Title: Safety and efficacy of nivolumab in treating high-risk oral leukoplakia

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Title: Safety and efficacy of nivolumab in treating high-risk oral leukoplakia

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Study Agents: *Nivolumab; supplied by Bristol-Myers Squibb*

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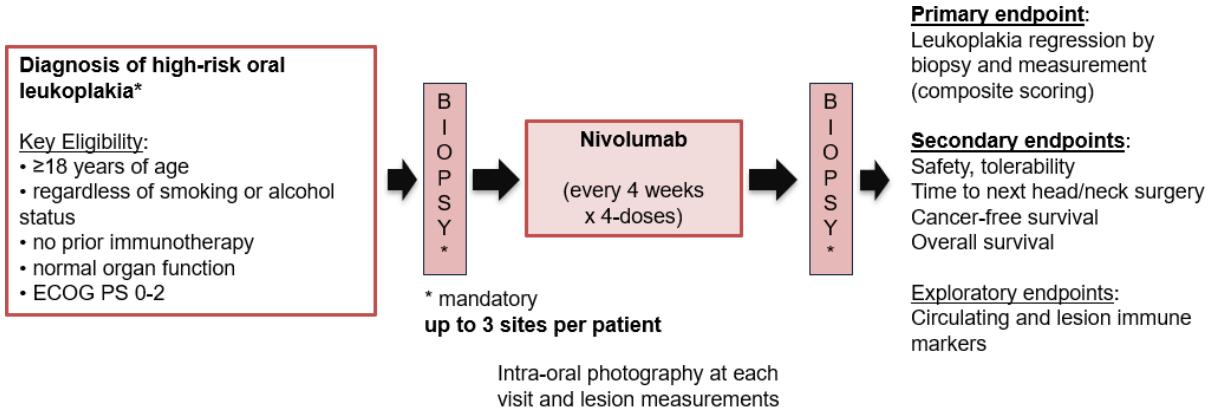
SCHEMA



***Diagnosis of high-risk oral leukoplakia defined by any of the following:**

1. Diagnosis of oral PVL with multifocal lesions (≥2) or contiguous lesions ≥3 cm or a single lesion ≥4 cm in largest diameter (at least one lesion with *any* degree of dysplasia)
2. Diagnosis of oral PVL *without* dysplasia on biopsy but with 4 oral cavity quadrant involvement
3. Diagnosis of leukoplakia in at least 1 lesion with *moderate dysplasia* (without a diagnosis of oral PVL) for which surgery is indicated, but not feasible or patient refused.
4. Diagnosis of erythroplakia or erythroleukoplakia with *any degree of dysplasia* for which surgery is indicated, but not feasible or patient refused.

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1. OBJECTIVES

1.1 Study Design

This is a phase II, open label, non-randomized, trial of nivolumab (anti-PD-1) in patients with high-risk oral (precancerous) lesions, specifically oral proliferative verrucous leukoplakia (PVL), leukoplakia with moderate dysplasia, and erythroleukoplakic lesions. Following initial biopsy of up to 3 sites per patient, four monthly doses of the nivolumab will be given. Patients will be followed for evidence of clinical regression (in bidimensional measurement) of lesions. After treatment, patients will undergo re-biopsy of the same leukoplakia site(s) which will be evaluated for regression of the degree of dysplasia (if applicable). The primary endpoint of the study is to evaluate the best overall response rate to nivolumab in high-risk oral leukoplakia patients. Secondary endpoints will include safety, toxicity assessments, quality of life scores, time to next head & neck cancer surgery, cancer-free survival (CFS), overall survival (OS) , and genomic and immune correlates of response.

We hypothesize that nivolumab will cause regression in both the size and the degree of dysplasia of high-risk oral precancerous lesions, leading to a longer time to the next head & neck surgery, as well as improved quality of life and improved survival.

1.2 Primary Objectives

- To evaluate the efficacy of nivolumab in treating high-risk oral leukoplakia (by bidirectional measurement and degree of dysplasia) based on best overall response

1.3 Secondary Objectives

- To evaluate safety and toxicity, and quality of life scores
- To evaluate the time to the next surgery for a head and neck malignancy
- To estimate CFS from the time of study registration
- To estimate OS from the time of study registration
- To characterize distinct tumor and circulating immunophentoypes and correlate these findings with outcomes

2. BACKGROUND

2.1 Study Disease(s)

Leukoplakia as defined by the World Health Organization (WHO) is “a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer” [1]. Oral proliferative verrucous leukoplakia (PVL) is recognized as an aggressive variant of leukoplakia with a higher malignant potential [2]. Oral PVL can involve a single site, but is frequently multifocal and often occurs on the gingiva, oral mucosa and tongue in both contiguous and noncontiguous regions of the oral cavity [1-4].

Lesions of oral PVL have a nodular or verrucous appearance and affect females more with no racial predilection [5-7]. The mean age at the time of diagnosis is in the seventh decade [8], approximately two-thirds occur in never smokers and there is no substantial association with alcohol consumption [3]. The diagnosis is based on expert oral clinicopathologic examination. Oral PVL is thought to progress in a step-wise fashion from hyperkeratosis or hyperplasia (now termed keratosis of undetermined significance [KUS]), to various degrees of dysplasia, and ultimately carcinoma in situ and/or invasive oral squamous cell carcinoma (OSCC) [8-10]. The estimated pooled prevalence of oral leukoplakia in the general population appears to be between 1.5% (1.4%-1.6%, 95% confidence interval [CI]) and 2.6% (1.7%-2.7%, 95%CI) [11].

The etiology of oral PVL remains largely unknown. In terms of molecular profiling, overexpression of p53 and deletions or mutations of the *p16INK4a* and *p14ARF* have been noted [12-14]. Lesions also develop aneuploidy and alterations in the Mcm2 complex [15, 16]. A causal relationship with the human papillomavirus (HPV) and oral PVL has not been established [13, 17-19]. A recent systematic review of 25 studies on oral PVL showed a mean malignant transformation (MT) rate of 63.9% with a mean follow-up time of 7.4 years [8]. The annual MT rate of oral PVL is approximately 10% per year [10] with an overall 40% mortality rate [3, 8]. Recent data from our group (n = 43) have shown that in patients with oral PVL a median of three biopsies (range: 1-26) was performed before MT occurred [20]. MT to invasive OSCC occurred in 71.4% patients (30/42) after a median of 37 months (range: 1-210) from their initial clinic visit. By far, the most common histopathologic diagnosis from biopsies taken at the initial visit (i.e. baseline) was hyperkeratosis without dysplasia (also known as KUS; n = 22; 56.4%) [21]. This was followed by mild (n = 14; 35.9%), moderate (n = 2; 5.1%) and severe dysplasia (n = 1; 2.6%). In addition to oral PVL, the extent and degree of dysplasia correlates with risk of transformation; and erythroplakia is a clinical feature that portends the highest risk of malignant transformation [10].

Management of high-risk oral leukoplakia conditions remains challenging. In oral PVL in particular, management is complicated by the multi-focality of this condition and surgical treatment has not been shown to impact the natural history of malignant transformation [22]. Patients are monitored closely every 3-6 months (depending of the histopathological diagnosis) with periodic biopsies to rule out dysplasia or invasive OSCC, especially when there has been a change in the character of the lesion(s): such as development of red and/or nodular/verrucous areas, induration and involvement of other sites [10]. Surgery is the most utilized treatment option, but recurrence rates remain high at 71.2%, particularly in oral PVL [8]. Other modalities of treatment that have been reported include: laser ablation, photodynamic therapy and medical therapy although none of these have demonstrated significant efficacy [23-25].

2.2 IND Agents

2.2.1 Nivolumab

2.2.1.1 Mechanism of action and pharmacology

It has become evident that tumor progression is promoted by immune evasion and abrogation of an effective immune response against cancer cells [26]. Mechanisms of tumor evasion include the development of T cell tolerance, modulation of inflammatory and angiogenic cytokines,

downregulation of antigen-processing machinery, and changes in immune checkpoint receptor ligands or receptors that can all facilitate tumor immune evasion [27-29]. These mechanisms serve to define immunotherapy targets for clinical development. Immune checkpoint receptors block normal T cell activation and costimulation to maintain a homeostatic immune response [30]. Programmed cell death protein-1 (PD-1, CD279), one such receptor, is expressed on the surface of immune cells and interact with its cognate ligands on antigen-presenting or tumor cells. High tumor expression of the ligands of PD-1 (PD-L1 or B7-H1/CD274 and PD-L2 or B7-DC/CD273) and/or PD-1 expression by T lymphocytes can attenuate T cell activation and drive T cell exhaustion to favor tumor immune evasion [31]. By modulating these inhibitory immune receptor-ligand interactions, the goal is to overcome tumor mediated immunosuppression and facilitate an anti-tumor response. Preclinical evidence to support the negative regulatory effects of PD-1 comes from murine models. PD-1 knockout mice develop organ-specific autoimmunity which can mimic known autoimmune disease, such as systemic lupus erythematosus and acute graft versus host disease (GVHD) – but this can present at various time points and relies on host genetic factors [32]. Beyond PD-1 deficient models, antibody blockade in several mouse models have demonstrated the emergence of similar autoimmune phenomena [33]. These findings strengthen the argument that PD-1 inhibition permits enhancement of antigen-specific T cell response, but also indicate that responses can be variable and depend largely on underlying host biology.

