A Phase II Study of Tadalafil and Pembrolizumab in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Joseph Califano, M.D.

PI Signature: _____

Date: _____

SYNOPSIS

Study Title:	A Phase II Study of Tadalafil and Pembrolizumab in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
Protocol Number:	190098
Study Phase:	2
Study Duration:	*36 months*
Sample Size	*Up to 30 patients will be enrolled*
Investigational Product and Reference Therapy:	Tadalafil will be supplied by Lilly as 10 mg tablets Pembrolizumab will be supplied commercially as a clear, colorless liquid formulated for intravenous administration.
Objectives:	**Primary Objective:** To determine the efficacy (overall survival at 12 months) and safety (rate of dose limiting toxicity) for the combination of Tadalafil and Pembrolizumab. **Secondary objectives are to assess**: • Response rate by RECIST 1.1 • Progression-free survival • Safety and toxicity profile • Duration of response
Study Design:	Open-label phase II single arm trial with a Pocock continuous safety stopping rule and a Simon 2 stage efficacy design. All patients will receive Tadalafil and Pembrolizumab
Population:	This study will enroll patients with head and neck squamous cell carcinoma not amenable to curative intent therapy with combined positive score (CPS) ≥1.
Centers:	University of California San Diego Moores Cancer Center
Selected Inclusion Criteria: *Refer to* Section 3.0 *for the complete and detailed list of inclusion/exclusion criteria.*	*Disease Related* • Histologically or cytologically proven squamous cell carcinoma of the head and neck not amenable to curative intent • Presence of measurable tumor lesions per RECIST criteria v1.1 • Detectable PD-L1 expression in tumor defined as CPS≥1 • Life expectancy greater than 12 weeks. *Laboratory* • Adequate hematologic, hepatic, and renal function • Negative serum or urine pregnancy test for women of child bearing potential *Demographic* • Men and women ≥ 18 years of age.

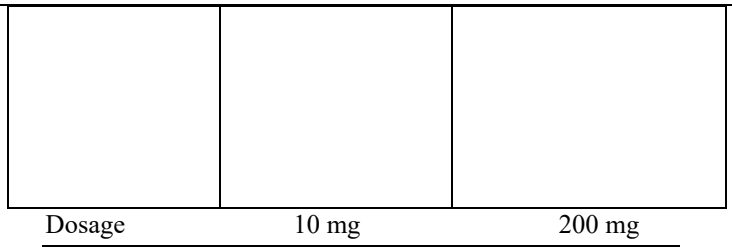
	• Eastern Cooperative Oncology Group (ECOG) performance status of 0-1

Selected Exclusion Criteria:	*Disease-Related* • Prior therapy with an PD-1 or PD-L1 inhibitor in the recurrent or metastatic setting • Uncontrolled central nervous system metastases (stable metastases permitted) • Active autoimmune disease *Concurrent Conditions* • Chemotherapy ≤28 days prior to first administration of study treatment and/or monoclonal antibody ≤8 weeks prior to first administration of study treatment. • History of other malignancies, except: • Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician. • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. • Adequately treated carcinoma in situ without evidence of disease. • Medical contraindication to biopsy of target lesion • Prior daily use of tadalafil or other long-acting PDE5 inhibitors for one month or greater within 3 months of trial enrollment • Current use of all other long-acting PDE5 inhibitors. • Known severe hypersensitivity to tadalafil or any of the excipients of this product • Current treatment with nitrates • Current systemic treatment with a potent cytochrome P450 3A4 (CYP3A4) inhibitor such as ketoconazole or ritonavir. • Current treatment with guanylate cyclase (GC) stimulators such as riociguat. • History of hypotension and/or blindness and/or sensorineural hearing loss during prior treatment with tadalafil or other PDE-5 inhibitors • History of known hereditary degenerative retinal disorders, including retinitis pigmentosa • Prior history of non-arteritic anterior ischemic optic neuropathy • Pregnant or breastfeeding; a negative pregnancy test is required within 14 days of randomization for all women of childbearing potential. • Concurrent malignancy or a history of previous malignancy treated with curative therapy within the last 3 months (other than squamous/basal cell cancer of the skin or cervical cancer), for which the survival prognosis is < 5 years • Treatment with a non-approved or investigational drug within 30 days before visit • Incomplete healing from previous oncologic or other major surgery

	• As judged by the investigator, any evidence of severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, cardiac, hepatic, or renal disease or impairment) • Evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the subject to participate in the trial • History of significant hypotensive episode requiring hospitalization • History of stroke within prior 6 months. • History of acute myocardial infarction within prior 3 months, uncontrolled angina, uncontrolled arrhythmia, or uncontrolled congestive heart failure • History of any of the following cardiac conditions: • Left ventricular outflow obstructions, such as aortic stenosis and idiopathic hypertrophic subaortic stenosis • Angina requiring treatment with long-acting nitrates • Angina requiring treatment with short-acting nitrates within 90 days of planned tadalafil administration • Unstable angina within 90 days of visit 1 (Braunwald 1989) • Positive cardiac stress test without documented evidence of subsequent, effective cardiac intervention • History of any of the following coronary conditions within 90 days of planned tadalafil administration: o Myocardial Infarction o Coronary artery bypass graft surgery o Percutaneous coronary intervention (for example, angioplasty or stent placement) o Any evidence of heart disease (NYHA ≥ Class II as defined in Protocol Attachment LVHG.3) within 6 months of planned tadalafil administration • Concurrent systemic immunosuppressant therapy (e.g., cyclosporine A, tacrolimus, etc., or chronic administration of >10 mg/day of prednisone or equivalent) • Prior organ transplantation • Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). • Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.

Study Treatment:	Treatment will be administered in 21 day cycles with the following dose schedule, for up to 24 months:

Drug	***Tadalafil (10mg po daily) for up to 12 months***	**Pembrolizumab will be administered at 200 mg IV q3 weeks for 24 months (35 cycles)**

Safety Plan:	Data safety and toxicity will be continuously monitored in the study under the guidance from the Data Safety Monitoring Committee.

Statistical Methods and Data Analysis:	This is a phase II study to investigate both safety and efficacy. The primary safety endpoint is the rate of DLT. The primary efficacy endpoint is overall survival (OS) at one year Secondary endpoints include progression free survival, best overall response rate by RECIST 1.1 and tolerability. Safety will be assessed by computing the DLT rate every 6 months, assuming an expected Grade 3 or 4 toxicity rate of 17% for Pembrolizumab alone. A Pocock sequential stopping boundary will be used, which will stop the trial early with 56% probability, and with < 2 expected excess events, if the rate of DLT is elevated to 30%. The trial will stop early with 89% probability and < 1 expected excess event if the DLT rate is elevated to 40%. If safety is satisfied, the primary efficacy analysis will use a Simon optimal design, testing one-year OS against a 51% null survival rate and a 74% alternative rate (survival with tadalafil and Pembrolizumab combination). [1] The Simon optimal 2 stage design will examine OS once 14 patients have been recruited. An OS rate of 8/14 or greater will result in study continuation. If 19 or more subjects experience survival of at least 12 months among these 30 subjects, the null hypothesis will be rejected and the conclusion will be that the survival rate is significantly elevated above 51%. Demographic and clinical characteristics of the patients will be summarized by treatment group using frequency counts and percentages, means and standard deviations or medians and interquartile ranges, as appropriate. Best overall response will be determined by RECIST 1.1 and will be summarized as proportion with 95% confidence intervals. Adverse events will be summarized by grade, type and patient. Progression-free survival, overall survival, and duration of response will be described by Kaplan-Meier models to plot these endpoints and estimate median times with a 95% confidence interval. Safety will be evaluated according to the CTCAE v5.0. Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests throughout the conduct of the study. Laboratory test abnormalities will be reviewed for clinical significance and only those deemed clinically significant will be reported as adverse events.
Sample Size Determination	Up to 30 patients will enroll on this trial, depending on initial safety assessment.

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1. OBJECTIVES

1.1 Primary Objective

To determine the efficacy for the combination of tadalafil and pembrolizumab, as assessed by the overall survival (OS) at 12 months post-enrollment.

To determine the safety for the combination of tadalafil and pembrolizumab, as assessed by the rate of dose limiting toxicity (DLT) at least possibly related to study treatment.

1.2 Secondary Objectives

Secondary objectives are to assess:

- Response rate by RECIST 1.1
- Progression-free survival
- Safety and toxicity profile
- Duration of response

2. BACKGROUND

2.1 Head and Neck Squamous Cell Carcinoma

Head and neck cancer is the sixth most common cancer worldwide with the predominant histology involving squamous cell carcinoma (HNSCC). Within the United States, HNSCC accounts for 3% of all cancers diagnosed annually and 2% of cancer-related deaths.[2] The majority of patients with HNSCC initially present with locally advanced disease. Despite aggressive, combined modality treatment, a significant proportion of patients will develop recurrent or metastatic (R/M) disease that is no longer amenable to curative therapy.[3] Existing treatment options including platinum based doublets, EGFR inhibition, and immunotherapy, but outcomes are generally poor, and most patients die within a year of diagnosis of R/M HNSCC.[4,5] Targeted immunotherapy promoting anti-tumor T-cell activity initially demonstrated improved survival and durable objective responses in advanced melanoma [12]. As PD-L1 expression is observed in close to 68% of HNSCC patients regardless of HPV status [13, 14], targeting PD1/PD-L1 in HNSCC was also a rational approach for study. Initially, Pembrolizumab was studied in a Phase Ib study in patients with recurrent/metastatic disease [15]. In this study a significant clinical benefit with a response rate of close to 18% as well as a prolonged PFS was noted in heavily pretreated patients. Furthermore, the benefit was comparable between HPV-positive and negative groups. Pembrolizumab is now approved for use in recurrent or metastatic platinum refractory disease. In addition, the results from Checkmate-141, a phase III trial randomizing patients with recurrent or metastatic platinum-refractory HNSCC to Nivolumab versus investigator's choice of chemotherapy, has shown a doubling of the 1-year overall survival (36.0% versus 16.6%, p= 0.01); this occurred regardless of p16 status [16]. Based on

these data Pembrolizumab is approved in patients with recurrent or metastatic platinum refractory HNSCC.

Recently, data from Keynote-048 have been released, demonstrating improved overall survival for single agent pembrolizumab compared to standard of care cytotoxic chemotherapy in first line, recurrent/metastatic head and neck squamous cell carcinoma with PD-L1 expression. [1] Single agent pembrolizumab demonstrated a 51% 12 month OS vs. 43.6% for EXTREME regimen (combination Cetuximab, carboplatin/cisplatin, and 5-fluorouricil), as well as superiority of pembrolizumab with a 30.2% vs 18.6% 24 month OS (p=0.0086). In addition, 12 month progression free survival was superior in the pembrolizumab arm (19.6% and 11.2% at 12 and 24 months, respectively) compared to the EXTREME arm (11.9 and 5.4% at 12 and 24 months, respectively), HR 1.16 (1.16 (0.96-1.39, 95% CI)) although not statistically significant. In addition, grade 3-5 toxicity in the pemrolizumab arm was 16.7% compared to 69% in the EXTREME arm.

These data define a new standard of care of single agent pembrolizumab as first line therapy in PD-L1 expressing recurrent or metastatic head and neck squamous cell carcinoma.

2.2 Pembrolizumab

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Other checkpoint inhibitors, including PD-1 inhibitors nivolumab and PD-L1 inhibitor durvalumab, have also been studied in head and neck cancer. Pembrolizumab and Nivolumab have shown activity in large trials and have been FDA approved for use in recurrent and metastatic HNSCC.

For the most comprehensive nonclinical and clinical information regarding Pembrolizumab background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology refer to the latest version of the pembrolizumab Investigator's Brochure.

