively compare the changes in SASP and LPFM expression levels from cycle 0 to cycle 1 between lead-in cohorts. Because these are a discovery study to generate hypotheses, no multiple comparison correction will be made. However, if either the sample size is less than 12 patients or a level (i.e., response vs. non-response) has less than 5 events; all secondary objectives will be exploratory and will be summarized descriptively. All statistical analyses will be based on complete data and no missing data analysis will be performed.

The secondary objective is to assess the effect of DEX on pembrolizumab in terms of overall response rate (ORR), which is the primary endpoint. Based on our previous pre-clinical and clinical studies, we hypothesize that the true ORR of DEX followed by pembrolizumab will be at least 33% (i.e., $p1 = 0.33$) vs. the historical control whose ORR is at most 7% (i.e., $p0 = 0.07$). The ORR will be statistically evaluated when the FLT-PET response trial enters the third stage, where the number of patients with the selected optimal DEX duration will be 21. Otherwise, the ORR will be summarized descriptively. The null hypothesis ($p0 = 7\%$) will be rejected if five or more responses are observed in 21 patients, which yields a 1-sided type I error rate of 5% and power of 87% when the true ORR is 33% (i.e.., $p1 = 33\%$).

We will also to explore the associations between ORR and the changes in expression levels of each of SASP and LPFM from cycle 0 to cycle 1, (ii) to explore the association between ORR and GR expression at cycle 0, and (iii) to explore the progression-free survival (PFS). The associations between ORR and the changes of SASP and LPFM and between ORR and the GR expression will be examined using logistic regression models and no multiple comparison correction will be made because these are a discovery study to generate hypotheses. The distribution of PFS will be summarized graphically using the Kaplan-Meier (KM) curve and the median PFS and associated 95% confidence interval will be estimated using KM estimate. If either the sample size is less than 12 patients or a level (i.e., response vs. non-response) has less than 5 events, the secondary objectives will be exploratory and will be summarized descriptively. All statistical analyses will be based on complete data and no missing data analysis will be performed.

11.2 Sample Size Justification

The clinical trial is a single arm phase II intervention trial in Veterans as second line therapy, after progression on initial chemo-immunotherapy or immunotherapy for NSCLC. The enrolled patient will be in the study for 3 months and will then be followed for up to 2 years. We currently see at least 2-3 patients per month who will satisfy eligibility criteria and thus

the enrollment will be completed within 2 years (min 21 and max 39 patients). A sample size of 21 patients will not be powered for all the comparisons. But the data information obtained from this study will provide us preliminary information to design a more definitive study

The sample size was justified based on the primary objective. The FLT-PET response will be evaluated using a Phase II single-arm three-stage design with three lead-in efficacy (futility) cohorts. The sample size was estimated to achieve 80% power with a 1-sided 5% type I error rate and the estimated sample size is varied according to the selected optimal duration, which ranges from 21 patients (when Cohort A is optimal) to 31 patients (when Cohort C is optimal). Considering up to 20% drop-out rate, the required sample size will be between 21 patients (i.e., no drop-out with Cohort A as the optimal duration) and 39 patients (i.e., 20% drop-out with Cohort C as the optimal duration). For the secondary objective, the use of 21 patients (when the FLT-PET response trial enters the third stage) will allow us to achieve 87% power when the true ORR is 33% with a 1-sided type I error rate of 5%. We expect that the accrual rate will be at least 35 eligible and evaluable patients per year.

11.3 Population for Analysis

Intent-to-Treat Population: All patients consented and enrolled in the trial.

Evaluable Population: Only those patients who have received at least one cycle of therapy with dexamethasone and pembrolizumab will be considered evaluable.

Safety Evaluable Population: Patients who receive any treatment on protocol will be considered evaluable for safety.

11.4 Analysis of Primary Objective: The primary objective is to identify the smallest duration of fixed dose Dex that results in a >30% reduction in FLTPET. We will utilize a 2 stage design with 3 cohorts (see Statistical schema). The hypothesis is that the true "response" in FLTPET (reduction in FLTPET by >30% following Dex in at least 1 target lesion) will be 60% (p1=60) vs. p0 30% (based on preliminary data that chemotherapy such as docetaxel results in irreversible cell cycle arrest as measured by S-phase surrogate on FLT-PET (*39*).