Efforts have focused on understanding PD-1/L1 expression patterns among various tumor types, in order to predict benefit from PD-1 blocking mechanisms. While estimates of tumor cell PD-L1 expression vary considerably based on tumor type [34, 35], studies have estimated PD-L1 expression in squamous cell carcinoma of the head and neck (SCCHN) at 30–70% with human papillomavirus (HPV) positive tumors more frequently harboring infiltrating immune cells that express PD-1 [36, 37]. Upregulation of PD-L1 expression by tumor cells may offer a strategy for evasion and protect the cell from apoptotic demise mediated by T cells, and itself may facilitate T cell apoptosis [38]. Additionally, elevated PD-L1 expression levels correlate with a poor prognosis in some solid tumor malignancies [39].

Beyond invasive carcinoma of the head and neck, recent studies have suggested that early immunologic intervention may benefit premalignant oral mucosal sites. Preclinical murine models harboring 4NQO-induced oral PVL have been treated with anti-PD-1 therapy and blockade of the PD-1 axis resulted in diminished progression of low-grade oral SCCHN lesions to high-grade lesions [40]. More infiltrating CD8+ T cells and T-regulatory cells were observed in the low-grade lesions following PD-1 blockade. Further, increased production of interferon-γ and granzyme B in the treated mice suggested that CD8+ T cell cytotoxic activity increased as well.

Nivolumab (BMS-936558, MDX-1106) is a fully human monoclonal antibody targeting the PD-1 or CD279 cell surface receptor that binds to PD-1 with nanomolar affinity and a high degree of specificity. This therefore precludes binding to cognate ligands, PD-L1 or PD-L2 [41]. In chronic simian immunodeficiency virus (SIV) infection in macaques, studies have shown that PD-1 blockade using an antibody to PD-1 was well tolerated and resulted in rapid expansion of virus-specific CD8 T cells [42]. PD-1 blockade also resulted in proliferation of memory B cells and increases in SIV envelope-specific antibody. These improved immune responses were associated with significant reductions in plasma viral load and also prolonged the survival of SIV-infected

macaques. In vitro assays have demonstrated the ability of nivolumab to potently enhance T-cell response and cytokine production (such as interferon alpha release); when later given to cynomolgus macaques at high concentrations, there were no adverse immune-related events, independent of circulating levels of anti-nivolumab antibodies [43]. In intravenous (IV) repeat-dose toxicology studies in cynomolgus macaques, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses.

The pharmacokinetics of nivolumab have been reported in human subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as subsequent doses at 2 to 4 week intervals. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The population pharmacokinetic (PPK) analysis suggested that the following factors had no clinically meaningful effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, and PD-L1 expression. Although patient performance status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment did have a mild effect on nivolumab clearance, the effect was not clinically meaningful [41]. Additionally, PPK and exposure response analyses have been performed to support the use of 240 mg IV flat dosing every 2 weeks and 480 mg IV flat dosing every 4 weeks in addition to the 3 mg/kg every 2 week regimen. Using the PPK model, exposure to nivolumab at 240 mg IV flat dose (every 2 weeks) or 480 mg IV flat dose (every 4 weeks) was identical to a dose of 3 mg/kg for subjects weighing 80 kg.

2.2.1.2 Clinical safety

In an early phase I study investigating a single IV infusion of anti-PD-1 (MDX-1106) in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg, followed by a 15-patient expansion cohort at 10 mg/kg (for a total of 39 patients), treatment was well tolerated. There was one serious adverse event, inflammatory colitis, observed in a patient with melanoma who received five doses at 1 mg/kg [44].

In a large registration trial which randomized advanced, platinum-refractory SCCHN patients to either nivolumab or single-agent standard chemotherapy, treatment-related grade 3 or 4 adverse events occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard arm [45]. In the nivolumab treated group, the most common adverse events were fatigue, nausea, rash, decreased appetite, and pruritis. Gastrointestinal events were less common than with standard chemotherapy. Pneumonitis was observed in 2.1% of nivolumab-treated patients and two treatment-related deaths occurred (one from hypercalcemia and one from pneumonitis).

The overall safety experience with nivolumab as monotherapy is based on experience from more than 8,000 subjects treated to-date in patients with varied cancer types. The safety profile appears similar across cancer types [46, 47]. Treatment-related adverse events of grade 3 or 4 were

reported in 7% of patients treated with nivolumab in advanced non-small cell lung cancer (NSCLC) of squamous histology and in 16.3% of unresectable, advanced stage melanoma patients.

2.2.1.3 Clinical efficacy

Results from an early phase I trial demonstrated a wide range of clinical activity, including complete, partial and mixed response rates in advanced solid tumor patients; including individuals with colorectal cancer, NSCLC, melanoma, and renal cell carcinoma (RCC) [44]. Thirty-nine patients received a single IV infusion of anti-PD-1 (MDX-1106) in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg, followed by a 15-patient expansion cohort at 10 mg/kg. Patients with evidence of clinical benefit at 3 months were eligible for repeated therapy. One durable complete response (CR) and two partial responses (PRs; melanoma, RCC) were observed. Two additional patients (melanoma, NSCLC) had significant tumor regression not meeting defined PR criteria. Following this early signal, numerous clinical trials emerged to investigate the clinical efficacy of nivolumab in advanced solid tumor and hematologic malignancies – with nivolumab (Opdivo™) now approved in six cancer types owing to its demonstrated clinical efficacy.

In a randomized phase III study (Checkmate-141) of patients with recurrent or metastatic, platinum-refractory SCCHN, 361 patients were assigned to nivolumab or standard chemotherapy in a 2:1 ratio with a primary endpoint of overall survival (OS) [45]. Nivolumab (at a dose of 3 mg/kg body weight IV) every 2 weeks or standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab) was administered. Additional end points included progression-free survival (PFS), objective response rate (ORR), safety, and patient-reported quality of life (QOL). The median OS was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) in the nivolumab group versus 5.1 months (95% CI, 4.0 to 6.0) in the group that received standard therapy. OS was significantly longer with nivolumab than with standard therapy (hazard ratio [HR] for death, 0.70; 97.73% CI, 0.51 to 0.96; p = 0.01), and the estimates of the 1-year survival rate were approximately 19 percentage points higher with nivolumab than with standard therapy (36.0% vs. 16.6%). Median PFS was 2.0 months (95% CI, 1.9 to 2.1) with nivolumab versus 2.3 months (95% CI, 1.9 to 3.1) with standard therapy (HR for disease progression or death, 0.89; 95% CI, 0.70 to 1.13; p = 0.32). The rate of PFS at 6 months was 19.7% with nivolumab versus 9.9% with standard therapy. The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group. Individuals in the study who were PD-L1 (≥ 1% of tumor or immune cells by immunohistochemistry [IHC]) or HPV positive appeared to have improved outcomes, although benefit was seen regardless of PD-L1 expression or HPV status in some patients. This study led to the approval of nivolumab in this setting in April of 2016.

2.3 Rationale

Oral proliferative verrucous leukoplakia (PVL), localized leukoplakia with moderate dysplasia, and erythroplakia are aggressive oral precancerous entities that are associated with a high rate of malignant transformation: up to 60-70% of affected patients are diagnosed with invasive oral cancer within a period of 3-5 years [5, 8, 9, 48]. The management of oral PVL in particular remains challenging due to the fact that no available treatments impact the natural progression to invasive cancer and there is also no consensus or “best practice” guidelines for treatment of

dysplastic lesions [49]. Current strategies focus on surgical excision, laser ablation techniques, photodynamic and topical therapies with variable success [25, 50-52]. Importantly, surgical excision of oral PVL has not been shown to improve rates of malignant transformation [9]. Therefore, patients are generally monitored with frequent sequential oral biopsies to evaluate for progression to cancer [5, 8]. When cancer is diagnosed, referral to a head & neck surgeon for oncologic resection is warranted. Despite adequate cancer treatment, recurrence rates exceed 70% in this high-risk population [8-10].

The evolution from oral precancerous or dysplastic changes in these conditions to invasive OSCC is not well understood, but is thought to progress in a step-wise accumulation of somatic gene alterations, DNA double-strand breaks and copy-number alterations [53, 54]. More recently, preclinical data has suggested that immune modulation plays a critical role in oral carcinogenesis [55]. With advances in immuno-oncology demonstrating the efficacy of immune checkpoint inhibitors targeting the programmed cell death protein-1 (PD-1) axis in advanced SCCHN [56, 57], there is significant interest in understanding the impact of PD-1 blockade in early SCCHN and in cancer prevention, particularly for those at high-risk for malignant transformation.