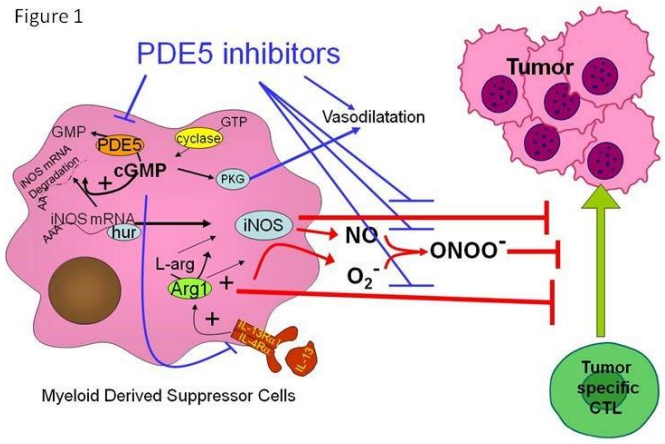
2.3 Tadalafil

Tadalafil is a PDE5 inhibitor marketed in pill form for treating erectile dysfunction (ED) and for the treatment of pulmonary arterial hypertension. In October 2011 the U.S. Food and Drug Administration (FDA) approved Cialis for treating the signs and symptoms of benign prostatic hyperplasia (BPH) as well as a combination of BPH and erectile dysfunction when the conditions coincide.

For the most comprehensive nonclinical and clinical information regarding tadalafil background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology refer to the latest version of the tadalafil Package Insert.

2.4 Antitumor immune effects of tadalafil

Figure 1



Efforts to augment anti-tumor immunity need to focus on overcoming the immunosuppressive mechanisms that currently represent the greatest barrier to clinically effective immunotherapy. Murine as well as human data are increasingly shedding light on putative targets and potential therapeutic interventions aimed at reversing NO production or arginase activity in MDSC-mediated immunosuppression. In fact, *in vitro* studies employing either L-norvaline or L-NMMA –inhibitors of arginase-1 or iNOS, respectively, augmented antigen specific responses. [6] However, their use in the clinical setting proved excessively toxic resulting in increased mortality. [7] Nitroaspirin derivatives have also been shown to reduce arginase-1 expression and to augment T cell function when combined with a DNA-based vaccine[8]. However, the absence of a measurable anti-tumor effect when administered as a single agent coupled to its unavailability for clinic studies limits its overall use. In attempting to develop a therapeutic strategy that can be quickly tested clinically, we focused on phosphodiesterase-5 (PDE5) inhibitors. As shown in **Figure 1,** PDE5 blockade increases intracellular cGMP which, in turn, destabilizes NOS2 mRNA by reducing the ubiquitous mRNA binding protein, human antigen-R (HuR) [9]. HuR binds the AU-rich elements in the 3'untranslated region (UTR) thereby increasing the mRNA half-life [10]. Through this mechanism, destabilization of NOS2 mRNA via PDE5 inhibition would abrogate NO-mediated immunosuppression more effectively than would the competitive inhibition of NO itself. However, considering the role of arginase-1 in MDSC-mediated immunosuppression, we also examined the impact of PDE5 inhibitors on Arg1 and found a significant reduction in its expression in MDSCs in the presence of sildenafil. One explanation is that high levels of cGMP induced by PDE5 blockade reduces cytosolic Ca^{2+} concentrations [11] leading to a reduction in the calcium-dependent protein kinase C (PKC) activity [12] that in turn prevents upregulation of IL-4Rα [13].

Clinical trials at Johns Hopkins and the University of Miami employed phase II, biomarker endpoint designs that treated patients for a brief 2-3 week interval prior to institution of standard therapy. [14,15] The Johns Hopkins clinical trial was conducted to test the hypothesis that a PDE5 inhibitor could be used to augment systemic immune function through inhibition of the cancer induced MDSCs. Placebo or tadalafil 20 mg QD was administered for 2 weeks prior to surgery

or radiation therapy in patients with head and neck squamous cell carcinoma (HNSCC). The major endpoints of the Johns Hopkins study were laboratory endpoints aimed at demonstrating the ability of PDE5 inhibition to modify endogenous immune function in tadalafil vs placebo treated patients as measured by peripheral T cell activation and other measures. The University of Miami used similar time intervals but the primary endpoint included assessment of tadalafil induced augmentation of tumor infiltrating lymphocytes (TILs) in primary tumors treated with placebo vs. tadalafil and functionally measuring the response of patients T cells to autologous tumor lysate from the patient's primary tumor. In addition the University of Miami study employed two doses of tadalafil, 10 mg QD vs 20 mg QD.

In the Johns Hopkins trial, tadalafil augmented immune response, increasing ex vivo T-cell expansion to a mean 2.4-fold increase compared with 1.1-fold in control patients ($P = 0.01$), reducing peripheral MDSC numbers to mean 0.81-fold change compared with a 1.26-fold change in control patients ($P = 0.001$), and increasing general immunity as measured by delayed type hypersensitivity response ($P = 0.002$). Tumor-specific immunity in response to HNSCC tumor lysate was augmented in tadalafil-treated patients ($P = 0.04$). These findings demonstrate that tadalafil augments general and tumor-specific immunity in patients with HNSCC and has therapeutic potential in HNSCC. Of note, the effects of tadalafil on immune parameters were independent of tumor site and HPV status.

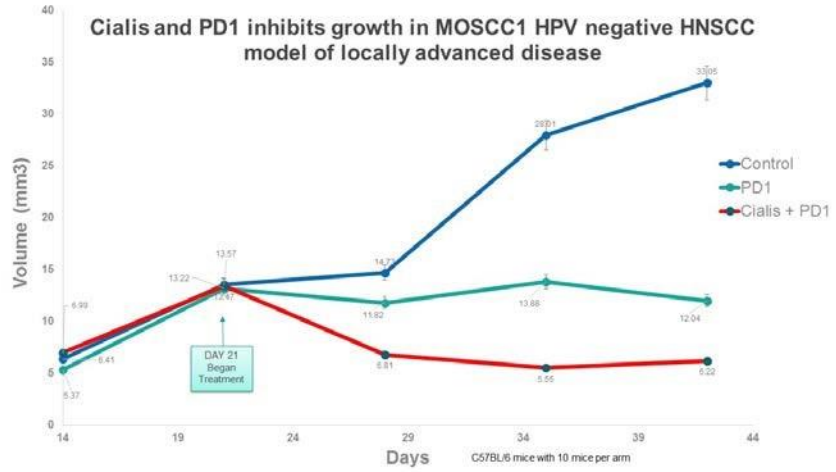
In the University of Miami trial, MDSCs were characterized in primary HNSCC specimens and their intratumoral presence significantly correlated with recurrence. Tadalafil treatment was well tolerated and significantly reduced both MDSCs and regulatory T cell concentrations in the blood and in the tumor ($P < 0.05$), and increased CD8+ T-cells in primary tumor. In addition, the concentration of peripheral blood CD8+ T-cells reactive to autologous tumor antigens significantly increased after treatment ($P < 0.05$). Taken together, both of these studies indicate that tadalafil reduces the inhibitory effect of MDSCs on T-cell function and localization to the tumor microenvironment in patients with HNSCC. In addition, no serious adverse events attributable to administration of tadalafil were noted in both of these trials.

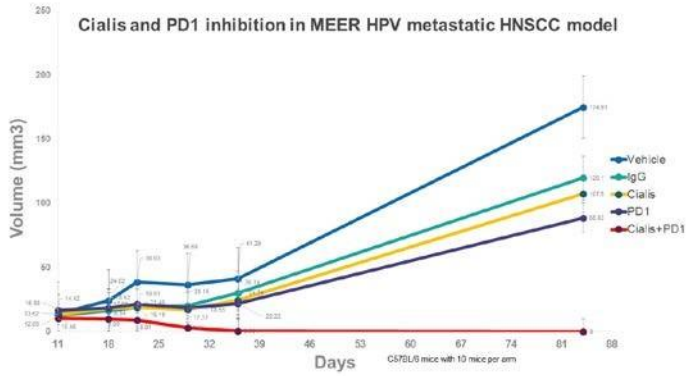
Dosing considerations in the University of Miami demonstrated no difference in immune effects in the 10 mg vs 20 mg dose, and even noted a potential for dosing advantages with the 10 mg QD dose, in that off target effects may be minimized at this dose, without sacrificing the desired immune stimulatory effects of tadalafil.

2.5 Preclinical data

Given the existing clinical trials data demonstrating effectiveness of PD-1 inhibitors in enhancing T-cell response in recurrent metastatic HNSCC, and clinical trials demonstrating inhibition of MDSC mediated suppression of T-cell response by tadalafil in HNSCC, we hypothesized that combination tadalafil and PD-1 inhibition may increase antitumor responses as compared to either agent alone. We based this upon the concept that these two therapies address two different mechanisms of endogenous suppression of T-Cell directed immune response in HNSCC, and

that treatment of MDSC mediated suppression may prevent escape from PD-1 inhibition mediated augmentation of antitumor T-cell response.





To test this hypothesis in an animal model, we used two immune competent, syngeneic mouse models in a C57BL/6 background, including a locally advanced, HPV negative MOSCC model and an HPV16 MEER model. Both models demonstrate a synergistic effect of combination tadalafil and PD-1 inhibition, with complete resolution of tumor in all animals in the MEER tadalafil-PD-1 inhibitor combination arm. This demonstrated in a HNSCC preclinical model animal data, the combination of PD-1 inhibition and PDE-5 inhibition is more effective in exhibiting objective tumor response in comparison to either therapy alone.

2.6 Current trials with combination tadalafil and PD1 checkpoint inhibitors

In a window of opportunity trial, investigators at Thomas Jefferson University are currently enrolling a two arm open label trial (NCT03238365) in which patients are treated with nivolumab alone days 3 and 17 vs nivolumab days 3 and 17 and tadalafil 10 mg po QD on days 3-31. Patients then undergo surgery on day 31 to determine biomarker endpoints. As of 5/22/2108, investigators have accrued 25 patients to the trial, and have only noted one grade 1 toxicity, headache that stopped once tadalafil administration was halted (Adam Luginbuhl, personal communication). As noted, headache is a known toxicity of tadalafil.

2.7 Rationale

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. For platinum refractory patients who develop recurrent or metastatic disease, treatment options are limited. Pembrolizumab is an approved treatment options for these patients, but response rates are low (<20%) and overall survival is short.

Recent phase II trials with tadalafil in HNSCC showed promising results in previously untreated patients in window of opportunity trials, demonstrating immunologic enhancement of T cell response to HNSCC via inhibition of myeloid derived suppressor cells (MDSCs). Immune competent animal models of HNSCC demonstrate that combination PDE-5 inhibitor (tadalafil) and PD-1 inhibitor therapy is more effective than either therapy alone based on the concept of targeting multiple immune repressive abnormalities simultaneously (PD-1 checkpoint and myeloid suppressive pathways). This trial will test the hypotheses that combination PD-1 inhibition and PDE-5 inhibition can be safely co-administered, and that the combination will be more effective than PD-1 inhibition alone in platinum refractory, recurrent/metastatic HNSCC.

We have chosen a tadalafil 10 mg daily dosing, as this has been demonstrated to be equivalent, and possibly superior to 20 mg daily dose by limiting off target effects in a prior HNSCC clinical trial. [14,15] Lower doses, including 5 mg daily dose, do not have data that support immune enhancing effects in head and neck cancer. A 40 mg daily dose of tadalafil is approved and safe for treatment of pulmonary hypertension.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed squamous cell carcinoma of the head and neck not amenable to curative intent therapy.

3.1.2 Presence of measurable disease via RECIST 1.1 criteria. Measurable disease in a previously radiated field is acceptable as long as there has been documented progression since completion of radiation.

3.1.3 Age ≥18 years.

3.1.4 ECOG performance status 0 or 1.

3.1.5 Life expectancy of greater than 12 weeks

3.1.6 Patients must have normal organ and marrow function as defined below:

absolute neutrophil count	≥1,500/mcL

Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL
total bilirubin	≤1.5 x upper limit of normal (ULN)
AST(SGOT)/ALT(SGPT)	≤2.5 × ULN or ≤5 x ULN (for subjects with documented metastatic disease to the liver)
creatinine clearance	≥30 mL/min (according to Cockcroft-Gault formula)

3.1.7 Archived tumor specimen available for correlative analysis or biopsy accessible disease

3.1.8 Detectable PD-L1 expression in tumor defined as combined positive score (CPS) ≥1.

3.1.9 Negative serum or urine pregnancy test for women of childbearing potential

3.1.10 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for at least 60 days after final treatment on study. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

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

3.2 Exclusion Criteria

3.2.1 Prior therapy with a PD-1 or PD-L1 inhibitor in the setting of recurrent or metastatic squamous cell carcinoma of the head and neck

3.2.2 Chemotherapy within 28 days prior to first administration of study treatment and/or monoclonal antibody therapy within 8 weeks prior to the first administration of study treatment.