Secondarily, we will compare FLTPET "response" to GR expression and generation of SASP and immune effector cells. We will also track the trend in immune effector cell response at later time points (cycle 2 and 3) to test contributory effects of pembrolizumab and Dex on the immune phenotype in the blood.

11.5 Analysis of Secondary Objectives The secondary objective is to establish that the true ORR of Dex followed by pembrolizumab will be at least 33% (p1 = 0.33) vs. docetaxel treatment (as the historical control) whose ORR is

≤ 7% (p0 = 0.07). The ORR will be assessed at a 12 week FDG PET scan. The required sample size for both lead-in FLTPET response and phase 2 studies will range 21 to 31 patients. As secondary objectives, we will explore associations of the change in FLT-PET with ORR assessed by FDG-PET, level of plasma SASP, and immune cell activation. The change in FLT-PET will be compared by ORR using an unpaired t-test and the associations with the level of plasma SASP and immune cell activation will be examined by a correlation analysis. The power is not formally justified because these are exploratory

12.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

12.1 Investigational Drugs

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 study drug in accordance with the protocol and any applicable laws and regulations.

Dexamethasone is available through commercial supply. It will be administered orally according to study schema.

Pembrolizumab is available through commercial supply. It will be administered intravenously every 21 days per institutional standard policy

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

Dexamethasone is available through commercial supply and will be administered 7 days prior with 3 days off before each pembrolizumab infusion.

Drug Name:	Dexamethasone
INN:	Dexamethasone
Formulation:	Tablet;

How Supplied:	2mg white, scored tablet 4mg green, scored tablet 6 mg aqua, scored tablet Come in high-density polyethylene bottles or equivalent with child-resistant caps. Patients may receive 1 or more strengths. Each bottle contains 100 tablets
Storage Conditions:	20-25 °C (68 and 77° F) protect from moisture

12.2 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the and trial site personnel are not blinded to treatment. Drug identity (name, strength) is included in the label text.

12.3 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

13.0 ADMINISTRATIVE AND REGULATORY DETAILS

13.1 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the PI of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

13.2 Quality Management System

The Ann Arbor VA Research Office audits clinical trials every quarter and random charts are examined for any discrepancies as relates to HIPPA adherence and IRB approved form usage

13.3 Data Management

All information will be recorded locally and entered into VA RedCap Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system. Online access is password protected.

CRFs will be reviewed and source verified by the PI and the study coordinator. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator

will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration
    - Subject entry into VA RedCap
        - Subject Status
        - Demographics
- During study participation
    - All data should be entered online within 10 business days of data acquisition. Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 9.3 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

13.4 Data and Safety Monitoring Procedures

A Data and Safety Monitoring Committee (DSMC) will be set up as an arm's length committee. The DSMC will be comprised of VA oncologists not involved with the study and VA Pharmacist. This committee is responsible for monitoring the safety and data integrity of the trial.

The committee is required to meet monthly to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented and reported to the IRB at the continuing review, or sooner (per policy)

14.0 APPENDICES

I. 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 Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

II. Common Terminology Criteria for Adverse Events V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (https://evs.nci.nih.gov/ftp1/CTCAE/About.html.)

III Procedure for patients on study

1. Patient will sign consent
2. Patient will have regular standard of care procedures and they will be reviewed and used for eligibility.
3. Patient will be scheduled for baseline FLT PET and FLT PET prior to Pembrolizumab and all future clinic appointments so they know when they will be ahead of time
4. Patient will be called the day before for a reminder of their FLT PET and to start Dexamethasone after FLT PET
5. Patient will go to the University of Michigan for FLT PET and take 1st dose of Dexamethasone immediately afterwards – Coordinator will meet patient for Research blood draw and reimburse patient for this visit ($25)
6. Patient will be called and reminded to stop taking dexamethasone
7. Patient will be called and reminded about their appointments the next day which are the last FLT PET, visit with Dr. Ramnath, cycle 1 of Pembrolizumab infusion
8. Patient will go to the University of Michigan for FLT PET and then come to VA Ann Arbor to begin Pembrolizumab treatment – Patient will be reimbursed to this visit ($25)
9. The same thing will happen for the next 2 cycles regarding starting and stopping dexamethasone without the FLT PET
10. Patients will have imaging (FDG-PET and CT-Chest, CT-Abdomen and Pelvis only required if disease is present in that area) at screening, C4D1 (±7days), then Every 12 weeks (±7days)

IVA. PATIENT'S MEDICATION DIARY COHORT 1 CYCLE __1 – 3__

Today's date _____ Agent: **Dexamethasone**

Patient Initials_____ Patient Study ID_____

INSTRUCTIONS TO THE PATIENT-**:**

- You will take **Dexamethasone orally twice a day, approximately 12 hours apart**
- You should take your capsule(s) at approximately the same time each morning and evening.