Recent data suggests that nearly 50% of high-grade oral leukoplakia samples are ligand of PD-1 (PD-L1) positive [58]. Moreover, PD-L1 positivity and CD8+ T cell count are significantly associated with the degree of dysplasia among these samples ($p < 0.001$) [58]. These findings suggest that anti-tumor immunity can be suppressed through upregulation of PD-L1 among dysplastic lesions which could promote malignant transformation – confirming the importance of immunoediting in oral carcinogenesis. Currently, a phase II trial [NCT02882282] is active but not enrolling patients with oral intra-epithelial neoplasia and the molecular high-risk profile of loss of heterozygosity (LOH) at 3p14 and/or 9p21, plus at least at one additional chromosomal site (4q, 8p, 11p, 13q, or 17p) for patients with no prior oral cancer, or LOH at 3p14 and/or 9p21 for those with a prior history of invasive oral cancer. Eligible patients receive four doses of pembrolizumab. In addition, a phase II trial of pembrolizumab is enrolling patients with a diagnosis of leukoplakia, erythroleukoplakia, or PVL with measurable lesions to receive therapy for 6-months with a primary endpoint of clinical response at 6- and 12-months [NCT03603223]. These studies provide a strong rationale for the early use of therapies targeting the PD-1:L1 axis in patients with high-grade oral precancerous lesions, such as oral PVL. Demonstrated efficacy or a response signal in this critical population would have significant implications regarding immune checkpoint blockade to delay or prevent oral carcinogenesis.

2.4 Correlative Studies Background

Given that response rates to PD-1 blockade in the advanced, platinum-refractory SCCHN setting approach 20%, there is strong interest in identifying biomarkers that predict clinical benefit. In a NSCLC population, PD-L1 expression in at least 50% of tumor cells yielded a response rate of 45.2%, compared with an objective response rate of 19.4% among all treated patients [59]. More recently, whole-exome sequencing of NSCLC tumors treated with PD-1 blockade revealed that higher mutational burden correlated with improved objective response rates [60]. Somatic alterations in tumor cells yield neoantigens which are thought to facilitate antigen-specific CD8+ T cell responses – suggesting that the genomic landscape of the tumor impacts PD-1 response. In SCCHN, stromal or tumor PD-L1 expression does appear to partially impact response, but even

PD-L1 negative patients may respond to treatment – suggesting important mechanisms beyond PD-1:L1 interactions [61, 62].

More recent work has sought to use more comprehensive immune-based metrics to characterize the tumor microenvironment. Cytometric profiling has identified immunologically 'hot' and 'cold' immunophenotypes which may identify tumors more likely to respond to immunotherapies [63, 64]. Studies confirming these findings in head and neck cancer patients are not yet published, although our own preliminary work has shown that a robust CD8+ T cell infiltrate and pattern of immune checkpoint co-expression may predict clinical benefit to PD-1 blockade in an advanced SCCHN population [65]. We hypothesize that similar immunophenotypes can be discerned in early invasive SCCHN samples and even in high-risk oral precancerous lesions. The design of the proposed study will allow evaluation of pre- and post-immunotherapy biopsy samples in high-risk oral leukoplakia patients, permitting investigation of immune microenvironment alterations to potentially identify mechanisms of response. Additionally, whether the circulating peripheral immune environment recapitulates the oral immune microenvironment remains an unanswered question. By evaluating both the oral biopsy and circulating immune profile, we hope to evaluate whether early peripheral blood changes in immune parameters could parallel an early indication of treatment response, avoiding the cost and risk of sequential biopsies. Understanding the genomic determinants which drive immunophenotype appear crucial and therefore whole exome and bulk RNA sequencing are also planned.

3. PARTICIPANT SELECTION

Participants must meet the following eligibility criteria on screening examination to be eligible to participate in the study:

Eligibility Criteria

3.1.1 Subject must have have a confirmed diagnosis of high-risk oral leukoplakia which is defined by *any of the following:*

(1) Diagnosis of oral PVL with multifocal lesions (≥2) or contiguous lesions ≥3 cm or a single lesion ≥4 cm in largest diameter (at least one lesion with any degree of dysplasia)

(2) Diagnosis of oral PVL without dysplasia on biopsy but with 4 oral cavity quadrant involvement

(3) Diagnosis of leukoplakia in at least 1 lesion with moderate dysplasia (without a diagnosis of oral PVL) for which surgery is indicated, but not feasible or patient refused.

(4) Diagnosis of erythroplakia or erythroleukoplakia with any degree of dysplasia for which surgery is indicated, but not feasible or patient refused.

3.1.2 Willing to provide blood and tissue from diagnostic biopsies

3.1.3 Any smoking history is permitted. A history of prior or current tobacco use is not an exclusion criteria. While discouraged, patients are permitted to continue tobacco use while on the study.

3.1.4 Age 18 years or older

3.1.5 ECOG performance status ≤ 2 (Karnofsky ≥60%, see Appendix A)

3.1.6 Participant must have normal organ and marrow function as defined below within 21 days prior to study registration:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,000/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤2.0 g/dL
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– creatinine	within normal institutional limits

OR

– creatinine clearance	≥60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal

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

3.1.8 Women of childbearing potential (WOCBP) must agree to use appropriate method(s) of contraception. WOCBP should plan to use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug

3.1.9 Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 iu/l or equivalent units of hcg) at screening. Pregnancy test will be repeated on the day of the first dose of study drug (before administration), although results of this test are not required for registration.

"Women of childbearing potential (WOCBP)" is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level greater than 40 mIU/mL

3.1.10 Men who are sexually active with WOCBP must agree to use any contraceptive method with a failure rate of less than 1% per year. Men who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men) do not require contraception

See Appendix B for further guidance on contraception.

Exclusion Criteria

3.1.11 Known carcinoma in situ (CIS) or invasive squamous cell carcinoma of the oral cavity. A history of a prior stage III (T1-2N1, T3N0) or IV (T1-3N2, T4N0) invasive head & neck squamous cell carcinoma treated with surgery and radiation with or without chemotherapy. Patients with prior locoregionally advanced tumors treated with surgery alone are eligible.

3.1.12 Existing significant autoimmune conditions. Patients with a history of Hashimoto thyroiditis who are stable on replacement hormone therapy are not excluded. Patients cannot be on long-term (> 4 weeks) corticosteroids at doses exceeding prednisone 20 mg (or its equivalent) prior to enrollment. Short-term corticosteroid dosing is permitted as long as steroids are discontinued within 2 weeks of study registration.

3.1.13 Subject who has had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.1.14 Subject who has been treated with immunotherapy. This includes prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

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

3.1.16 Known human immunodeficiency virus carrier or a diagnosis of immunodeficiency.

3.1.17 Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g., Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA is negative).

3.2.7 A personal history of hematopoietic stem cell or solid organ transplant.

3.2.8 Known non-infectious pneumonitis or any history of interstitial lung disease.

3.2.9 A personal history of other active malignancies, with the exception of non-melanomatous skin cancers, low-risk prostate adenocarcinoma on active surveillance, or treated cancers in remission for the last 5 years.

3.2 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Eligible subjects will be registered by a member of the study team in the Clinical Trials Management System (CTMS) "OnCore". Registrations must occur prior to the initiation of protocol therapy. Any subject not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than nivolumab (BMS-936558) may be administered with the intent to treat the participant's oral high-risk leukoplakia during the course of treatment.

5.1 Pre-Treatment Criteria

Eligibility and exclusion criteria are provided in Section 3. These criteria will be assessed 21 days prior to study registration to establish eligibility and baseline values.

Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments.

Demographic information and baseline characteristics will be collected at the Screening Visit. Standard demographic parameters include age, sex, and race/ethnicity (recorded in accordance with prevailing regulations). Baseline characteristics will include ECOG PS (Appendix A), disease status, and focused medical histories.

5.2 Treatment Regimen

Pre-medications are not required. There is no need to wait for the result of TSH level to treat. Each treatment cycle will be 28 days long. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab. Participants should be carefully monitored for

infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to the algorithm described in Appendix D.

Nivolumab 480 mg will be administered by IV infusion on Day 1 of each 28-day cycle. Treatment with the study drug will continue for a maximum of 4 cycles or until unacceptable toxicity or withdrawal of consent. Nivolumab will be administered over 60 +/-10 minutes via a low protein binding infusion set with 0.2-1.2 micron in-line filter.

5.2.1 Cycle 1, Day 1

If screening assessments occur within a week before start of study treatment, then they may serve as the baseline cycle 1 day 1 visit and cycle 1 day 1 labs do not need to be performed. Day 1 labs do not need to re-meet eligibility criteria.

5.3 Agent Administration

Detailed administration instructions will be provided separately, in the Investigator's Brochures.

5.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of IND agents with other concomitantly administered drugs through the cytochrome P450 system, the Overall PI should be alerted if the participant is taking such agents prior to beginning protocol treatment.

5.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids
- Any anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)

5.4.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 20 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of the first dose of study treatment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses ≤ 20 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

5.4.3 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses ≤ 20 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for

prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Adverse events will be continuously monitored throughout the trial by the study team with decisions made accordingly regarding the study status and patient entry throughout the duration of the trial.

Any adverse event(s) attributed to the study medication should result in a delay in future dosing. Therapy can be resumed at the discretion of the treating physician or PI. Duration of therapy will depend on individual tolerance and response. In the absence of treatment delays due to adverse event(s), treatment may continue for four cycles or until one of the following criteria applies:

- A diagnosis of invasive squamous cell carcinoma of the head and neck is confirmed at any point during study screening or on study. Note: if pre-treatment target lesions are increasing in size during the study period then the patient is permitted to continue with treatment until formal response assessment after the four planned doses of nivolumab. However, it is at the discretion of the treating physician whether to re-biopsy any target site before completion of the four planned doses of study treatment. If the patient develops a new measurable site during the treatment period, the patient can receive the four planned doses of treatment if an on-study biopsy of the new site confirms dysplasia without carcinoma in situ or invasive squamous cell carcinoma. A diagnosis of invasive squamous cell carcinoma at any point during the study warrants referral to a head & neck surgeon for consideration of oncologic resection.

- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements

- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify ***Glenn Hanna, MD***

5.6 Duration of Follow-Up

Participants, regardless if they receive the full course of therapy, will be followed for best overall response and development of first invasive OSCC and for survival for 5 years from the time of study registration throughout the course of the trial. Participants removed from protocol therapy for unacceptable adverse event and if they have not developed first invasive OSCC at time of discontinuation of protocol therapy, will continue to be followed until first invasive OSCC and survival until death or 5 years from study registration (whichever occurs first).

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

There will be no dose reductions for nivolumab permitted. Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Although this is not a phase I protocol, the use of these drugs and the combination in the oral precancerous setting is relatively novel, and therefore we plan to include a safety run-in to ensure that treatment is well tolerated in this setting. A separate safety run in will be performed for the initial study participants, as described in detail in *Section 13,* Statistical Considerations.

Administration of the study drug should be delayed for the following adverse events:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
  Note: see Appendix D for guidelines on managing immune-related toxicities

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria (as described below) are met. Participants with a delay in dosing beyond 10 weeks should be considered for discontinuation of protocol treatment and discussed with the Overall PI.

Subsequent dosing may be re-started if subjects continue to meet laboratory criteria (baseline values). The investigator will determine if subsequent dosing is appropriate for subjects who have laboratory or clinical abnormalities that do not meet dose discontinuation criteria (described below). All related grade 2 toxicities should be discussed with the Overall PI, prior to subsequent dosing.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial.

7.1 Adverse Event Characteristics:

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm].

- **Attribution** of the AE:
    - Definite – The AE is clearly related to the study treatment.
    - Probable – The AE is likely related to the study treatment.
    - Possible – The AE may be related to the study treatment.
    - Unlikely – The AE is doubtfully related to the study treatment.
    - Unrelated – The AE is clearly NOT related to the study treatment.
- In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI

7.2 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

7.3 Expected Toxicities

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list in the Investigator's Brochure or is included in the informed consent document as a potential risk. Management of expected toxicities is described in Appendix D.

Most common adverse reactions (>20%) related to nivolumab were: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia.

The following hospitalizations are not considered SAEs in BMS supported clinical studies:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAES

7.4 Routine Adverse Event Reporting

Investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE version 5.0) will be utilized for AE reporting. The CTEP Active Version of the CTCAE version 5.0 is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7.4.1 Routine Adverse Event Reporting to BMS

Adverse Events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month.

The Adverse Event information required to be sent to BMS is noted in an attached 'Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan' (Appendix D) which describes the method of collection and submission to BMS via the mailbox:

When the file is submitted to BMS, it must be noted that the file contains all "Non Serious Adverse Events" (only adverse events not previously submitted to BMS within the 3 months)

7.5 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 90 days of discontinuation of dosing. All SAEs should be followed to resolution or stabilization.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g., a follow-up skin biopsy). The sponsor-investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

The sponsor-investigator will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email or fax upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

7.6 Expedited Adverse Event Reporting to Overall PI

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 90 days of the last dose of treatment on the local institutional SAE form.

Investigators will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy, using the local institutional SAE form.

7.7 Expedited Adverse Event Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria below for expedited reporting.

Report any unexpected fatal or life-threatening suspected adverse reactions to the Division of Oncology Products 2, Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, no later than 7 calendar days after initial receipt of the information.

Report any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting.

7.8 Expedited Adverse Event Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.9 Expedited Adverse Event Reporting to BMS

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on the MedWatch form (Form FDA 3500) ; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address:

SAE Facsimile Number:

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in section 7.3 and the details can be found in the Investigator's Brochures (IBs), provided by BMS.

Product information table: please also see respective product investigator brochures

Table 1. Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	10 mL vial	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing

8.1 Storage and Stability

Nivolumab must be stored at 2º-8ºC (36º-46ºF) and protected from light and freezing. IV bags containing undiluted and diluted solutions of Nivolumab prepared for dosing may be stored up to 20 hours in a refrigerator at 2°-8°C (36°-46°F) and used within 8 hours at room temperature and under room light. The maximum 8-hour period under room temperature and room light conditions for undiluted and diluted solutions of Nivolumab injection in the IV bag should be inclusive of the product administration period.

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558-01(nivolumab) investigator brochure section for "recommended storage and use conditions".

8.2 Preparation

Dilute nivolumab with either 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP to prepare an infusion with a final concentration ranging from 1 to 10 mg/ml. Mix diluted solution by gentle infusion. Do not shake. The maximum allowable volume of final infusion is 120 ml.

8.3 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.4 Availability

Free of cost, investigational supply of nivolumab, will be provided by Bristol-Myers Squibb.

8.5 Ordering

Dana-Farber Research Pharmacy will request supply of nivolumab from Bristol-Myers Squibb, by submitting an order form, provided by Bristol-Myers Squibb.

8.6 Accountability

Accountability for investigational agents at the study site is the responsibility of the sponsor-investigator. Study drug will be dispensed only to eligible patients by Dana-Farber Research Pharmacy. The appropriate study personnel will maintain records of study drug receipt and dispensing at Dana-Farber Research Pharmacy. A careful record of the inventory and disposition of the agent will be maintained, using the NCI Drug Accountability Record Form (DARF).

8.7 Destruction and Return

Unused supplies and expired supplies of the investigational agents will be destroyed on site, by the Dana-Farber Research Pharmacy, per DFCI institutional policy.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Correlative studies are planned as part of this study. At the time of initial biopsy (before study drug dosing), oral precancerous tissue (obtained from up to 3 sites per patient) will be sent for multiparametric flow cytometry DFCI), a portion of fresh-frozen, paraffin-embedded (FFPE) tissue will be obtained for genomic sequencing and for immunohistochemistry (IHC) for immune marker staining (e.g. PD-1, PD-L1/L2) and/or multiplexed immunofluorescence (MIF). Flow cytometry, sequencing and IHC/MIF data will be gathered to characterize distinct immunophentoypes and these findings will be correlated with outcomes. Additionally, peripheral blood samples will be collected at various time points for circulating immune profiling.

9.1 Biomarker Studies

Oral precancerous high-risk leukoplakia is a requirement to be enrolled on this study. A separate, fresh research biopsy (and up to 3 per patient) is mandatory prior to starting treatment on study, archival tissue will not be accepted. At the time of biopsy, after adequate tissue for pathological assessment has been harvested as deemed appropriate by the proceduralist, remaining tissue will be collected for research purposes. If relevant, tissue may also be obtained at the time of an invasive oral cancer diagnosis for research purposes.

Oral mucosal biopsies should not generally be performed late on Friday afternoons, as there may not be time for processing of fresh tissue samples.

Each oral biopsy and blood sample obtained will be assigned a unique coded identifier in order to preserve the confidentiality of the participant. The coded samples will be linkable to the participant, but the key that links that person to the unique identifier will be stored in a database housed on a server at the DFCI. Access to participant identity will be provided only to the principal investigator and study staff (not laboratory staff). There are multiple firewalls and passwords protecting the data from unwanted viewers. Patient privacy will be maintained by strictly curtailing access to the electronic file via passwords and firewalls. The coded samples will be cryopreserved and stored in secure locked freezers. Once all research is complete, the link between the coded samples and patient identifiers will be destroyed.

At the time of oral mucosal biopsy (see *Study calendar*), 4 cores are requested from the dominant or largest precancerous lesion:

1. 2 cores each in its own Roswell Park Memorial Institute (RPMI) containing 10% fetal bovine serum (FBS) 5 mL microcentrifuge tube for multiparametric flow cytometry
2. 1 core in 10% neutral buffered formalin in a standard orange-top specimen cup for tissue block and slide preparation allowing for immunohistochemistry
3. 1 core in 5 mL of RPMI media in a 5-15 mL conical tube for genomic sequencing

If the patient has 2 or 3 oral mucosal biopsy sites for characterization of dysplasia, only the dominant or largest lesion requires 4 cores for correlative studies. The remaining 1-2 sites are only biopsied to evaluate the degree of dysplasia and monitor for invasive transformation.

At the time of blood sample collection (see *Study calendar*), 2 tubes are requested:

- 2 tubes drawn in 8 mL whole blood, purple top tubes for circulating immune profiling

Multiparametric flow cytometry

At the time of pre- and post-treatment biopsy, two cores of fresh tissue will be allocated to two 1.5 mL centrifuge tubes (one core in each tube) in RPMI containing 10% fetal bovine serum (FBS). The specimen will be de-identified and labeled with the participant's initials, study ID number and the date of acquisition. After collection, the two tubes should be delivered

immediately to the lab of

The specimen must arrive in a timely fashion to facilitate processing for evaluation of immune cells. Tissue will be prepared as a cell suspension that will be stained using fluorescently-conjugated antibody cocktails for human immune markers (surface antibodies include: CD45, CD3, CD4, CD8, CD69, CD38, CCR7, LAG-3, TIM-3, PD-1, CD45RA, CTLA-4, CD16, CD158b, CD158, CD56, CD160, PD-L1, GITR, CD15, CD19, and CD14). Cells will be analyzed within 72 hours of fixation on a BD Fortessa cell analyzer with FACSDiva software v8.0.1 (BD Biosciences) and gated using FlowJo software v10.