3.2.3 Uncontrolled central nervous system metastases. Stable, asymptomatic brain metastases not requiring escalating steroid doses are permitted.

3.2.4 Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

3.2.5 Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible

3.2.6 Prior organ transplantation including allogenic stem-cell transplantation

3.2.7 Active infection requiring systemic therapy

3.2.8 Known history of testing positive for HIV or known acquired immunodeficiency syndrome

3.2.9 Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)

3.2.10 Vaccination within 4 weeks of the first dose of Pembrolizumab and while on trials is prohibited except for administration of inactivated vaccine

3.2.11 As judged by the investigator, any evidence of severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, cardiac, hepatic, or renal disease)

3.2.12 History of significant hypotensive episode requiring hospitalization

3.2.13 History of stroke within prior 6 months.

3.2.14 History of any of the following cardiac conditions:

- Left ventricular outflow obstructions, such as aortic stenosis and idiopathic hypertrophic subaortic stenosis
- Angina requiring treatment with long-acting nitrates
- Angina requiring treatment with short-acting nitrates within 90 days of planned tadalafil administration
- Unstable angina within 90 days of visit 1 (Braunwald 1989)
- Positive cardiac stress test without documented evidence of subsequent, effective cardiac intervention
- History of any of the following coronary conditions within 90 days of planned tadalafil administration:
- Myocardial Infarction
- Coronary artery bypass graft surgery
- Percutaneous coronary intervention (for example, angioplasty or stent placement)
- Any evidence of heart disease (NYHA≥Class II as defined in Protocol Attachment LVHG.3) within 6 months of planned tadalafil administration

3.2.15 Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >10 mg/day of prednisone or equivalent)

3.2.16 Prior solid organ transplantation

3.2.17 Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5.0 Grade ≥ 3)

3.2.18 Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 3 months prior

to enrollment), unstable angina, congestive heart failure within 6 months of planned tadalafil administration (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

3.2.19 Persisting toxicity related to prior therapy (NCI CTCAE v. 5.0 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.

3.2.20 Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

3.2.21 History of other malignancies within the past three years, except:

- Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated carcinoma in situ without evidence of disease.

3.2.22 Medical contraindication to biopsy of target lesion

3.2.23 Prior daily use of tadalafil or other long-acting PDE5 inhibitors for one month or greater within 3 months of trial enrollment

3.2.24. Current use of other long-acting PDE5 inhibitors.

3.2.25 Known severe hypersensitivity to tadalafil or any of the excipients of this product

3.2.26 Current treatment with nitrates

3.2.27 Current treatment with guanylate cyclase stimulators such as riociguat.

3.2.28 Current systemic treatment with a potent cytochrome P450 3A4 (CYP3A4) inhibitor such as ketoconazole or ritonavir

3.2.29 History of hypotension and/or blindness and/or sensorineural hearing loss during prior treatment with tadalafil or other PDE-5 inhibitors

3.2.30 History of hereditary degenerative retinal disorders, including retinitis pigmentosa

3.2.31Use of alpha-blockers or α-adrenoreceptor antagonists

3.2.32 Daily intake of 5 or more alcoholic drinks

3.2.33 Prior history of non-arteritic anterior ischemic optic neuropathy

4. TREATMENT PLAN

4.1 Dosing and Agent Administration

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Dose Schedule		
	Tadalafil (PO daily, days 1-21 of 21 day cycle)	***Pembrolizumab (IV on days 1 of 21 day cycle)***
Dose	10 mg	200 mg

Each cycle of therapy will be 21 days.

4.2 Pembrolizumab Administration

Pembrolizumab will be administered 200 mg IV once every three weeks. The recommended dose of pembrolizumab is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression
Premedication: In order to mitigate infusion-related reactions, a premedication with an antihistamine and with acetaminophen 30 to 60 minutes prior to the first four infusions of Pembrolizumab is mandatory (25-50 mg diphenhydramine IV or oral and 500-650 mg acetaminophen IV or oral). Premedication should be administered for subsequent pembrolizumab infusions based upon clinical judgment and presence/severity of prior infusion reactions. This may be modified based on local treatment standards and guidelines, as appropriate.

- ***Setting:*** Pembrolizumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

- ***Observation period:*** Following pembrolizumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

Pembrolizumab will be supplied as standard of care drug obtained from commercial sources by the infusion pharmacy.

4.3 Tadalafil Administration

Tadalafil will be administered in pill form of 10 mg. Patients will be instructed to take their assigned dose once daily. Patients will be encouraged to take their dose at approximately the same time each day.

Tadalafil will be supplied by Lilly.

If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. Tadalafil can be swallowed with water but cannot be crushed or dissolved in water.. If the patientis unable to swallow the pills, the medication can be provided in the form of oral suspension.
Patients will be instructed to keep a diary of pill compliance and pill counts will be monitored by study personnel.

4.4 Definition of Dose-Limiting Toxicity (DLT)

Toxicities will be described according to NCI-CTCAE version 5.0. Dose-limiting toxicity is defined as toxicity that is possibly, probably, or definitely attributable to the study regimen in the opinion of the principal investigator and that is:

- Grade 3 or higher non-hematologic toxicity excluding nausea and vomiting and skin rash
- Grade 4 neutropenia, febrile neutropenia, or grade 4 thrombocytopenia
- Grade 3 or higher nausea and vomiting that cannot be controlled within two weeks with anti-emetics
- Grade 4 skin rash

As an exception, if the toxicity is regarding as being possibly related to the study regimen but in the opinion of the principal investigator is felt to be more likely related to a concurrent medication, the underlying malignancy, a co-morbid condition, or some factor other than the study regimen, the principal investigator may choose to not regard it as a DLT for the purposes of the study.

Any DLT that occurs within the first cycle of therapy (21 days) will be used to make decisions about proceeding to the subsequent cohort.

4.5 General Concomitant Medication and Supportive Care Guidelines

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted.

4.5.1 Medication Interactions – CYP3A Inhibitors/Inducers

Tadalafil is primarily metabolized by CYP3A. Coadministration with a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of tadalafil in healthy subjects by 87%.

Concomitant use of strong CYP3A inhibitors (including clarithromycin, indinavir, itraconazole, ketozonale, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole) should be avoided during therapy with tadalafil. Patients will also be told to avoid grapefruit or grapefruit juice during therapy.

Coadministration of tadalafil with a strong CYP3A inducer can decrease the plasma exposure of tadalafil. Concomitant use of strong CYP3A inducers (phenytoin, rifampin, carbamazepine, and St John's Wort) should be avoided. Concomitant use of moderate CYP3A inducers (bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also decrease the plasma exposure of tadalafil and should be avoided.

A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

4.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

If a patient discontinues tadalafil of the study drugs for toxicity reasons, the patient may continue treatment with pembrolizumab, provided the treating clinician agrees.

Patients may continue treatment following progression if the principal investigator and the treating clinician believe the patient continues to benefit from therapy.

4.7 Duration of Follow Up

Patients will be followed for up to 2 years for survival status after removal from study treatment or until death, whichever occurs first. These follow-ups may occur by phone and will occur about every 3 months. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

4.8 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed above applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5. DOSE MODIFICATIONS

Dose reductions are permanent once instituted. If it is unclear what medication is causing toxicity, dose modifications will be discussed between the treating clinician and the principal investigator.

5.1 Dose Modifications for Pembrolizumab

Please refer to the Pembrolizumab Investigator Brochure for toxicity management algorithms which include specific treatment guidelines. These algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study chair is recommended.

In all of the tables for dose modification and holds in this section, the guidelines are for adverse events thought at least possibly attributed to study drug. Generally we strongly encourage early evaluation while withholding drug, and appropriate treatment as indicated in the management tables and event specific guidelines.

ALL OTHER EVENTS	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below). Resume at same level at investigator discretion.
Grade 3	Off protocol therapy (exceptions as noted below)
ALL OTHER EVENTS	**Management/Next Dose for Pembrolizumab**
Grade 4	Off protocol therapy
Recommended management: As clinically indicated	

Exceptions:

- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

- Any grade 2-4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, transfusion or insulin or that does not require treatment does not require hold/discontinuation.
- Tolerable and clinically stable grade 2 toxicities attributed to study drug may remain on study with PI approval (e.g. thrombosis that is being anticoagulated).

Skin Rash and Oral Lesions	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	No change in dose *
Grade 2	Treatment may continue at investigator discretion. A short course of steroids is permitted. If treatment is held, resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off protocol therapy
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines	

Liver Function AST, ALT, Bilirubin	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	Treatment may be continued at investigator discretion. Dose level is maintained.
Grade 2	Hold until ULN or baseline. Resume at same dose level.
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. **LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.	
Recommended management: see Hepatic AE management algorithm	

Diarrhea/ Colitis	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	Symptomatic treatment but continue therapy. No change in dose
Grade 2	Hold until baseline. No change in dose
Grade 3	Hold until baseline. No change in dose.

Grade 4	Off protocol therapy
See GI AE Algorithm for management of symptomatic colitis. Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

Symptomatic Pancreatitis	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	Continue therapy.
Grade 2	Continue therapy.
Grade 3	Patients who develop symptomatic pancreatitis or DM should be taken off treatment
Grade 4	Patients who develop symptomatic pancreatitis or DM should be taken off treatment
Patients with any grade lipase/amylase elevation may continue treatment at investigator discretion if asymptomatic. Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm	

Pneumonitis	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO2. Resume no change in dose after pulmonary and/or ID consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes pembrolizumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off protocol therapy if steroids are required.
Grade 3	Hold dose pending evaluation. Refer to Appendix III for diagnostic and treatment guidelines.
Grade 4	Off protocol therapy
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not	
respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary Adverse Event Management Algorithm	

Other GI N-V	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. For a second occurrence of a grade 3 event, patients should go off protocol therapy.
Grade 4	Off protocol therapy.
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	No change in dose.
Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume at same dose level.
Grade 4	Hold until ≤ Grade 2. Resume at same dose level.
Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation	

Neurologic events	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline.
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy)
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, Myasthenia Gravis should be off study.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Pembrolizumab**
≤ Grade 1	Asymptomatic TSH elevation * May continue therapy pending evaluation, consider endocrine consult
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids patients must be stable off steroids for two weeks. Resume at same dose level.
Grade 3	See Appendix III for diagnostic and management algorithm.
Grade 4	See Appendix III for diagnostic and management algorithm.
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	
Recommended management: See Endocrine Management Algorithm	

Renal	**Management/Next Dose for Pembrolizumab combination**
≤ Grade 1	May continue therapy per investigator discretion.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off protocol therapy

Infusion reaction	**Management/Next Dose for Pembrolizumab combination**
≤ Grade 1	May continue therapy per investigator discretion.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off protocol therapy
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	
See Section 8. Infusion reactions	

Fever	**Management/Next Dose for Pembrolizumab combination**
≤ Grade 1	Evaluate and continue at same dose level

Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off protocol therapy
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	
See Section 8. Infusion reactions.	

Cardiac*	**Management/Next Dose for Pembrolizumab Cardiac Toxicities**
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.
Grade ≥ 2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥ 2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

- Drug will be held for grade 2 cardiac dysfunction pending evaluation
- Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur
- Treatment with steroids as clinically indicated

If treatment is delayed >6 weeks for an adverse event, the study chair must be consulted for any consideration of further therapy.

Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.

Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.

Any patients who require additional immune suppressive treatment beyond steroids should go off study therapy.

Patients requiring > two dose delays for the same event should go off protocol therapy.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 should be obtained to document baseline. However, if urgent steroid use is clinically required, steroid treatment should not be delayed for bloodwork.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Patients may be dose-delayed for evaluation and restarted depending on results.

Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator.

5.2 Dose Modifications for Tadalafil

Tadalafil has a record of safe administration at study does (10 mg/day). The most common side effects include back pain, dyspepsia, and headache.

In tadalafil clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbency. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported with a low frequency (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required treatment, a mild narcotic (e.g.,codeine) was used. Please refer to the Tadalafil Package Insert for more information.