Dexamethasone Taper

4mg Dex morning and evenings on Days 10-16; then again on Days 31-37

2mg Dex morning and evenings on Day 17; then again on Day 38

1mg Dex morning and evenings on Day 18; then again on Day 39

Day	Date	Time of Dose		Dexamethasone		Comments
		AM	PM	_____ mg		
	F	**FLT PET @ UM @ _____; Blood Draw; Start Dexamethasone**				
		AM	PM	_____mg AM	_____mg PM	
	Sa	AM	PM	_____mg AM	_____mg PM	
	Su	AM	PM	_____mg AM	_____mg PM	
	M	AM	PM	_____mg AM	_____mg PM	
	Tu	AM	PM	_____mg AM	_____mg PM	
	W	AM	PM	_____mg AM	_____mg PM	
	Th	AM	PM	_____mg AM	_____mg PM	
	F	AM	PM	_____mg AM	_____mg PM	
	Sa	AM	PM	_____mg AM	_____mg PM	
	Su	**No Dexamethasone**				
	M	**No Dexamethasone**				
	Tu	**No Dexamethasone**				
1	W	**FLT PET @ UM @_____; Blood Draw; RV w/Ramnath @ _____; PEMBROLIZUMAB INFUSION (Cycle 1 Day 1 = 1st Dose)**				
2	Th					
3	F					
4	Sa					
5	Su					
6	M					
7	Tu					
8	W					
9	Th					
10	F	AM	PM	_____mg AM	_____mg PM	

11	Sa	AM	PM	_____mg AM	_____mg PM	
12	Su	AM	PM	_____mg AM	_____mg PM	
13	M	AM	PM	_____mg AM	_____mg PM	
14	Tu	AM	PM	_____mg AM	_____mg PM	
15	W	AM	PM	_____mg AM	_____mg PM	
16	Th	AM	PM	_____mg AM	_____mg PM	
17	F	AM	PM	_____mg AM	_____mg PM	
18	Sa	AM	PM	_____mg AM	_____mg PM	
19	Su	**No Dexamethasone**				
20	M	**No Dexamethasone**				
21	Tu	**No Dexamethasone**				
22	W	**Blood Draw; RV w/Ramnath @ _____; PEMBROLIZUMAB INFUSION (Cycle 2 Day 1 = 2nd Dose)**				
23	Th					
24	F					
25	Sa					
26	Su					
27	M					
28	Tu					
29	W					
30	Th					
31	F	AM	PM	_____mg AM	_____mg PM	
32	Sa	AM	PM	_____mg AM	_____mg PM	
33	Su	AM	PM	_____mg AM	_____mg PM	
34	M	AM	PM	_____mg AM	_____mg PM	
35	Tu	AM	PM	_____mg AM	_____mg PM	
36	W	AM	PM	_____mg AM	_____mg PM	
37	Th	AM	PM	_____mg AM	_____mg PM	
38	F	AM	PM	_____mg AM	_____mg PM	
39	Sa	AM	PM	_____mg AM	_____mg PM	
40	Su	**No Dexamethasone**				
41	M	**No Dexamethasone**				
42	Tu	**No Dexamethasone**				
43	W	**Blood Draw; RV w/Ramnath @ _____; PEMBROLIZUMAB INFUSION (Cycle 3 Day 1 =3rd Dose)**				

IVB. PATIENT'S MEDICATION DIARY COHORT 2 CYCLE __1 – 3__

Today's date _____ Agent: **Dexamethasone**

Patient Initials_____ Patient Study ID_____

INSTRUCTIONS TO THE PATIENT-**:**

- You will take **Dexamethasone orally twice a day, approximately 12 hours apart**
- You should take your capsule(s) at approximately the same time each morning and evening.