Circulating immune profiling

At the time of pre- and post-treatment biopsy and a specified time points during and after treatment, two tubes of peripheral blood (obtained at a minimum of 3 time points during the study) will be obtained per standard collection protocols – drawn in phlebotomy or clinic and captured in 8 mL whole blood, purple top tubes. The volume of blood to be collected per blood draw for study purposes will not exceed 40 mL. The specimen will be de-identified and labeled with the participant's initials, study ID number and the date of acquisition. After collection, the blood sample should be delivered immediately to lab The specimen must arrive in a timely fashion to facilitate processing for evaluation of immune cells. Blood must be spun within 3 hours of collection for 15 min at 3000 rpm. The plasma is then aliquoted into 2 x 60 µL aliquots and immediately frozen at -80ºC. Plasma is thawed on ice prior to usage. 50 µL of plasma is sufficient for each assay, where triplicate measurements per sample per time point are envisaged. Plasma is diluted 1:4 (15 µL in 50 µL reaction) prior to transfer to plate-based assay. We will utilize a multiplex magnetic bead-based sandwich ELISA assay to simultaneously measure the soluble form of 14 immune checkpoint molecules (BTLA, CTLA-4, PD-1, PD-L1, PD-L2, GITR, HVEM, IDO, LAG-3, TIM-3, CD27, CD28, CD80 and CD137). Each bead is encoded with a ratiometric concentration of 2 IR dyes and act as a barcode, unique to each protein. The final detection complex is formed with the addition of streptavidin-phycoerythrin (SA-PE) conjugate, where the phycoerythrin serves as the fluorescent reporter. Plasma concentration levels, measured in pg/mL, for each protein are derived from 5-parameter curve fitting models. Fold change relative to pre-treated baseline are calculated and plotted as log2FC to establish biological significance. The changes in secretion levels will be correlated with tumor immune parameters and clinical response.

Immunohistochemistry

At the time of pre- and post-treatment biopsy, one core of fresh tissue will be allocated to a standard orange-top specimen cup containing 10% neutral buffered formalin. The specimen will be labeled with the participant's initials, medical record number and the date of acquisition. After collection, the specimen will be sent to the Brigham & Women's Hospital (BWH) pathology division for processing. Following standard tissue processing, sectioning and slide preparation for histopathologic review, the specimen will be stored in accordance with BWH protocols (both tissue blocks and tissue slides). At a later time, we will then request tissue block retrieval through the Pathology Specimen Locator Core with preparation of 5 unstained slides through the Specialized Histopathology (SHP) Core service at BWH. SHP will then prepare 1 stained

hematoxylin & eosin slide, 1 slide stained for PD-1, 1 slide stained for PD-L1 and 2 unstained slides will be stored for additional studies. These slides will be retrieved from the SHP in Thorn Building, 6th floor, room 603 at the BWH by the study principal investigator. In collaboration with an oral maxillofacial pathologist, Dr. Sook-Bin Woo of the BWH Department of Oral Medicine and Dentistry, the slides will be analyzed and scored based on stained immune parameters.

Genomic sequencing

At the time of pre- and post-treatment biopsy, one core of fresh tissue will be allocated to 5 mL of RPMI media in a 5-15 mL conical tube for the purposes of DNA and RNA sequencing efforts. Once prepared, aliquoted core material for sequencing will be delivered immediately to the laboratory of Dr. Ravindra Uppaluri at the DFCI

10. STUDY CALENDAR

Screening evaluations are to be conducted within 3 weeks prior to study registration. Procedures done within a week of study registration don't need to be repeated to establish baseline. Scans and x-rays must be done ≤4 weeks prior to study registration. In an event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Each treatment cycle in this study is 28 days long.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Studies	**Screening**	**Enrollment**	**Treatment phase**				**End of Treatment[h]**	**Follow up visit 30 days after the last dose[h]**	**Survival Follow up**
			Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**			
			Day	Day	Day	Day			
Informed consent	X								
Medical History	X								
Physical exam (Ht, Wt, VS, PS)	X		X	X	X	X	X	X	
Routine labs [b]	X		X	X	X	X	X	X	
B-HCG (WOCBP only) [c]	X		X	X	X	X	X	X	
FSH test [d]	X								
ECG	X						X		

Photographs, measurements [e]	X		X	X	X	X		X [h]	X [h]
Biopsy samples [f]	X							X	X [h]
Correlative biopsies [f]	X							X	X [h]
Correlative blood			X	X	X	X		X	
Nivolumab			X	X	X	X			
Quality of life survey [g]	X				X		X	X	
Adverse event evaluation			X	X	X	X	X	X	
Survival Status									X [h]

a) Physical exam is symptom directed. Height measured at screening only.
b) Routine labs include: CBC with differential, LFTs, chemistries, TSH, phosphorous. Baseline HCV antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody testing is required at screening only.
c) Serum or urine within 24 hours prior to first dose.
d) Follicle Stimulating Hormone test will be performed only on women who are under 55 years of age.
e) Color digital photographs capturing all oral precancerous sites but including the entire oral cavity (any site biopsied should be photographed). Bidimensional measurements of each oral precancerous lesion should be obtained and recorded, using the largest maximum diameter of each site.
f) Baseline biopsy can be performed any time after the subject has consented up until C1D1. Archival tissue is not acceptable. Fresh biopsy is mandatory (at up to three sites per patient). Fresh tissue is also collected following completion of treatment. Biopsy will also be recommended if the patient progresses to invasive squamous cell carcinoma of the head and neck. Fresh tissue may also be collected at time of progression.
g) Quality of life surveys will be completed at screening, after 2 cycles of treatment, at the end of treatment, and at 30-day follow-up. Patients will complete the chronic oral mucosal diseases quality of life questionnaire (COMD QLQ [66]). This is a validated instrument that assesses various aspects of oral health and function that has been shown to perform well in patients with oral mucosal diseases, including oral precancerous conditions. *See Appendix C* for the full questionnaire.
h) Participants, regardless if they receive the full course of prescribed therapy, will be followed for best overall response and development of first invasive OSCC every cycle during treatment (including a survival status update). Post end-of-protocol treatment, if first invasive OSCC has not been confirmed, assessments will continue every 3-6 months until best overall response and first invasive OSCC are documented (with survival status updates during this time period as well). After documentation of first invasive OSCC, survival status will continue to be updated every 3 months until death or 5 years from study registration (whichever occurs first). Photographs and measurements may continue at PI discretion after first invasive OSCC and during survival follow up. Clinically indicated biopsies that occur at or following first invasive OSCC can be used for study correlatives at PI discretion during survival follow up.

11. MEASUREMENT OF EFFECT

11.1 Measurement of Effect – OPVL lesions

For the purposes of this study, participants will be re-evaluated for change in the measurements of each oral leukoplakia site at every study visit following initial study drug dosing. In addition, re-biopsy of initial oral leukoplakia sites (up to 3 per patient) will be obtained at the end of treatment, and to development of invasive oral cancer up to 5 years form study registration. Timelines are described in *Section 10*.

Response will be measured by: (1) measuring the change in size of each oral leukoplakia lesion,

and (2) by assessing histopathological change (a change in the degree of dysplasia as defined by histologic features) [modified from Wan der Waal I, et al. *Oral Oncol* 2000; 36(3)264-6]. *See Response Criteria below.*

11.1.1 Definitions

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

Evaluable Non-Target Disease Response. Participants 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.

11.1.2 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 ≥ 10 mm by bidirectional measurements on oral examination. All lesion measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of leukoplakia), including small lesions (longest diameter < 10 mm), are considered non-measurable disease.

Target lesions. All measurable lesions up to a maximum of 3 lesions 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 the degree of high-risk oral leukoplakia, 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 all oral leukoplakia lesions) for all target lesions will be calculated and reported as the baseline sum diameters. 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 leukoplakia) including any measurable lesions over and above the 3 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.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or a digital (photographic) measurement tool. 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. Color photographs of target lesions is preferred at each follow-up visit to accompany measurements.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

STEP 1: Grade each individual lesion by size and histology to achieve the individual score of each site (up to 3 per patient).

Size	**Criteria**
L1	A lesion measuring < 2 cm in largest diameter
L2	A lesion measuring 2-3 cm in largest diameter
L3	A lesion measuring > 3 cm in largest diameter

Histology	**Criteria**
P0	Keratosis of unknown significance with or without mild atypia (hyperkeratosis should not be reactive, such as from friction or factitial injury)
P1	Mild dysplasia
P2	Moderate dysplasia
P3	Severe dysplasia

Examples:
Patient A has 3 sites (1 cm, mild dysplasia = L1P1; 2.5 cm, mild dysplasia = L2P1; 2 cm, severe dysplasia = L2P3)
Patient B has 1 site (4 cm, moderate dysplasia = L3P2)

STEP 2: Score the patients individual sites using the below grid. A higher score reflects more advanced disease.

Points	**Composite of Size / Histology**
2	L1 P0
4	L1 P1
6	L1 P2
8	L1 P3
12	L2 P0
14	L2 P1
16	L2 P2

18	L2 P3
22	L3 P0
24	L3 P1
26	L3 P2
28	L3 P3

Examples:
Patient A has 3 sites (L1P1 = 4; L2P1 = 16; L2P3 = 18; total points = 38 is the composite score)
Patient B has 1 site (L3P2 = 26; total points = 26 is the composite score)

STEP 3: Following nivolumab, repeat measurements and histologic assessments. Recalculate the above score for each patient to assess the change in the composite score. Then calculate the change over the total baseline composite score as a (%) to the first decimal place.