Any Grade 4 adverse drug reactions (ADRs) require treatment discontinuation with Pembrolizumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management

Any Grade 3 ADRs require treatment discontinuation with tadalafil except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, back pain, nausea, emesis that resolves to Grade ≤ 1
- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration)

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, administration of tadalafil should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment with tadalafil.
- Upon the second occurrence of the same Grade 2 ADR in the same subject, treatment with tadalafil has to be permanently discontinued.

6. ADVERSE EVENTS AND REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

Definitions Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.
- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE.

Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

- **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

Serious Adverse Events

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

- Death

- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization

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

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Severity Criteria (Grade 1-5)
Definitions found in the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) will be used for grading the severity (intensity) of AEs. The CTCAE v5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE v5.0, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the patient's daily activities

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the patient, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the patient's usual daily activity, and require systemic drug therapy or other treatment

- Grade 4 (Life-threatening or disabling AE) – experiences which cause the patient to be in imminent danger of death

- Grade 5 (Death related to AE) – experiences which result in patient death

Causality (Attribution)

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Definitely Related:	The AE is clearly related to use of the investigational product.

Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as

anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation timepoints during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time signed and dated ICF is obtained until 30 days following the last dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported.

All Grade 3 – 5 adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.
If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

6.1 Reporting Requirements for Adverse Events

Expedited Reporting

A. The **Study Chair** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

B. Please see Section 6.2 for expedited reporting to Lilly.

C. The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

D. The **FDA** must be notified according to the following timelines:

- Within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- Within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

Routine Reporting Requirements

A. The **UCSD HRPP** must be notified of any serious adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.
B. The **FDA** must be notified of all non-serious adverse events annually at the time of the annual report.

6.2 Safety Reporting to Lilly

The investigator's primary responsibilities in the safety reporting are to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to the local regulatory authorities and Lilly, as required by local regulations (for regulatory reporting) and IIR agreement (for reporting to Lilly).

The following reportable events must be submitted to Lilly within 24 hours (or immediately for death or life-threatening events) using the provided *Investigator-Initiated Research Serious Adverse Event Form (IIR SAE)* with the *Lilly Reportable Events Fax Cover Sheet* with each SAE submission.

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

Detailed guidance on the safety reporting is provided in the *Safety Reporting Reference Manual.*

Contact information for submission of reportable events to Lilly:

Fax: ARC/Global Patient Safety fax 317-453-3402 or toll free 866-644-16971697

or

E-mail: MAILINDATA_GSMTINDY@LILLY.COM
- PROTOCOL:
- SUBJECT:
- SITE/PI:
- SAE/ONSET:

7. PHARMACEUTICAL AGENT SAFETY INFORMATION

7.1 Pembrolizumab safety information:

Pembrolizumab can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving Pembrolizumab, including grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%) pneumonitis, and occurred more frequently in patients with a history of prior thoracic radiation (6.9%) compared to those without (2.9%). Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for grade 2 or greater pneumonitis. Withhold pembrolizumab for grade 2; permanently discontinue Pembrolizumab for grade 3 or 4 or recurrent grade 2 pneumonitis.

Pembrolizumab can cause immune-mediated colitis. Colitis occurred in 48 (1.7%) of 2799 patients receiving Pembrolizumab, including grade 2 (0.4%), 3 (1.1%), and 4 (<0.1%) colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for grade 2 or greater colitis. Withhold Pembrolizumab for grade 2 or 3; permanently discontinue Pembrolizumab for grade 4 colitis.

Pembrolizumab can cause immune-mediated hepatitis. Hepatitis occurred in 19 (0.7%) of 2799 patients receiving Pembrolizumab, including grade 2 (0.1%), 3 (0.4%), and 4 (<0.1%) hepatitis. Monitor patients for changes in liver function. Administer corticosteroids for grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue Pembrolizumab.

Pembrolizumab can cause hypophysitis. Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving Pembrolizumab, including grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%) hypophysitis. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold Pembrolizumab for grade 2; withhold or discontinue for grade 3 or 4 hypophysitis.

Pembrolizumab can cause thyroid disorders, including hyperthyroidism, hypothyroidism, and thyroiditis. Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving Pembrolizumab, including grade 2 (0.8%) and 3 (0.1%) hyperthyroidism. Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving Pembrolizumab, including grade 2 (6.2%) and 3 (0.1%) hypothyroidism. The incidence of new or worsening hypothyroidism was higher in patients with hnscc, occurring in 28 (15%) of 192 patients with hnscc, including grade 3 (0.5%) hypothyroidism. Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving pembrolizumab, including grade 2 (0.3%) thyroiditis. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue pembrolizumab for grade 3 or 4 hyperthyroidism.

Pembrolizumab can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold pembrolizumab and administer antihyperglycemics in patients with severe hyperglycemia.

Pembrolizumab can cause immune-mediated nephritis. Nephritis occurred in 9 (0.3%) of 2799 patients receiving pembrolizumab, including grade 2 (0.1%), 3 (0.1%), and 4 (<0.1%) nephritis. Nephritis occurred in 1.7% (7/405) of patients receiving pembrolizumab in combination with pemetrexed and platinum chemotherapy. Monitor patients for changes in renal function. Administer corticosteroids for grade 2 or greater nephritis. Withhold pembrolizumab for grade 2; permanently discontinue pembrolizumab for grade 3 or 4 nephritis.

Immune-mediated rashes, including stevens-johnson syndrome (sjs), toxic epidermal necrolysis

(ten) (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and based on the severity of the adverse reaction, withhold or permanently discontinue pembrolizumab and administer corticosteroids. For signs or symptoms of sjs or ten, withhold pembrolizumab and refer the patient for specialized care for assessment and treatment. If sjs or ten is confirmed, permanently discontinue pembrolizumab.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving pembrolizumab. While immune-mediated adverse reactions usually occur during treatment with programmed death receptor-1 (pd-1)/pd-l1 blocking antibodies, they may occur after discontinuation of treatment. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids. Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume pembrolizumab when the adverse reaction remains at grade 1 or less following corticosteroid taper. Permanently discontinue pembrolizumab for any grade 3 immune-mediated adverse reaction that recurs and for any lifethreatening immune-mediated adverse reaction.

The following clinically significant immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients: arthritis (1.5%), uveitis, myositis, guillain-barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials, including classical hodgkin lymphoma (chl), and postmarketing use.

Solid organ transplant rejection has been reported in postmarketing use of pembrolizumab. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with pembrolizumab vs the risk of possible organ rejection in these patients.

Pembrolizumab can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients. Monitor patients for signs and symptoms of infusion-related reactions, including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For grade 3 or 4 reactions, stop infusion and permanently discontinue pembrolizumab.

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic hematopoietic stem cell transplantation (hsct) after treatment with pembrolizumab. Of 23 patients with chl who proceeded to allogeneic hsct after pembrolizumab, 6 developed graftversus-host disease (gvhd) (1 fatal case) and 2 developed severe hepatic veno-occlusive disease (vod) after reduced-intensity conditioning (1 fatal case). Cases of fatal hyperacute gvhd after allogeneic hsct have also been reported in patients with lymphoma who received a pd-1

receptor–blocking antibody before transplantation. Follow patients closely for early evidence of transplant-related complications such as hyperacute gvhd, grade 3 to 4 acute gvhd, steroidrequiring febrile syndrome, hepatic vod, and other immune-mediated adverse reactions, and intervene promptly.

In patients with a history of allogeneic hsct, acute gvhd, including fatal gvhd, has been reported after treatment with pembrolizumab. Patients who experienced gvhd after their transplant procedure may be at increased risk for gvhd after pembrolizumab. Consider the benefit of pembrolizumab vs the risk of gvhd in these patients.

In clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of these patients with a pd-1 or pd-l1 blocking antibody in this combination is not recommended outside of controlled clinical trials.

Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant during treatment, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose of pembrolizumab.

In keynote-006, pembrolizumab was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of pembrolizumab occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions with pembrolizumab vs ipilimumab were fatigue (28% vs 28%), diarrhea (26% with pembrolizumab), rash (24% vs 23%), and nausea (21% with pembrolizumab). Corresponding incidence rates are listed for ipilimumab only for those adverse reactions that occurred at the same or lower rate than with pembrolizumab.

In keynote-189, when pembrolizumab was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous nsclc, pembrolizumab was discontinued due to adverse reactions in 20% of 405 patients. The most common adverse reactions resulting in permanent discontinuation of pembrolizumab were pneumonitis (3%) and acute kidney injury (2%). The most common adverse reactions (≥20%) with pembrolizumab were nausea (56%), fatigue (56%), constipation (35%), diarrhea (31%), decreased appetite (28%), rash (25%), vomiting (24%), cough (21%), dyspnea (21%), and pyrexia (20%).
In keynote-010, pembrolizumab monotherapy was discontinued due to adverse reactions in 8% of 682 patients with metastatic nsclc. The most common adverse event resulting in permanent discontinuation of pembrolizumab was pneumonitis (1.8%). Adverse reactions leading to interruption of pembrolizumab occurred in 23% of patients; the most common (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%). The most common adverse reactions (occurring in at

least 20% of patients and at a higher incidence than with docetaxel) were decreased appetite (25% vs 23%), dyspnea (23% vs 20%), and nausea (20% vs 18%).

In keynote-012, pembrolizumab was discontinued due to adverse reactions in 17% of 192 patients with hnscc. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The most common adverse reactions (reported in at least 20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with hnscc were generally similar to those occurring in patients with melanoma or nsclc, with the exception of increased incidences of facial edema (10% all grades; 2.1% grades 3 or 4) and new or worsening hypothyroidism.

In keynote-087, pembrolizumab was discontinued due to adverse reactions in 5% of 210 patients with chl, and treatment was interrupted due to adverse reactions in 26% of patients. Fifteen percent (15%) of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, pyrexia, dyspnea, gvhd, and herpes zoster. Two patients died from causes other than disease progression; 1 from gvhd after subsequent allogeneic hsct and 1 from septic shock. The most common adverse reactions (occurring in ≥20% of patients) were fatigue (26%), pyrexia (24%), cough (24%), musculoskeletal pain (21%), diarrhea (20%), and rash (20%).

In keynote-170, pembrolizumab was discontinued due to adverse reactions in 8% of 53 patients with pmbcl, and treatment was interrupted due to adverse reactions in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 26% of patients and included: arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment. The most common adverse reactions (occurring in ≥ 20% of patients) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), cough (26%), fatigue (23%) and dyspnea (21%).

In keynote-052, pembrolizumab was discontinued due to adverse reactions in 11% of 370 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (in ≥20% of patients) were fatigue (38%), musculoskeletal pain (24%), decreased appetite (22%), constipation (21%), rash (21%), and diarrhea (20%). Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with pembrolizumab experienced sepsis which led to death, and 3 patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of pembrolizumab occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients, the most frequent (≥2%) of which were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

In keynote-045, pembrolizumab was discontinued due to adverse reactions in 8% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reaction resulting in permanent discontinuation of pembrolizumab was pneumonitis (1.9%). Adverse reactions leading to interruption of pembrolizumab occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). The most common adverse reactions (≥20%) in patients who received pembrolizumab vs those who received chemotherapy were fatigue (38% vs 56%), musculoskeletal pain (32% vs 27%), pruritus (23% vs 6%), decreased appetite (21% vs 21%), nausea (21% vs 29%), and rash (20% vs 13%). Serious adverse reactions occurred in 39% of pembrolizumab-treated patients, the most frequent (≥2%) of which were urinary tract infection, pneumonia, anemia, and pneumonitis.

In keynote-158, pembrolizumab was discontinued due to adverse reactions in 8% of 98 patients (in cohort e) with recurrent or metastatic cervical cancer. Serious adverse reactions occurred in 39% of patients receiving pembrolizumab. The most frequent serious adverse reactions reported included anemia (7%), fistula, hemorrhage, and infections [except urinary tract infections] (4.1% each). The most common adverse reactions (occurring in ≥20% of patients) were fatigue (43%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22% each), and decreased appetite (21%).

It is not known whether pembrolizumab is excreted in human milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with pembrolizumab and for 4 months after the final dose.