Dexamethasone Taper

4mg Dex morning and evenings on Days 6-15; then again on Days 27-36
2mg Dex morning and evenings on Day 16-17; then again on Day 37-38
1mg Dex morning and evenings on Day 18; then again on Day 39

Day	Date	Time of Dose		Dexamethasone		Comments
		AM	PM	_____ mg		
	M	**FLT PET @ UM @ _____; Blood Draw; Start Dexamethasone**				
		AM	PM	_____mg AM	_____mg PM	
	Tu	AM	PM	_____mg AM	_____mg PM	
	W	AM	PM	_____mg AM	_____mg PM	
	Th	AM	PM	_____mg AM	_____mg PM	
	F	AM	PM	_____mg AM	_____mg PM	
	Sa	AM	PM	_____mg AM	_____mg PM	
	Su	AM	PM	_____mg AM	_____mg PM	
	M	AM	PM	_____mg AM	_____mg PM	
	Tu	AM	PM	_____mg AM	_____mg PM	
	W	AM	PM	_____mg AM	_____mg PM	
	Th	AM	PM	_____mg AM	_____mg PM	
	F	AM	PM	_____mg AM	_____mg PM	
	Sa	AM	PM	_____mg AM	_____mg PM	
	Su	**No Dexamethasone**				
	M	**No Dexamethasone**				
	Tu	**No Dexamethasone**				
1	W	**FLT PET @ UM @_____; Blood Draw; RV w/Ramnath @ _____; PEMBROLIZUMAB INFUSION (Cycle 1 Day 1 = 1st Dose)**				
2	Th					
3	F					
4	Sa					
5	Su					
6	M	AM	PM	_____mg AM	_____mg PM	
7	Tu	AM	PM	_____mg AM	_____mg PM	

8	W	AM	PM	_____mg AM	_____mg PM	
9	Th	AM	PM	_____mg AM	_____mg PM	
10	F	AM	PM	_____mg AM	_____mg PM	
11	Sa	AM	PM	_____mg AM	_____mg PM	
12	Su	AM	PM	_____mg AM	_____mg PM	
13	M	AM	PM	_____mg AM	_____mg PM	
14	Tu	AM	PM	_____mg AM	_____mg PM	
15	W	AM	PM	_____mg AM	_____mg PM	
16	Th	AM	PM	_____mg AM	_____mg PM	
17	F	AM	PM	_____mg AM	_____mg PM	
18	Sa	AM	PM	_____mg AM	_____mg PM	
19	Su	**No Dexamethasone**				
20	M	**No Dexamethasone**				
21	Tu	**No Dexamethasone**				
22	W	**Blood Draw; RV w/Ramnath @ _____; PEMBROLIZUMAB INFUSION (Cycle 2 Day 1 = 2nd Dose)**				
23	Th					
24	F					
25	Sa					
26	Su					
27	M	AM	PM	_____mg AM	_____mg PM	
28	Tu	AM	PM	_____mg AM	_____mg PM	
29	W	AM	PM	_____mg AM	_____mg PM	
30	Th	AM	PM	_____mg AM	_____mg PM	
31	F	AM	PM	_____mg AM	_____mg PM	
32	Sa	AM	PM	_____mg AM	_____mg PM	
33	Su	AM	PM	_____mg AM	_____mg PM	
34	M	AM	PM	_____mg AM	_____mg PM	
35	Tu	AM	PM	_____mg AM	_____mg PM	
36	W	AM	PM	_____mg AM	_____mg PM	
37	Th	AM	PM	_____mg AM	_____mg PM	
38	F	AM	PM	_____mg AM	_____mg PM	
39	Sa	AM	PM	_____mg AM	_____mg PM	
40	Su	**No Dexamethasone**				
41	M	**No Dexamethasone**				
42	Tu	**No Dexamethasone**				
43	W	**Blood Draw; RV w/Ramnath @ _____; PEMBROLIZUMAB INFUSION (Cycle 3 Day 1 =3rd Dose)**				

IVC. PATIENT'S MEDICATION DIARY COHORT 3 CYCLE __1 – 3__

Today's date _____ Agent: **Dexamethasone**

Patient Initials_____ Patient Study ID_____

INSTRUCTIONS TO THE PATIENT-**:**

- You will take **Dexamethasone orally twice a day, approximately 12 hours apart**
- You should take your capsule(s) at approximately the same time each morning and evening.