Examples:
Patient A has 3 sites now (1 cm, mild dysplasia = L1P1; 2 cm, no dysplasia = L2P0; 1 cm, mild dysplasia = L1P1)
Patient B has 1 site now (2 cm, moderate dysplasia = L2P2)

Patient A has 3 sites now (L1P1 = 4; L2P0 = 12; L1P1 = 4; total points = 20 is the new composite score)
Patient B has 1 site now (L2P2 = 16; total points = 16 is the new composite score)

Patient A has 3 sites (38 – 20 points = Δ18), 18/38 = 47.4%
Patient B has 1 site (26 – 16 points = Δ10), 10/26 = 38.5%

STEP 4: Using the difference in the composite score for each patient, match to the response grid below.

Definition Best Overall Response

A decrease of > 80% or more	CR
A decrease of 40-80%	PR
Neither PR or PD	SD
An increase of 10% or more	PD

Examples:
Patient A has 3 sites (38 – 20 points = Δ18), 18/38 = 47.4%, called PR
Patient B has 1 site (26 – 16 points = Δ10), 10/26 = 38.5%, called SD

Complete Response (CR): A decrease of >80% in the total composite score, for at least 4 weeks.

Partial Response (PR): A decrease of 40-80% in the total composite score.

Progressive Disease (PD): At least a 10% increase in the total composite score.

(Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions, as assessed visually, for at least 4 weeks.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

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).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial documentation when the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from study registration until first disease progression/diagnosis of invasive OSCC (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 histologic criteria.

Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥ 4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not	No	PR	

	evaluated			
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 weeks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See 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: Participants 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.

Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

11.1.5 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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.

11.1.6 Cancer-Free Survival and Overall Survival

Overall Survival: Overall Survival (OS) is defined as the time from study registration to death due to any cause, or censored at date last known alive.

Cancer-Free Survival: Cancer-Free Survival (DFS) is defined as the time from study registration to development of invasive oral cancer or death due to any cause. Participants alive without disease progression or recurrence (of invasive oral cancer) are censored at date of last disease evaluation.

11.1.7 Time to Next Surgery

Time to Next Surgery: Time to Next Surgery is defined as the time from the first study treatment to any head & neck surgery or resection for biopsy-proven carcinoma in situ (CIS) or invasive oral carcinoma (including all stages).

11.1.8 Quality of life Assessment

Quality of Life Assessment: The chronic oral mucosal diseases quality of life questionnaire (COMD QLQ, *see Appendix C*) will be used to assess the effect of the participants mouth condition on daily life activities. The survey consists of 24 questions with five response options per item. The response for each item is coded from 0 to 4 with "not at all = 0" and "extremely = 4" (at time of scoring, for 3 questions, the likert scale is reversed). The summary of the overall score ranges from 0 to 104, with a higher score indicating a poorer patient-assessed quality of life score.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Study team is responsible for entering data in the eDC system (InForm), within the timeframe, in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that

raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

The primary objective of this trial is to evaluate best overall response rate (CR+PR). A two-stage design (Simon's optimal design) will be used to minimize the number of patients enrolled. Sixteen eligible patients who start protocol treatment are to be accrued in the first stage. If there are ≤ 1 patients with disease in response, accrual to this trial will be closed with the expectation that there is little evidence that the response rate will reach 25%. The probability that the trial will close early is 51.5% if the true response rate is 10%. If there are >1 patients with disease in response, accrual will continue until a total of 33 eligible patients who start protocol treatment are entered. If there are > 5 patients with disease in response among 33 eligible patients who began protocol treatment, further testing of this regimen will be considered. If the true response rate is 25%, the probability of concluding the regimen is effective is 84.3%, if the true response rate is 10%, the probability of concluding the regimen is effective is 9.8%. Allowing for patients to be declared ineligible or to not start protocol treatment after registration, a total of 35 patients will be entered.

The primary efficacy population includes all eligible patients who begin protocol treatment. Best overall response will be summarized as a proportion with a corresponding exact 95% confidence interval (CI) (if the trial closes to accrual after the first stage), or a corresponding 95% (two-stage) CI if the trial closes to accrual after the second stage.

For secondary objectives:

- Adverse events will be classified and graded according to the CTCAE v.5.0. Frequencies of adverse events will be summarized among patients who begin protocol therapy. The following stopping rule will be used to monitor excessive protocol related toxicity: if 3 or more of the first 10 patients who begin protocol treatment experience treatment related toxicities which cause extreme delays (protocol treatment needed to be stopped >10 weeks) or excessive treatment related toxicities, accrual to the trial will be suspended to further evaluate the events and decisions made regarding the overall status of the trial. If the true rate due to toxicity is 10% then the probability of suspending accrual is 7%; if the true rate is 20%, then the probability of suspending accrual is 32%; if the true delay rate is 30% then the probability of suspending accrual is 62%. Adverse events will be continuously monitored throughout the trial by the study team with decisions made accordingly regarding the study status and patient entry throughout the duration of the trial.

• The distributions of time-to-event endpoints will be estimated using the Kaplan-Meier method with corresponding 95% confidence intervals for the median or time-specific event time.

• Another endpoint is to assess quality of life (QOL). QOL will be assessed via self-report questionnaires at the timepoints outlined in the Study Calendar. Descriptive statistics from the questionnaires will be summarized across timepoints of assessment. Rates of drop-out/non-response to QOL assessments and corresponding reason will also be summarized across timepoints of assessment.

• Several correlative studies are also planned. Given the small sample size of this trial, these studies are exploratory. Samples will be collected at baseline and at post-baseline timepoints as outlined in the Study Calendar. Human immune cell markers (see 9.1 Biomarker Studies) from patients with evaluable tumor and peripheral blood samples will be summarized descriptively and graphically. Within subject changes in these markers will also be analyzed. Correlation between immune checkpoint receptor ligands and best overall response will be analyzed. Assuming 27 evaluable patients with baseline and a post-baseline value provides 80% power to detect .58 SD mean difference (Wilcoxon sign rank test two-sided 0.05 alpha level) in any given circulating or tumor immune marker.

With an estimated monthly accrual of 3 patients, the first stage is estimated to complete accrual in approximately 6 months. Due to possible delays in initiation of approval and/or in initiation of accrual itself, accrual to the first stage could take longer. As is customary with this type of design, accrual will be suspended after the first stage (n = 16 eligible patients who begin protocol therapy) in order to assess outcome; however, this suspension is also dependent on the actual observed accrual rate and the number of patients with confirmation of disease response status while the first stage of the trial is accruing.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A 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 B GUIDANCE ON CONTRACEPTION

Highly Effective Methods of Contraception
Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

For WOCBP
Highly effective methods of birth control include the following:
• Progestogen only hormonal contraception associated with inhibition of ovulation
• Hormonal methods of contraception including oral contraceptive pills
(combination of estrogen and progesterone), vaginal ring, injectables, or implants
• Intrauterine devices (IUDs) (hormonal or non-hormonal)
• Intrauterine Hormone-releasing System (IUS)
• Bilateral tubal ligation
• Vasectomy
• Complete abstinence (complete avoidance of heterosexual intercourse)

For male subjects with partners that are WOCBP
• Condom

All male subjects who have partners who are WOCBP must use condoms as their second method of contraception.

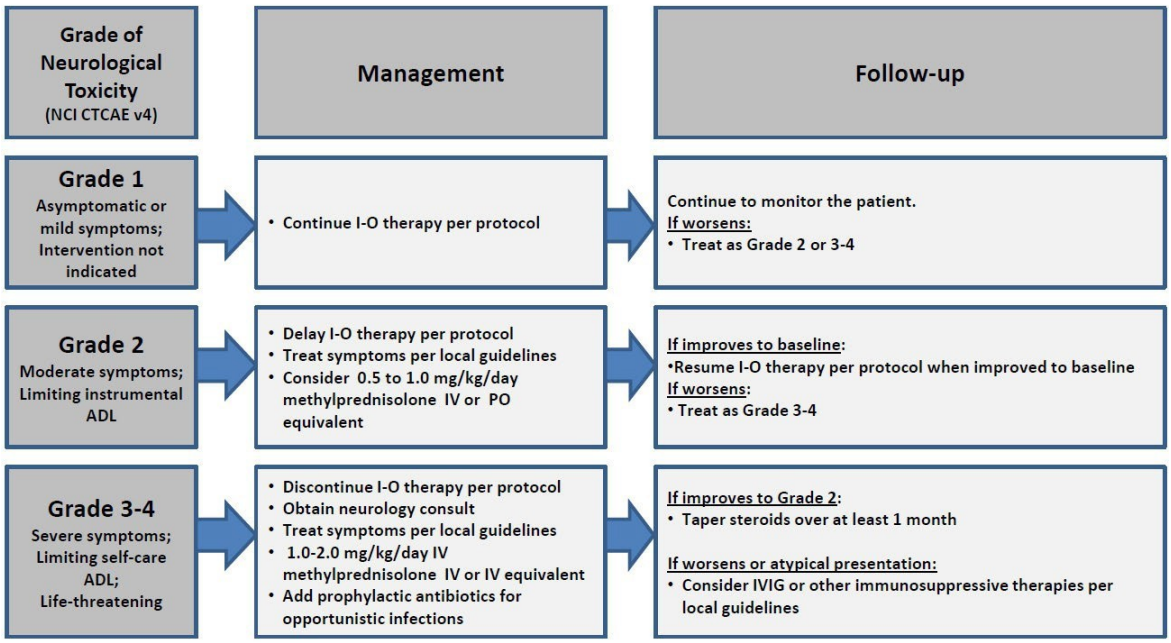
Women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of nivolumab.