There is limited experience in pediatric patients. In a study, 40 pediatric patients (16 children aged 2 years to younger than 12 years and 24 adolescents aged 12 years to 18 years) with advanced melanoma, lymphoma, or pd-l1–positive advanced, relapsed, or refractory solid tumors were administered pembrolizumab 2 mg/kg every 3 weeks. Patients received pembrolizumab for a median of 3 doses (range 1–17 doses), with 34 patients (85%) receiving 2 doses or more. The safety profile in these pediatric patients was similar to that seen in adults treated with pembrolizumab. Toxicities that occurred at a higher rate (≥15% difference) in these patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), hypertransaminasemia (28%), and hyponatremia (18%). Her2/neu = human epidermal growth factor receptor 2.

Please see the latest pembrolizumab investigator's brochure for the latest safety information.

7.1 Tadalafil Safety Information

Tadalafil has been used by approximately 29,549 subjects participating in ongoing and completed clinical trials, and it is estimated that over 72 million patients have been exposed to tadalafil worldwide in the post-approval/post-marketing setting for the treatment of ED, BPH, and PAH. The most common side effects when using tadalafil are headache, stomach discomfort or pain, indigestion, burping, acid reflux, back pain, pain the extremities, muscle aches, flushing, and stuffy or runny nose. These side effects reflect the ability of PDE5 inhibition to cause

vasodilation (cause blood vessels to widen), and usually go away after a few hours. Back pain and muscle aches can occur 12 to 24 hours after taking the drug, and the symptom usually disappears after 48 hours.

In May 2005, the U.S. Food and Drug Administration found that tadalafil (along with other PDE5 inhibitors) was associated with vision impairment related to NAION (non-arteritic anterior ischemic optic neuropathy) in certain patients taking these drugs in the post-marketing (outside of clinical trials) setting. Non-arteritic anterior ischemic optic neuropathy (NAION) is a rare condition and a cause of decreased vision, including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥50. An observational case-crossover study evaluated the risk of NAION when PDE5 inhibitor use, as a class, occurred immediately before NAION onset (within 5 half-lives), compared to PDE5 inhibitor use in a prior time period. The results suggest an approximate 2-fold increase in the risk of NAION, with a risk estimate of 2.15 (95% CI 1.06, 4.34). A similar study reported a consistent result, with a risk estimate of 2.27 (95% CI 0.99, 5.20). Other risk factors for NAION, such as the presence of "crowded" optic disc, may have contributed to the occurrence of NAION in these studies.

Individuals with "crowded" optic disc are also considered at greater risk for NAION compared to the general population; however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including CIALIS, for this uncommon condition.

In October 2007, the FDA announced that the labeling for all PDE5 inhibitors, including tadalafil, requires a more prominent warning of the potential risk of sudden hearing loss as the result of post-marketing reports of deafness associated with use of PDE5 inhibitors.

Tadalafil has been evaluated extensively for safety. Currently tadalafil is marketed FDA approved as 5 mg daily chronic dosing and a 10 mg daily on demand dosage for erectile dysfunction, as well as a 40 mg daily dose for pulmonary arterial hypertension. Studies do not demonstrate any gender related differences in pharmokinetics or adverse effects.[16,17] A recent meta-analysis did not demonstrate any higher cardiovascular risk compared to placebo.[30] Hypotension has been noted in patients concurrently taking nitrates, but these patients are excluded from the study. Non-arteritic anterior ischemic optic neuropathy has been proposed as a rare side effect of PDE5 inhibitors, but definitive data have not been provided due to the rarity of this phenomenon in both the population and subject using PDE-5 inhibitors, as well as the widespread use of PDE-5 inhibitors.[18] Back pain has been noted and our recent trial of tadalafil has noted that three of 40 patients discontinued drug due to back pain, but this side effect resolves within 24 hours of drug discontinuation. A trial of 581 men with benign prostatic hypertrophy with 116 patients assigned to 20 mg daily tadalafil for 12 weeks found that this dose was well tolerated.[19]. Studies that examine 40 mg daily dosing for pulmonary hypertension (Reviewed in reference [20]) have similarly shown that this dose is well tolerated with treatment duration of 4 weeks[21], as well as 16 weeks duration [22,23].

Recent updates on the safety profile of tadalafil demonstrate a small potential increase in risk of non-arteritic ischemic neuropathy but no defined clear risk of sensorineural hearing loss or evidence for increased rates of other adverse effects, including prostate cancer and melanoma risk had been defined, and the FDA has not included prostate cancer and melanoma development as risks associated with tadalafil or use of other PDE-5 inhibitors. [24-26]

For the most comprehensive nonclinical and clinical information regarding tadalafil background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology, refer to the latest version of the tadalafil Package Insert.

7.2 Safety of Combination Tadalafil and PD-1 inhibitor Therapy

In a window of opportunity trial, investigators at Thomas Jefferson University are currently enrolling a two arm open label trial in resectable head and neck squamous cell carcinoma, (NCT03238365) in which patients are treated with nivolumab alone days 3 and 17 vs nivolumab days 3 and 17 and tadalafil po QD on days 3-31. Patients then undergo surgery on day 31 to determine biomarker endpoints. As of 5/22/2108, investigators have accrued 25 patients to the trial, and have only noted one grade 1 toxicity, headache that stopped once tadalafil administration was halted (Adam Luginbuhl, personal communication). As noted, headache is a known toxicity of tadalafil.

8. STUDY PROCEDURES AND CALENDAR

8.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated. The screening procedures include:

- Written informed consent *(within 28 days)*.
- Review of inclusion and exclusion criteria.
- Complete medical/oncology history.
- Demographics.
- Documentation of concomitant medications.
- Complete physical examination, including vital signs and height.
- Performance status assessment.
- Laboratory tests *(within 28 days; pregnancy test within 7 days)*.
- Documentation of tumor staging.
- Tumor biopsy tissue collection.

8.2 Informed Consent

Written informed consent will be given by each patient prior to undergoing protocol specific evaluations and prior to receiving treatment.

8.3 Medical History and Physical Exam

A complete medical history and physical exam consistent with standard of care medical history and physical exam performed in preparation for standard of care Pembrolizumab therapy is performed including vital signs, height, and weight should be obtained within 28 days prior to initiation of therapy on study. ECOG performance status should be recorded at this visit. Of note, no additional history and physical exam for enrollment in addition to routine standard of care laboratory studies will be performed.

8.4 Clinical Laboratory Tests

Blood based clinical laboratory tests that are ordinarily performed for standard of care therapy with Pembrolizumab will be obtained within 28 days prior to the start of protocol therapy. Of note, no additional testing related to enrollment in addition to routine standard of care laboratory studies will be performed. Laboratory studies will be performed on day 1 of each cycle (+/-3 days), on days 8 and 15 of cycle 1 only (+/- 3 days), and at the end of treatment visit. These tests will include:

Hematology profile: complete blood count with differential and platelet count
Chemistry profile: BUN, creatinine, sodium, potassium, carbon dioxide, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase

Additional testing:

Pregnancy test: Serum or urine pregnancy test will be obtained at baseline within 7 days prior to treatment in all women of child-bearing potential at baseline and again at least monthly and more frequently if clinically indicated.
T4 and TSH: within 28 days prior to the start of therapy and every 9weeks (+/- 3 days). Also at the end of treatment (if not performed in the previous 8 weeks)

8.5 Tumor tissue from initial biopsy

Tumor procurement: Patients with accessible tumor of the head and neck that are amenable to biopsy in an office setting, either by transcutaneous core biopsy or transoral biopsy will undergo biopsy of tumor within 28 days prior to initiating study treatment and during Week 4-6 after initiation of therapy. Coordinator will be present at time of biopsy to collect tissue. See lab manual for specific instructions on tissue collection

When possible, 4 core biopsies should be taken for lesions > 1.5 cm, otherwise 2 cores should be taken.

- If 4 cores are obtained, 1 core should be fresh frozen and the rest should be formalin fixed paraffin embedded (FFPE).

- If < 4 cores are obtained, tissue for research should be FFPE after being divided into the research and diagnostic documentation blocks according to the Pathology staff's specifications.

Ten (10) unstained sections (4-5 micron slices) or one (1) 20 micron roll-ups from FFPE tissue are desired.

Fresh frozen samples should be stored in liquid nitrogen and FFPE samples at room temperature until shipment.

8.6 Peripheral Blood Mononuclear Cells (PBMCs)

Blood for PBMCs will be collected prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests) and four weeks after treatment initiation.

Blood samples will be collected in five heparin green top tubes (approximately 50 ml). Samples should be processed the day of collection according to the PBMC isolation protocol in the Laboratory Manual.

PBMCs should be stored at -80°C.

8.7 Buffy Coat

Blood samples will be collected in one EDTA purple top tube (approximately 10 ml) prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests) and four weeks after treatment initiation.

Samples should be processed the day of collection according to the buffy coat isolation protocol in the Laboratory Manual.

Samples should be stored at -80°C.

8.8 Specimen Handling

Sample handling and storage may be coordinated by the locations below:

Sharmeela Kaushal
Moores Cancer Center, 3345/3G, GG
3855 Health Sciences Drive
La Jolla, CA 92093-0819
Phone: 858-822-7661

Califano Lab
Moores Cancer Center
Room 2345, Bay 2L + 2M
3855 Health Sciences Drive,
La Jolla, CA 92037

8.9 Specimen Banking

Patient samples collected for this study will be retained in the UCSD Moores Cancer Center laboratories of Dr. Joseph Califano and Dr. Judy Varner for analysis and future cancer research. Specimens will be stored indefinitely or until they are used up. Samples will be labeled with the protocol number, subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

The study research coordinator at each local site will review their subject's medical record for demographic and clinical information pertaining to the subject's general medical history, diagnosis, and outcomes of any treatments received. This information will be transmitted to and retained by UCSD. Samples and data extracted from the subject's medical record will be coded with a de-identified study number so that the subject's name and identifying information will be removed. A log that links the subject's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the subject's clinical information will be entered by study personnel.

Dissemination of specimens for research is at the discretion of the Study Chair, Dr. Califano. Potential research collaborators outside of UCSD who approach the Moores Cancer Center for clinical specimens will be required to complete an agreement (Material Transfer Agreement or recharge agreement) stating that the specimens will only be released for use in disclosed research, and any specimen left over from research will either be returned to the Cancer Center or destroyed. Any data obtained from the use of clinical specimen will be the property of UCSD for publication and any licensing agreement will be strictly adhered to. These outside collaborators may include for-profit biotechnology corporations interested in collaborating with UCSD investigators in research diagnostic, prognostic assays and drug development.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

8.10 Radiographic Assessment

Imaging studies will be performed within 28 days (+7 days) prior to the initiation of study treatment as per standard of care for patients undergoing therapy with Pembrolizumab. These include a CT of the chest and may include other studies, as clinically indicated. Additional

imaging studies will be performed per standard of care every three months to assess disease status.

8.11 Extended Safety Follow-Up

Given the potential risk for delayed immune-related toxicities, safety follow-up must be 90 days (+14 days) after the last dose of Pembrolizumab administration.

This extended safety follow-up beyond 30 days after last study drug administration may be performed either via a clinic visit or via a telephone call with subsequent site visit requested in case any adverse events of clinical concern (e.g. events possibly related to study drug(s) or serious adverse events) are noted during the telephone call. All patients will be assessed for adverse events during the clinic visit or telephone call. If there are adverse events of clinical concern which require further medical evaluation as determined by a qualified investigator, subjects will come in for a clinic visit and standard of care procedures will be completed. These may include a physical exam, vitals, labs, or other procedures, as clinically indicated.