Dexamethasone Taper

4mg Dex morning and evenings on Days 9-21; then again on Days 37-49

2mg Dex morning and evenings on Days 22-24; then again on Days 50-52

1mg Dex morning and evenings on Day 25; then again on Day 53

Day	Date	Time of Dose		Dexamethasone		Comments
		AM	PM	_____ mg		
	TH	**FLT PET @ UM @ _____; Blood Draw; Start Dexamethasone**				
		AM	PM	_____mg AM	_____mg PM	
	F	AM	PM	_____mg AM	_____mg PM	
	Sa	AM	PM	_____mg AM	_____mg PM	
	Su	AM	PM	_____mg AM	_____mg PM	
	M	AM	PM	_____mg AM	_____mg PM	
	Tu	AM	PM	_____mg AM	_____mg PM	
	W	AM	PM	_____mg AM	_____mg PM	
	Th	AM	PM	_____mg AM	_____mg PM	
	F	AM	PM	_____mg AM	_____mg PM	
	Sa	AM	PM	_____mg AM	_____mg PM	
	Su	AM	PM	_____mg AM	_____mg PM	
	M	AM	PM	_____mg AM	_____mg PM	
	Tu	AM	PM	_____mg AM	_____mg PM	
	W	AM	PM	_____mg AM	_____mg PM	
	Th	AM	PM	_____mg AM	_____mg PM	
	F	AM	PM	_____mg AM	_____mg PM	
	Sa	AM	PM	_____mg AM	_____mg PM	
	Su	**No Dexamethasone**				
	M	**No Dexamethasone**				
	Tu	**No Dexamethasone**				
1	W	**FLT PET @ UM @_____; Blood Draw; RV w/Ramnath @ _____; PEMBROLIZUMAB INFUSION (Cycle 1 Day 1 = 1st Dose)**				
2	Th					

3	F					
4	Sa					
5	Su					
6	M					
7	Tu					
8	W					
9	Th	AM	PM	_____mg AM	_____mg PM	
10	F	AM	PM	_____mg AM	_____mg PM	
11	Sa	AM	PM	_____mg AM	_____mg PM	
12	Su	AM	PM	_____mg AM	_____mg PM	
13	M	AM	PM	_____mg AM	_____mg PM	
14	Tu	AM	PM	_____mg AM	_____mg PM	
15	W	AM	PM	_____mg AM	_____mg PM	
16	Th	AM	PM	_____mg AM	_____mg PM	
17	F	AM	PM	_____mg AM	_____mg PM	
18	Sa	AM	PM	_____mg AM	_____mg PM	
19	Su	AM	PM	_____mg AM	_____mg PM	
20	M	AM	PM	_____mg AM	_____mg PM	
21	Tu	AM	PM	_____mg AM	_____mg PM	
22	W	AM	PM	_____mg AM	_____mg PM	
23	Th	AM	PM	_____mg AM	_____mg PM	
24	F	AM	PM	_____mg AM	_____mg PM	
25	Sa	AM	PM	_____mg AM	_____mg PM	
26	Su	**No Dexamethasone**				
27	M	**No Dexamethasone**				
28	Tu	**No Dexamethasone**				
29	W	**Blood Draw; RV w/Ramnath @ _____; PEMBROLIZUMAB INFUSION (Cycle 2 Day 1 = 2nd Dose)**				
30	Th					
31	F					
32	Sa					
33	Su					
34	M					
35	Tu					
36	W					
37	Th	AM	PM	_____mg AM	_____mg PM	
38	F	AM	PM	_____mg AM	_____mg PM	
39	Sa	AM	PM	_____mg AM	_____mg PM	

40	Su	AM	PM	_____mg AM	_____mg PM	
41	M	AM	PM	_____mg AM	_____mg PM	
42	Tu	AM	PM	_____mg AM	_____mg PM	
43	W	AM	PM	_____mg AM	_____mg PM	
44	Th	AM	PM	_____mg AM	_____mg PM	
45	F	AM	PM	_____mg AM	_____mg PM	
46	Sa	AM	PM	_____mg AM	_____mg PM	
47	Su	AM	PM	_____mg AM	_____mg PM	
48	M	AM	PM	_____mg AM	_____mg PM	
49	Tu	AM	PM	_____mg AM	_____mg PM	
50	W	AM	PM	_____mg AM	_____mg PM	
51	Th	AM	PM	_____mg AM	_____mg PM	
52	F	AM	PM	_____mg AM	_____mg PM	
53	Sa	AM	PM	_____mg AM	_____mg PM	
54	Su	**No Dexamethasone**				
55	M	**No Dexamethasone**				
56	Tu	**No Dexamethasone**				
57	W	**Blood Draw; RV w/Ramnath @ _____; PEMBROLIZUMAB INFUSION (Cycle 3 Day 1 =3rd Dose)**				

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