APPENDIX C TOXICITY MANAGEMENT ALGORITHMS

- These general guidelines constitute guidance to the Investigator. The guidance applies to all immuno-oncology (I-O) agents and regimens.
- A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.
- Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
- Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.
- The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

Neurological Adverse Event Management Algorithm

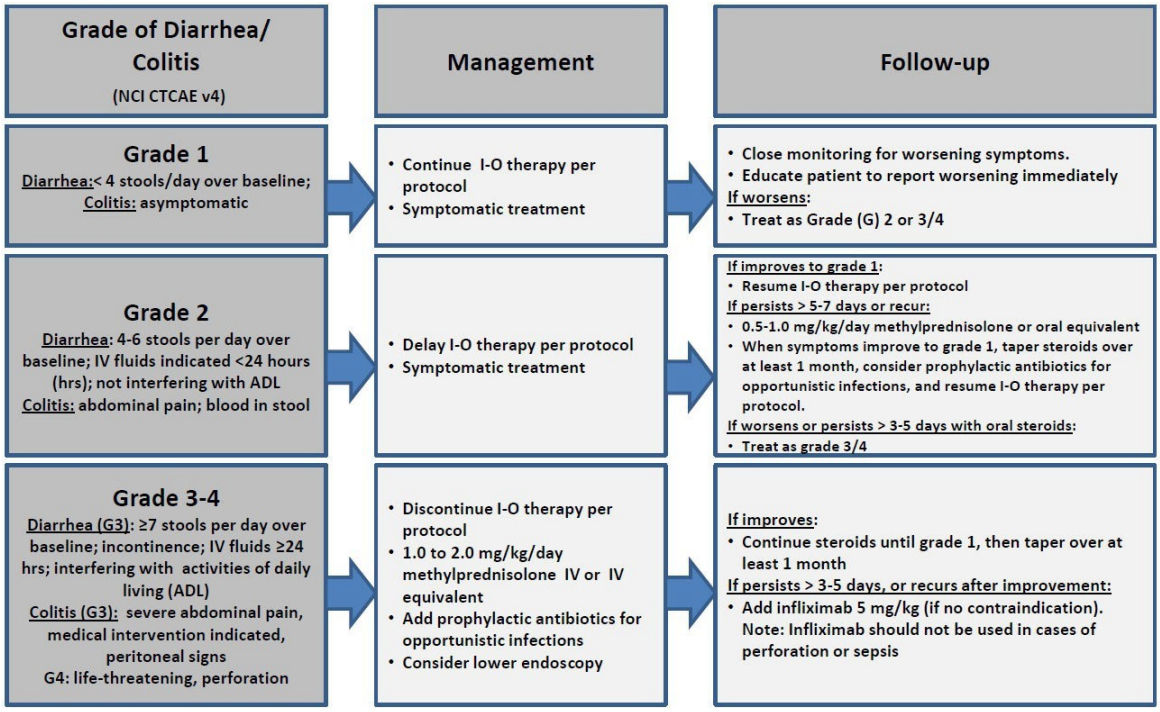
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

GI Adverse Event Management Algorithm

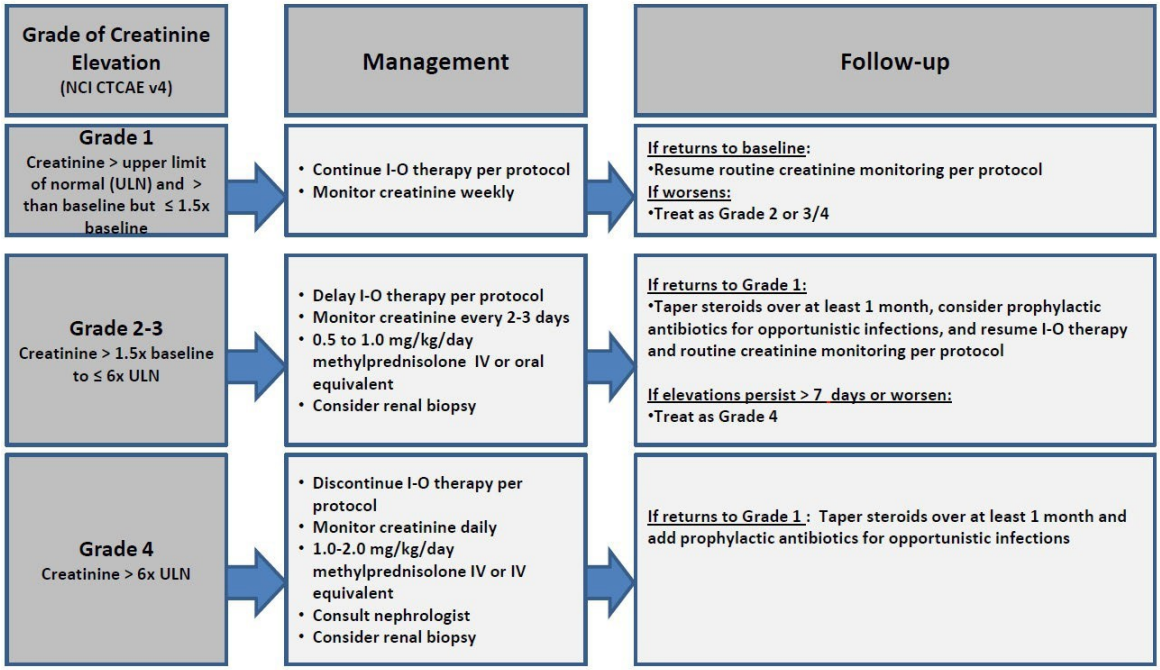
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

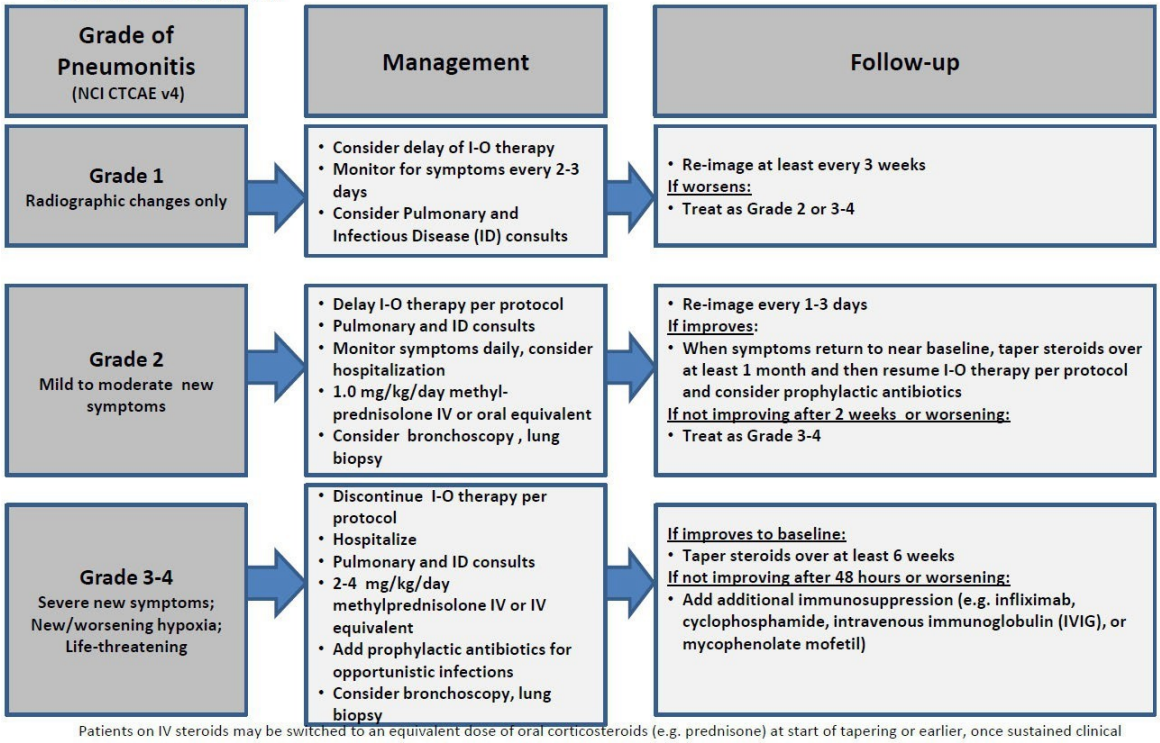
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