8.12 Discontinuation from Study Participation

Patients may be removed from study participation for the following reasons (in addition to those listed for discontinuation of study treatment):

- The patient or legal representative withdraws consent for follow-up;
- The patient is lost to follow-up;
- The patient dies;
- It is the decision of the investigator.
- Severe allergic or anaphylactic reaction to pembrolizumab or cialis
- Disease progression prior to surgery
- Pregnancy
- Severe or life-threatening toxicity

8.13 Study Calendar

Required Procedures	Baseline	During Treatment	During Treatment	End of Treatment	Long Term Follow-Up
Timing	Within 28 days prior to treatment initiation unless otherwise specified	Every 3 weeks, ± 3 days, unless otherwise specified	Every 3 months, +/- 14 days, unless otherwise specified	Within 30 days after the last dose of study medication unless otherwise specified	
Treatment History	X				
Medical History	X				
Demographics	X				
Physical Exam	X	X		X	

Vital Signs	X	X		X	
Height	X				
Weight	X	X		X	
ECOG PS	X				
Symptoms & Toxicities	X	X On an ongoing basis throughout study		X	X
Concomitant Medications	X	X On an ongoing basis throughout study		X	
Hematology Profile	X	X*		X	
Chemistry Profile	X	X*		X	
T4/TSH	X	X (every 9 weeks)		X	
Pregnancy Test (serum or urine) for all women of child bearing potential	X Within 7 days prior to treatment	X		If/when clinically indicated	
Tumor Biopsy and blood harvest	X	X**			
Radiology & Tumor Measurements	X Within 35 days prior to treatment	As indicated to assess response as per standard of care	Radiographic studies as clinically indicated		
Tadalafil Compliance		X At each clinic visit			
Extended Safety Follow Up					90 days (+ 14 days) after last dose of study drug+
Subsequent Anticancer Therapy					X
Survival Status					X

* Will also be obtained on days 8 and 15 of cycle 1 only (+/- 3 days)

** Tumor Biopsy and blood collection at Week 4 after first day of treatment (+/- 3 days). A core needle biopsy may be obtained at any accessible tumor site (primary or regional metastatic); ultrasound-may be needed to assist during the biopsy procedure. Blood will be collected regardless of the ability to biopsy.

+Extended safety follow up will include an assessment of adverse events, and may include additional standard of care procedures, if there are clinical concerns.

9. MEASUREMENT OF EFFECT

9.1 Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response every three months plus or minus 14 days.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[27] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

9.1.1 Study populations

Safety population. All patients will be evaluable for toxicity from the time of their first treatment with any agent on this study.

Modified Intent to treat population (mITT). Patients who have measurable disease present at baseline, and have received at least one cycle of therapy 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.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

9.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the*

conditions under which such lesions should be considered must be defined in the protocol.

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.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for nonnodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

9.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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 is preferred to evaluation by 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 (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If 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).

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in

assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDGPET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

9.1.4 Response Criteria

9.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

9.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: 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. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

9.1.4.3 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	
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	
PD	Any	Yes or No	PD	
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

*	See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
**	Only for non-randomized trials with response as primary endpoint.
***	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.

9.1.5 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 progressive 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, including the baseline measurements.

9.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

9.1.7 Overall Survival

Overall survival (OS) is defined as the duration of time from start of treatment to time of death.

10. DATA REPORTING / REGULATORY REQUIREMENTS

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

10.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Patient Registration

All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office before enrollment to the study. Prior to registration, eligibility criteria must be confirmed with the UCSD Study Coordinator. To register a patient, call (858)-246-0357 Monday through Friday, 8:00am-4:30pm Pacific Time. Patients will be given a unique sequential study number at the time of enrollment. UCSD will fax the outside study site for confirmation of patient registration, the patient's study number, and ability to start study treatment.

10.4 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

10.5 Data and Safety Monitoring/Auditing

Data and Safety reporting will be supported by the study statisticians according to the attached monitoring plan (appendix V). Briefly, comprehensive safety and data monitoring reports will

be generated semi-annually for review by the study team before being sent to the UCSD DSMC, described below. The study will use the VELOS electronic data capture system at UCSD.

In addition to adverse event monitoring and clinical oversight by the Study Chair, site principal investigator and co-investigators, quality assurance of the study will be performed by the UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon risk-based assessments.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported annually and will include:

1) the protocol title, IRB protocol number, and the activation date of the study. 2) the number of patients enrolled to date.
3) the date and site of patients' enrollment.
4) a summary of all adverse events regardless of grade and attribution.
5) a response evaluation for evaluable patients when available.
6) a summary of any recent literature that may affect the ethics of the study.

10.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

10.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate apparent immediate hazards/risks to trial subjects without prior IRB approval. Any such emergency modification implemented must be noted and reported to the IRB along the lines of a protocol deviation or violation, depending on the nature of the modification.

10.6.2 Protocol Violations

Any unplanned variance from an IRB approved protocol is considered a violation and must be reported to the IRB in a timely fashion. For the UCSD IRB:

- Major violations must be reported to the IRB within 10 working days of awareness of the violation.
- Major violations include:
    - Instances that have harmed or increased the risk of harm to one or more research participants.
    - Instances that have damaged the scientific integrity of the data collected for the study.

- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

- Minor violations may be reported to the IRB at the time of the continuing review.
  - Minor violations have no substantive effect on the risks to participants or on the scientific integrity of the research plan or the value of the data collected.

10.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB and submitted to the FDA by the Study Chair for approval prior to implementation.

10.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including subinvestigators and other study staff members, adhere to the study protocol and all

FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design

This is an open label, single arm phase II study using a single dose of combination therapy. There is a continuous Pocock stopping boundary for safety, and a Simon minimax 2 stage design for efficacy.

11.1.1 **Primary endpoints**

The primary safety endpoint is the rate of dose limiting toxicity (DLT) at least possibly attributable to study treatment.

The primary efficacy endpoint is overall survival (OS) at 12 months post-enrollment.

11.1.2 **Secondary endpoints**

Secondary endpoints include best response within 1 year by RECIST 1.1, progression free survival, adverse event rates, and tolerability.

11.1.3 **Accrual.**

We anticipate accruing 15 patients per year, over a period of 2 years.

11.1.4 **Safety stopping rule.**

We anticipate the rate of DLT's with Pembrolizumab alone in this patient population will be 17%. [1] Given the extensive safety record of Tadalafil, as well as the prior experience of combination therapy in 25 patients (section 7.3), in which only 1 grade 1 AE was observe, we do not anticipate the baseline rate of DLTs will be increased above 17% with the combination therapy.

We will use a Pocock sequential boundary to monitor the rate of DLTs throughout the study. [28] If at any time the number of DTL's at least possibly attributed to study drug is equal to or exceeds *bn* out of *n* accrued patients in Table 1 below, the study will be halted for safety.

Table 1.

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	9	9	9	9	10	10	10	10	11	11	10	11								
Boundary, b_n	-	-	3	4	4	4	5	5	5	5	6	6	6	7	7	7	7	8	8	8

Number of Patients, *n*	21	22	23	24	25	26	27	28	29	30
Boundary, b_n	9	9	9	9	10	10	10	10	11	11

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	4	4	4	5	5	5	5	6	6	6	7	7	7	7	8	8	8

Number of Patients, *n*	21	22	23	24	25	26	72	28	29	30	31	32	33	34	53	63	37	38	39	04
Boundary, b_n	9	9	9	9	10	10	10	10	11	11										

This stopping rule has 95% probability to continue if the true DLT rate is 17%. On the other hand, if the DLT rate is 30% the study will stop early with 42% probability, and the expected number of subjects accrued would be 24 (assuming most DLT's occur within 30 days).

The stopping rule will be assessed twice per year with a formal safety report, included in the annual DSMB report and the semi-annual study report. Given the anticipated rate of accrual, this will result in assessments approximately every 5 patients accrued.

11.1.5 **Primary safety analysis**

If the study continues without stopping early, the conclusion will be that there is no evidence of an elevated DLT rate due to the combination therapy. At the end of the study, the DLT rate with a 95% confidence interval will be presented, adjusted for the sequential stopping boundary. The safety population will be used for the stopping rule and primary safety analysis.

11.1.6 **Primary efficacy analysis and sample size**

The efficacy analysis will use a two -stage Simon optimal design. [29] In the KEYNOTE-048 study, with a similar patient population (CPS >=1), 257 subjects were treated with

Pembrolizumab alone 200 mg Q3W, and experienced 51% survival at one year postrandomization. [1] Hence the null hypothesis will be 50% survival at one year. With 30 subjects at the final analysis, if the true OS rate is 74%, we will have 80% power to reject the null hypothesis at the 5% significance level.

The analysis will be as follows: at the first stage, 14 subjects will be recruited. The interim analysis will be assessed when the 14th subject has been on study 12 months or has otherwise completed the study. If at this point 8 or fewer subjects have experienced 12 months survival, the study will stop. Otherwise, an additional 16 subjects will be recruited, for a total of 30. If 19 or more subjects experience survival of at least 12 months among these 30 subjects, the null hypothesis will be rejected and the conclusion will be that the survival rate is significantly elevated above 51%. Kaplan-Meier curves and 95% confidence interval for the final survival rate will be given, adjusting for the 2-stage design.

Accrual will not be halted for the interim analysis, but the study stopping rule will be monitored bi-annually in the study safety reports. If at any point it becomes clear that the stopping conditions will be met, the study will be halted. If the null hypothesis is true, the study has 77% chance of stopping early.

11.1.7 **Secondary analyses**

Demographic and clinical characteristics of the patients will be summarized by treatment group using frequency counts and percentages, means and standard deviations or medians and interquartile ranges, as appropriate. Best overall response will be determined by RECIST 1.1 and will be summarized as proportion with 95% confidence intervals. Adverse events will be summarized by grade, type and patient. Progression-free survival, overall survival, and duration of response will be described by Kaplan-Meier models to plot these endpoints and estimate median times with a 95% confidence interval.

Safety will be evaluated according to the CTCAE v5.0. Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests throughout the conduct of the study. Laboratory test abnormalities will be reviewed for clinical significance and only those deemed clinically significant will be reported as adverse events.

All adverse events of any grade occurring in the first 48 hours following combinatorial treatment administration will also be assessed as potential infusion reactions. The number and percent of subjects who develop any adverse event consistent with an infusion reaction will be summarized by overall grade.

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APPENDIX I PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX II ECOG PERFORMANCE STATUS

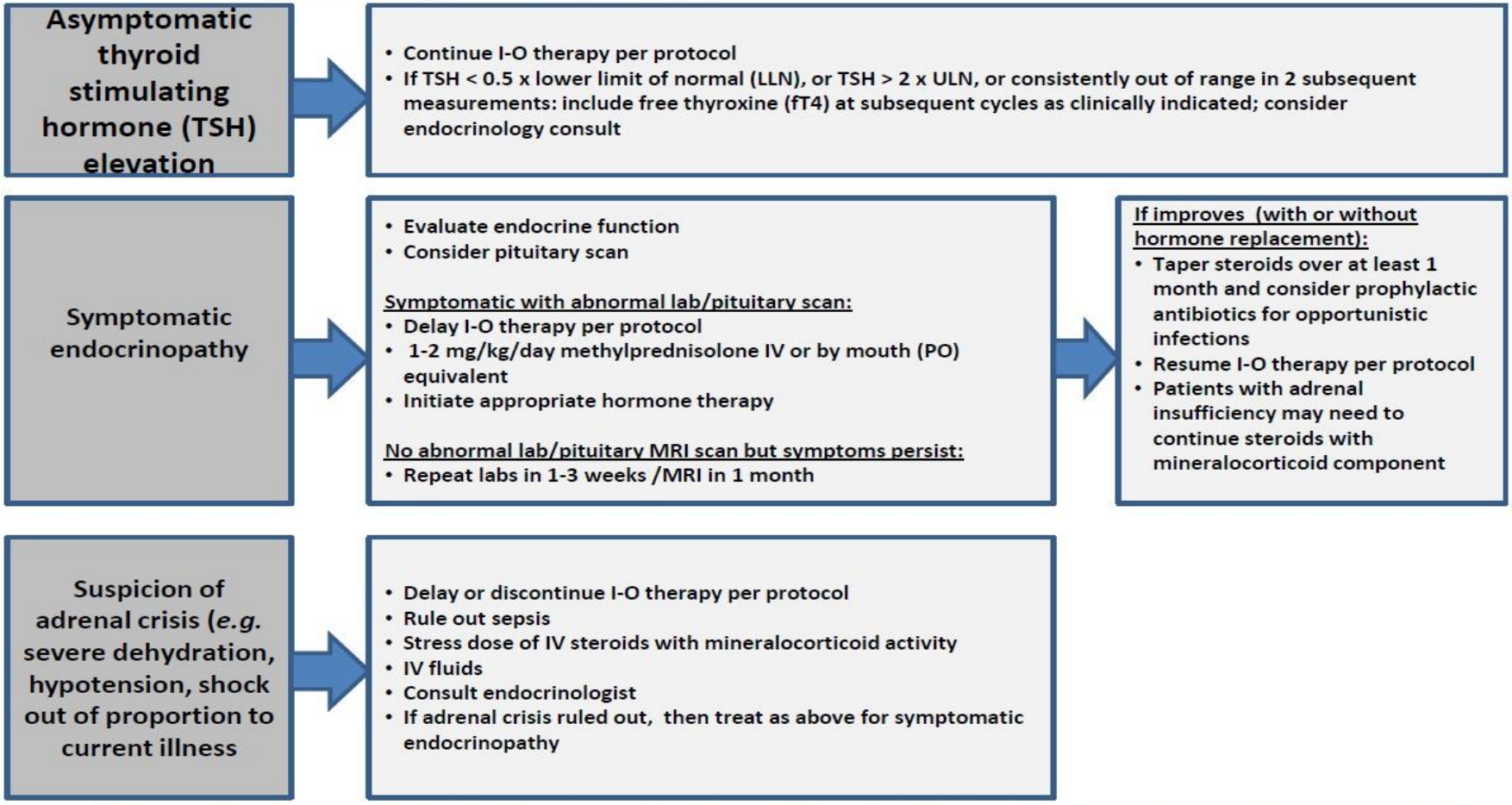
PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX III MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL,

HEPATIC, NEUROLOGICAL, PULMONARY, RENAL, AND SKIN ADVERSE EVENTS

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. **If worsens:** • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	**If improves to baseline:** •Resume I-O therapy per protocol when improved to baseline **If worsens:** • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	**If improves to Grade 2:** • Taper steroids over at least 1 month **If worsens or atypical presentation:** • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

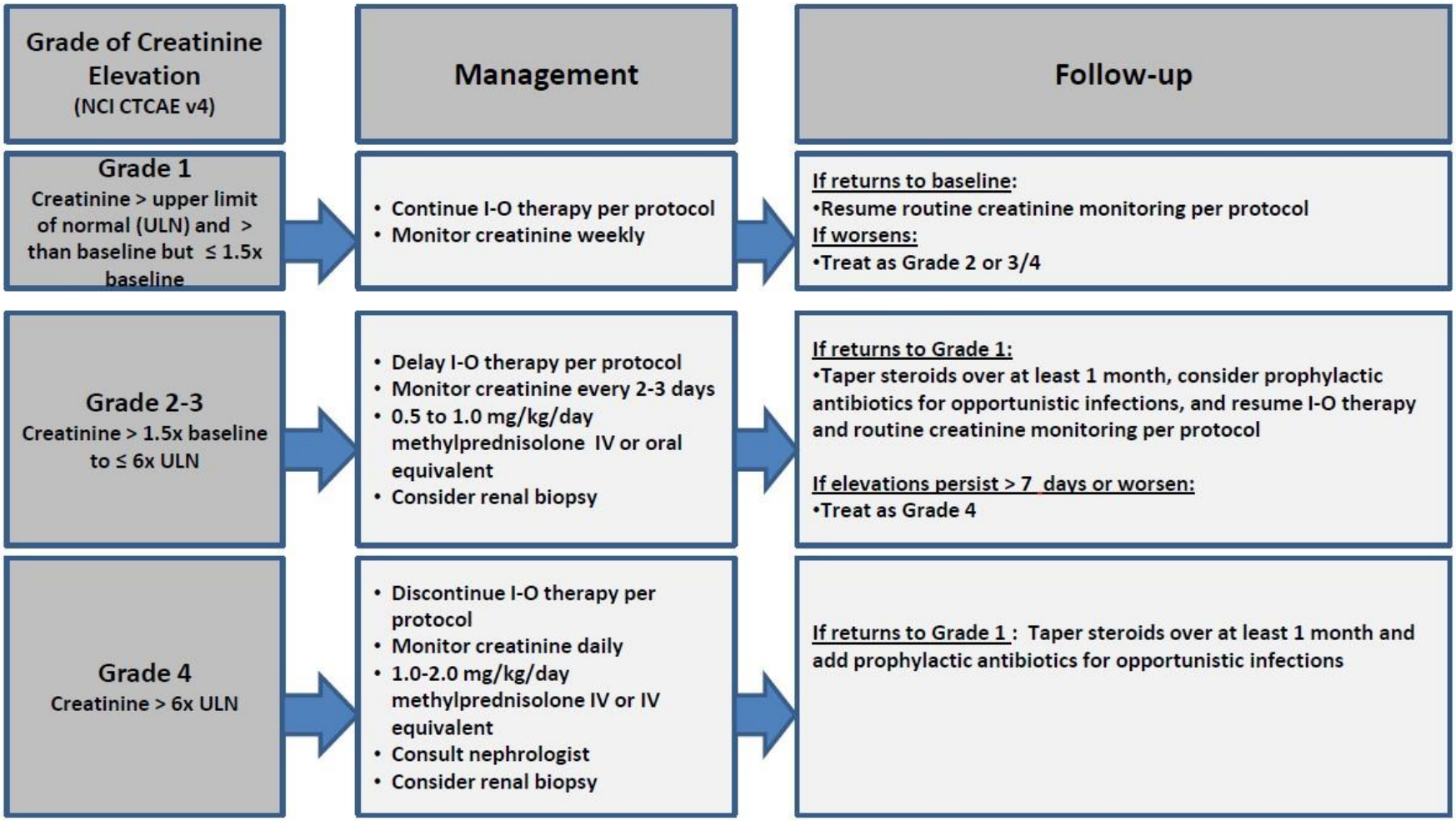
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and Infectious Disease (ID) consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

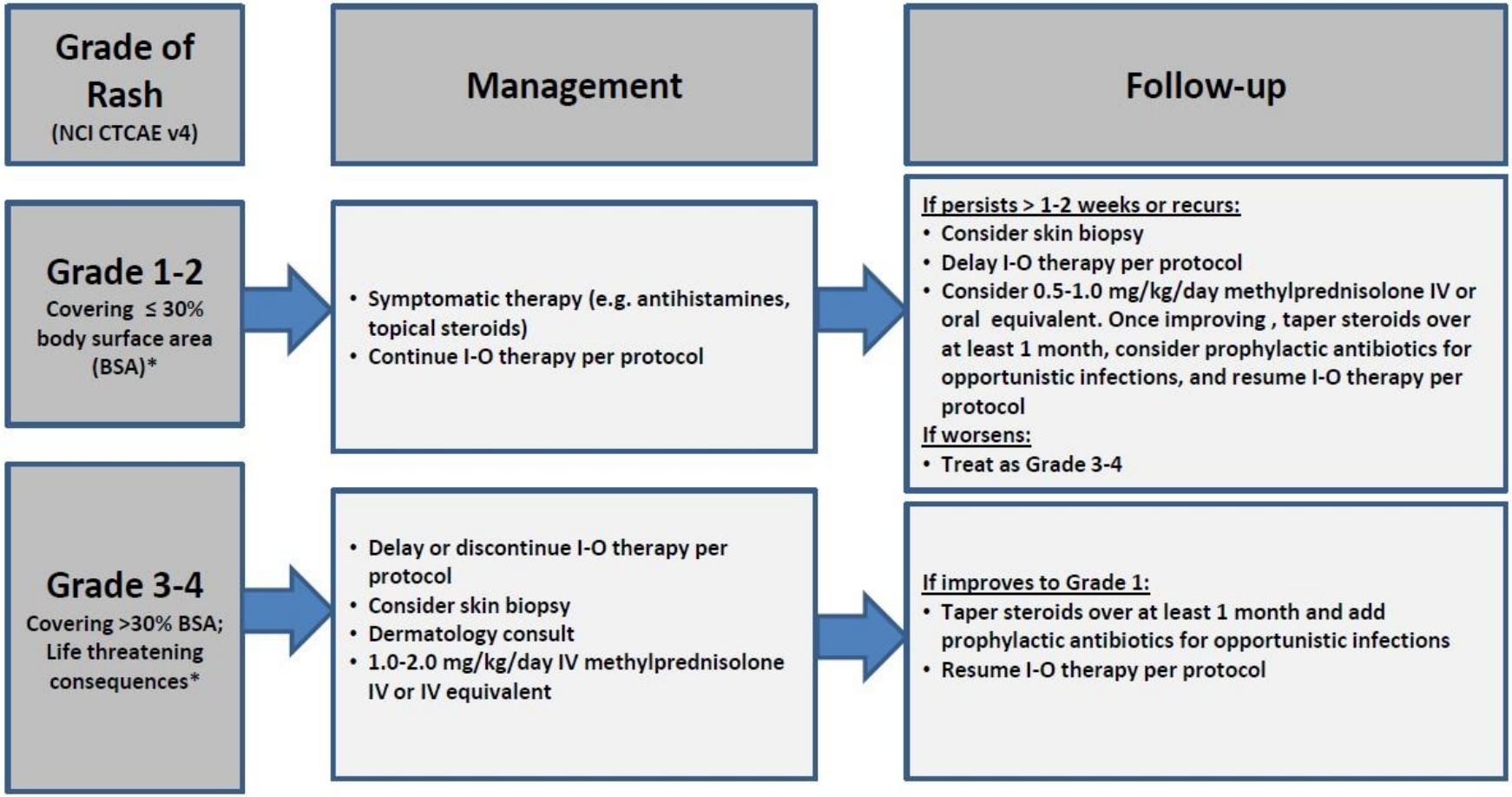
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

APPENDIX IV
INSTRUCTIONS FOR REPORTING PREGNANCIES ON A CLINICAL TRIAL

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on pembrolizumab or within 28 days of the patient's last dose of pembrolizumab must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported as an
Adverse Event

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the Adverse Event report. **What else do I need to know when a pregnancy occurs to a patient?**
- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status in Adverse Events reporting mechanism
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the UCSD DSMB

- *It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial AE report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* AE report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects.

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as "*A death in utero.*"

It must be reported as an Adverse Event as a Grade 4 "*Pregnancy Loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A pregnancy loss should **NOT** be reported as a Grade 5 event as currently the database recognizes this event as a patient's death. **Reporting a Neonatal Death**

A neonatal death is defined in CTCAE as "*A newborn death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational
agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported as an AE AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to pembrolizumab must also be reported as an AE. It must be reported as Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions."

A neonatal death should **NOT** be reported as a Grade 5 event as CTCAE recognizes this event as a patient's death.

APPENDIX V - UCSD Moores Cancer Center Data Monitoring Plan

Title: A Phase II Study of Tadalafil and Pembrolizumab in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

Introduction

This data reporting plan outlines the routine monitoring reports that are to be generated by the study statistician or the study data manager, based on the data that have already been entered into the electronic data capture data base (VELOS).

The purposes of these reports are to monitor the progress of trials and the safety of participants, to assure data accuracy, data completeness and protocol compliance.

All the study personnel listed on the VELOS Clinical study information and personnel contact information page will receive these reports. (see Appendix A).

For an outline of the report see Appendix B.

I. Table of Contents

II. Executive Summary –

The Executive Summary will be an overarching description of the data analyzed.

III. Protocol Synopsis -

The Protocol will be an overarching description of the study.

IV. Study Data Report –

The Study Report will include the following Tables:

- Table 1: Overall Enrollment
- Table 2: Monthly Enrollment
- Table 3: Consent and Treatment Dates
- Table 4: Screen Failures
- Table 5: Off Treatment
- Table 6: Gender, Race, Ethnicity
- Table 7: Age (years)
- Table 8: Subjects Demographics
- Table 9: Deaths
- Table 10: All Adverse Events
- Table 11: Adverse Events Summary
- Table 12: Serious Adverse Events
- Table 13: 12-month Overall Survival

Additional tables related to stopping rules will be added dependent on the study design. This protocol will have an efficacy interim report of 12 month Overall Survival following subject 14; Table 13 will provide this data, when appropriate. This study requires formal semi-annual safety and efficacy reports sent to the Principal Investigator. The UCSD MCC DSMC will be informed of any results from these semi-annual reports that require their attention.

Only, the Principal Investigator will received reports of outcome data and appendices that include treatment assessment, response assessment, baseline characteristics and data issues, as determined by study statistician.

Below has details for each of the tables/reports listed above. The frequencies of running the reports will be modified according to each study protocol.

1. Overall Enrollment - Table 1

- Purpose

To monitor enrollment; to ensure that accrual goals are met in a timely manner; to notify the team when accrual goal is nearing completion

- Components

Accrual (number of patients and percentages) by site (if more than one) and month.

- Frequency: first two week data analysis, semi-annually, annually

2. Study Status Report – Tables 2-5

- Purpose

To provide a summary of the status of study subjects.

- Components

1) Total number of accrual as of date; number of subjects who are on/off study; number of subjects who are still on study treatment (s); number of subjects who are still on study but off study treatment (s).

2) Listings of off study/off treatment with subject ID, date, week and reason.

- Frequency: first two week data analysis, semi-annually, annually

3. Baseline Characteristics Report –Tables 6-8 and Appendix

- Purpose

To provide a summary of subjects' baseline characteristics

- Components

Baseline variables which are crucial to study design and analysis

For categorical variables frequency tables will be generated.

For continuous variables, mean (range) will be reported.

- Frequency: first two week data analysis, semi-annually, annually for general demographics (Tables 6-8); other baseline characteristics will be analyzed in the final report.

4. Toxicity/Adverse Event Report – Tables 9-12

- Purpose:

To monitor toxicities; to evaluate unexpected toxicities; to ensure that toxicity rates are acceptable. All participants receiving investigational agents will be evaluated for safety. This study is under continuous toxicity analysis (Pocock rule).

- Components: adverse events reported to the investigator by participants.

1) Listing of all deaths.

2) Frequency tables of all the signs and symptoms or laboratory toxicities by grade and across grades

3) Listing of all adverse events. The list will include patient number, toxicity name, severity of reaction (grade), relationship to study drug (definitely, possibly, probably, unlikely or not related; or unknown relationship).

- Frequency: first two week data analysis, semi-annually, annually.

5. Stopping Rules (Table 13)

- Components: Analysis of DLTs and 12-month OS

- Frequency: first two week data analysis, semi-annually, annually

6. Treatment and Dose Modifications Report (Treatment Form)

- Purpose: To monitor treatment and dose adjustment

- Components: Listings of study treatment (s) and their corresponding dosages, including treatment start date, treatment modification dates and off treatment date.

- Frequency: first two week data analysis, semi-annually, annually

7. Issues with Data including Data Completeness Report (various data forms)

- Purpose:

To ensure that clinic visits and other endpoint-related visits are conducted according to schedule; that endpoint-related data are collected appropriately and in a timely manner; to correct the database; to make sites and site principal investigators (PIs) aware of specific problems and to ensure that the compliance rate for visits and sample acquisition is high enough to satisfy protocol objectives.

- Frequency: first two week data analysis, semi-annually, annually

Timeline for Reports

Date	Accrual*	Study Status	Baseline Characteristics*	Study Completeness	Toxicity/Adverse Event	Treatment and Dose Modifications
x**	X	X	X	X	X	X
x	X	X	X	X	X	X
x	X	X	X	X	X	X
x	X	X	X	X	X	X
x	X	X	X	X	X	X
x	X	X	X	X	X	X
x	X	X	X	X	X	X
x	X	X	X	X	X	X
x	X	X	X	X	X	X

*****Accrual and Baseline Characteristics Reports may be discontinued following closing the study to accrual

** The first data reports will be two weeks after the study opens or after the first subject

Division of Biostatistics & Bioinformatics

Report Type

Trial: A Phase II Study of Tadalafil and Pembrolizumab in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (UCSD IRB #: 190098)

CONFIDENTIAL DOCUMENT

Date

Principal Investigator: Joseph A Califano III, MD
Statisticians: Karen Messer, PhD and XXX

Contents:

1. Executive Summary

- Report Overview

This report reviews enrollment and safety data available in the study VELOS database as of xxxx (data lock dates will be every six months following enrollment of first patient). Tables are provided in the body of the report.

- Study Site Status

Report of UCSD activation

- Enrollment Status

XXX subjects have been screened for this study.
XXX subjects have been enrolled.

- Off Treatment Status

XXX treated subjects have been discontinued (withdrawn) from the study. XXX treated subjects have completed treatment.

- Stopping/Halting Rules

Safety: We will use a Pocock sequential boundary to monitor the rate of DLTs throughout the study. Safety will be assessed by computing the DLT rate every 6 months. Any DLT that occurs within the first cycle of therapy (28 days) will be used to make decisions.

Efficacy: The primary efficacy analysis will use a Simon optimal design, testing one-year OS. The Simon optimal 2 stage design will examine OS once 14 patients have been recruited. An OS rate of 8/14 or greater will result in study continuation.

- Safety Summary

XXXX adverse events have occurred in XXX subjects. XXX serious adverse events have occurred in XXX subjects.
Of the XX adverse events: XX were mild (grade 1), XX were moderate (grade 2) and XX were severe (Grade 3+).

- Quality Management

Quality management reviews are performed semi-annually and were last completed on xxxx.

2. Protocol Synopsis

Protocol Title: A Phase I/II Study of Tadalafil and Pembrolizumab in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
Principal Investigators: Joseph Califano, MD
Study Sites: Single-center (UCSD)
Study Activation Date:
Planned Accrual: N = 30
Study Design: Open-label phase I, II single arm trial with a Pocock continuous safety stopping rule and a Simon 2 stage efficacy design. All patients will receive Tadalafil and Pembrolizumab
Primary Objective(s): Identify the toxicity for the combination of Tadalafil and Pembrolizumab and assess efficacy
Treatment Description: Treatment will be administered in 21 day cycles with the following dose schedule, for up to 12 months: *Tadalafil (10mg po daily) and* Pembrolizumab will be administered at 200 mg IV q3 weeks for 24 months (35 cycles)
Tadalafil will be supplied by Lilly as 10 mg tablets
Pembrolizumab will be supplied as a clear, colorless liquid formulated for intravenous administration. Commercial supply or drug supplied by Merck will be used.
Primary Endpoint:
The primary safety endpoint is the rate of DLT.
The primary efficacy endpoint is overall survival (OS) at one year

Definition of Dose-Limiting Toxicity (DLT)

Toxicities will be described according to NCI-CTCAE version 5.0. Dose-limiting toxicity is defined as toxicity that is possibly, probably, or definitely attributable to the study regimen in the opinion of the principal investigator and that is:

- Grade 3 or higher non-hematologic toxicity excluding nausea and vomiting and skin rash
- Grade 4 neutropenia, febrile neutropenia, or grade 4 thrombocytopenia
- Grade 3 or higher nausea and vomiting that cannot be controlled within two weeks with anti-emetics
- Grade 4 skin rash

As an exception, if the toxicity is regarding as being possibly related to the study regimen but in the opinion of the principal investigator is felt to be more likely related to a concurrent medication, the underlying malignancy, a co-morbid condition, or some factor other than the study regimen, the principal investigator may choose to not regard it as a DLT for the purposes of the study.

Any DLT that occurs within the first cycle of therapy (28 days) will be used to make decisions about proceeding to the subsequent cohort.

Study Stopping Rules:
Safety: Safety will be assessed by computing the DLT rate every 6 months, assuming an expected Grade 3 or 4 toxicity rate of 17% for Pembrolizumab alone. A Pocock sequential stopping boundary will be used, which will stop the trial early with 56% probability, and with < 2 expected excess events, if the rate of DLT is elevated to 30%. The trial will stop early with 89% probability and < 1 expected excess event if the DLT rate is elevated to 40%. If at any time the number of DTL's at least possibly attributed to study drug is equal to or exceeds *bn* out of *n* accrued patients in Table below, the study will be halted for safety. The stopping boundaries are given below:

Patient enrollment, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	4	4	4	5	5	5	5	6	6	6	7	7	7	7	8	8	8
Patient enrollment, n	21	22	23	24	25	26	27	28	29											
Boundary, b_n	9	9	9	9	10	10	10	10	11											

Efficacy: If safety is satisfied, the primary efficacy analysis will use a Simon optimal design, testing one-year OS against a 51% null survival rate and a 74% alternative rate (survival with tadalafil and Pembrolizumab combination). The Simon optimal 2 stage design will examine OS once 14 patients have been recruited. An OS rate of 8/14 or greater will result in study continuation. If 19 or more subjects experience survival of at least 12 months among these 30 subjects, the null hypothesis will be rejected and the conclusion will be that the survival rate is significantly elevated above 51%.

3. Report Overview

The purpose of this report is to review cumulative enrollment and safety data for the subjects enrolled in the Tadalfil + Pembro study. This report reflects data from the study database as of xxx. Within the body of the report are summary tables of enrollment, demographic characteristics, and adverse events. Readers of this report are asked to maintain the confidentiality of the information provided in this report.

4. Quality Management

4.1 Clinical Trials Office Quality Assurance: This study was monitored by the UCSD Moores Cancer Center CTO xxxxx

4.2 Protocol deviations/violations:

5. **Methods** – Data Set

This report is based on all data downloaded on xxxx from the VELOS portal (https://velos.ucsd.edu).

6. Participant Status

6.1 Overall Enrollment: This section summarizes the participant status and enrollment by study month. Enrollment is defined as XXXX

Table 1: Overall Enrollment

Consented	Eligible	Screen Failures

Table 2: Monthly Enrollment Status

Study Month	Year & Month	N Subjects Enrolled
1		
2		
3		

XX Subjects have been enrolled in X sites since study initiation. This trial is accruing at a rate of X subjects per month.

6.2 Consent and Treatment Dates

Table 3: Consent and Treatment Start Dates

Subject ID	Consent Date	Treatment Start Date

6.3 Screen Failures

Table 4: Screen Failures

Subject ID	Consent Date	Screen Failure Date	Reason for Screen Failure

6.4 **Off Treatment** (Separated by early discontinuation, treatment completion or other reasons, if applicable)

Table 5: Off Treatment

Subject ID	Off Treatment Date	Off Treatment Reason	Duration of Treatment

7. Demographics

7.1 Demographic Summary
Categorical measures: Categorical variables are summarized using frequency tables and percentages by Arm

Table 6: Gender, Race, Ethnicity

	Frequency	Proportion
Gender		
Female		
Male		
Race		
White		
Black, African- American		
Asian		
Native America		
Unknown or Not Reported		
Ethnicity		
Non-Hispanic		
Hispanic		

Continuous measures: Continuous variables are summarized with N, mean, standard deviation, median.

Table 7: Age (years)

	N	Mean	SD	Median
Age				

7.2 Demographic Information for All Treated Subjects

Table 8: Subjects Demographics

Subject ID	Stage	Gender	Ethnicity	Race

8. Safety

8.1 Deaths

Table 9: Deaths

Subject ID	Date of Death	Reason for Death	Within 30 days of last treatment?

8.2 Adverse Events by Stage

Table 10: List of All Adverse Events

Patient Study ID	Stage	AE week	Adverse Event Name	Severity/Grade	Start Date	Stop Date	Attribution

Adverse Events Summary

8.3 Adverse Events Summary

Severity	N Adverse Events
Mild (grade 1)	
Moderate (grade 2)	
Severe (grade 3)	
Life-threatening (grade 4)	
Fatal (grade 5)	
Total	

Note: These are all AEs; SAEs are also reported in next section.

8.3 Serious Adverse Events

Table 12: Serious Adverse Events

Experimental Treatment Arm

Patient Study ID	Serious Adverse Event Name	Severity/Grade	Start Date	Stop Date	Attribution

9 Stopping Rule for safety

Safety stopping rule will be assessed after each patient has reached 28 days. DLT rate will be calculated at every 6 months for the DSMC reviews.

Patient Study ID	Stage	Treatment Start Date	Did Patient have a DLT?	Please specify the DLT

10 Stopping Rule for efficacy: 12 months overall survival

Patient Study ID	Stage	Treatment Start Date	Death Date	Did Patient achieve 12 month survival?

11 Appendices

11.1 Treatment Assessment
11.2 Response Assessment
11.3 Issues with data

BSR data checks include verification of doses, number of appropriate drug and response cycles based on treatment start date, redundant and/or missing data, and other data elements as needed based on study protocol.