Pulmonary Adverse Event Management Algorithm

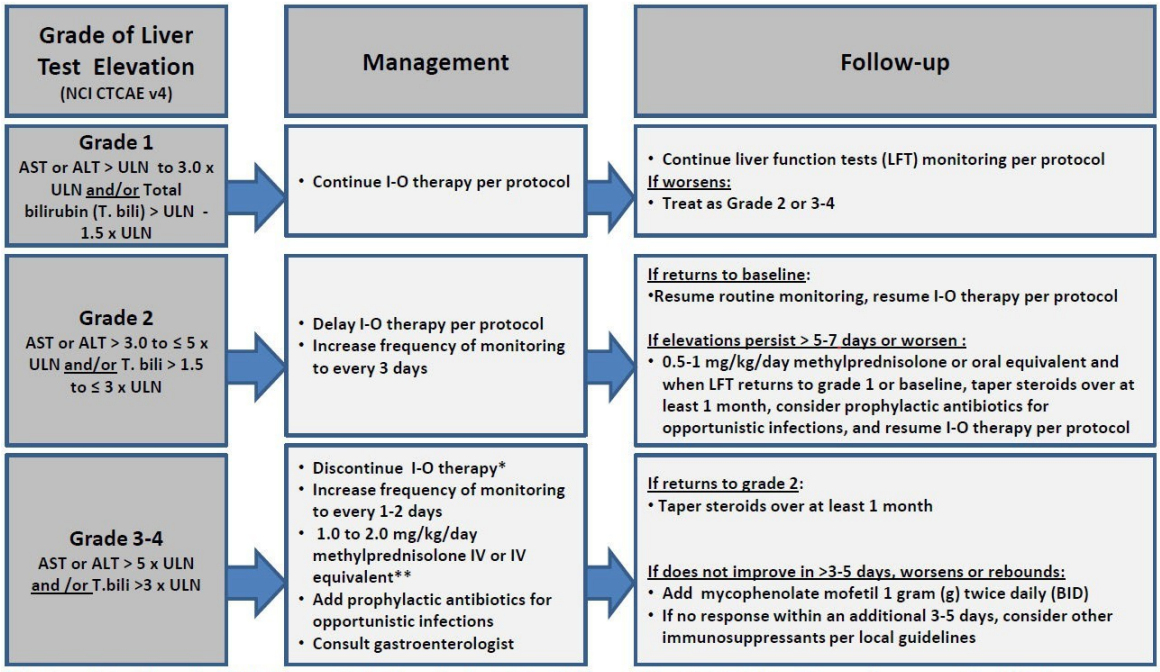
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.



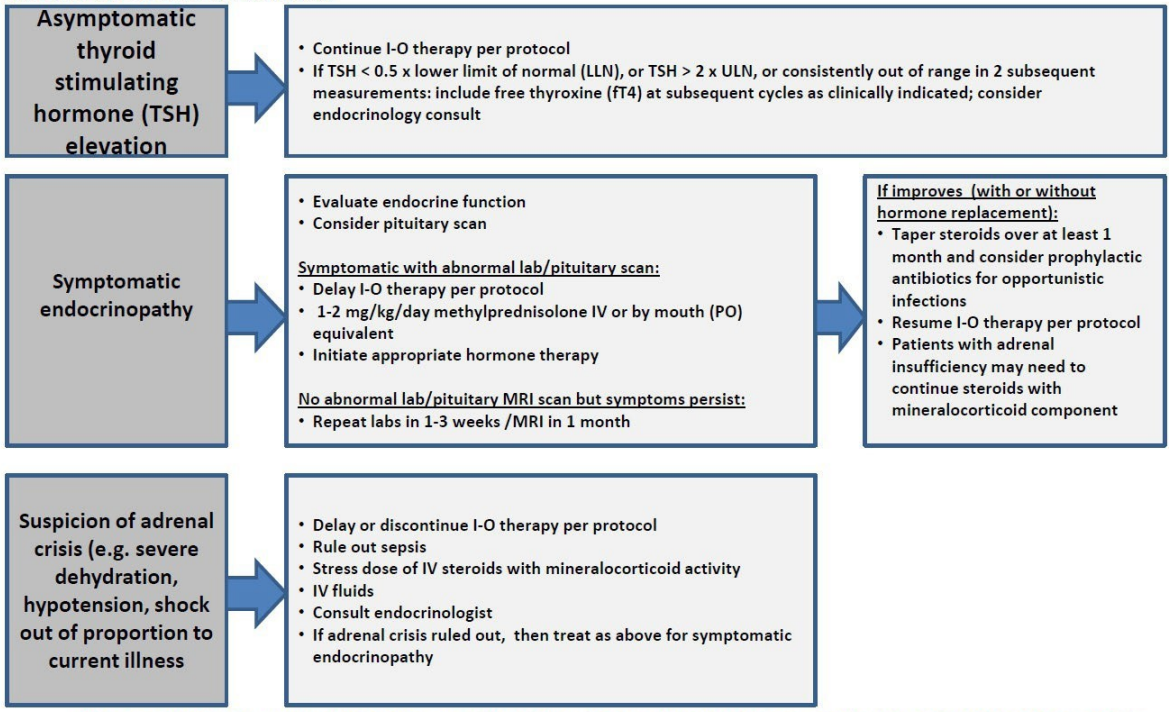
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Endocrinopathy Management Algorithm

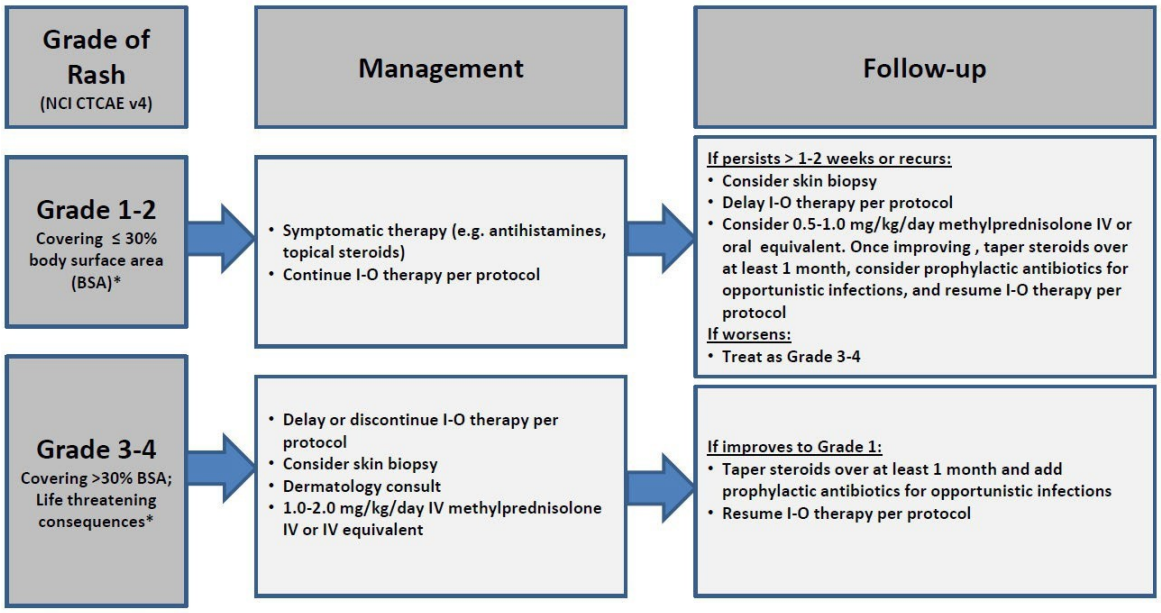
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

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.

Summary of major changes: Protocol Amendment # 1, dated November 27th, 2018

Protocol Section	Change
Section 5.1 and 5.4	Removed language mandating reporting of concomitant medications within case report forms.
Section 7.9	Added clarifying language about reporting SAEs to BMS.
Section 9.1	Replaced Dr. Michaela Bowden with Dr. Ravindra Uppaluri and Dr. Patrick Lizotte.
Section 10	Study calendar updates: Added FSH test at screening visit, moved end of treatment biopsy to the 30 day Follow-up visit and consolidated correlative blood sample collections at the C1D1 and 30 day Follow-up visits.

Summary of major changes: Protocol Amendment # 2, dated January 3rd, 2019

Protocol Section	Change
Section 10	Study calendar updates: Typographical changes to the calendar and removed the requirement of performing photographs and lesion measurements at the End of Treatment visit.

Summary of major changes: Protocol Amendment # 3, dated January 29th, 2019

Protocol Section	Change
Appendix C	Added fields for “Patient Name” and “Date” along with formatting changes to the survey.
Section 10	Study calendar updates: Specified the requirement of performing Phosphorous test as part of routine labs. Clarified the timeline of performing the screening biopsy procedure.

Summary of major changes: Protocol Amendment # 6, dated January 29th, 2020

Protocol Section	Change
Appendix C	Made survey standalone document
Section 10	Study calendar updates: Added “Survival Follow up” column. Clarified that “photographs and measurements” are to be performed at each Survival Follow up visit. Allowed for study team to collect research tissue on biopsies performed at potential first invasive OSCC and during survival follow up. Added that study team may perform photographs

	and measurements after first invasive OSCC at PI discretion. Added "Survival Status" row to Study Calendar, clarified survival status will be collected every 3-4 months.
Section 9.1	Clarified tubes used for fresh tissue collection.
Section 7.5 and 7.6	Updated SAE reporting from 30 days from last dose to 90 days from last dose. SAEs will be reported to Sponsor and to IRB 90 days from last dose.
Cover Page	Removed Dr. Alessandro Villa, DDS, PhD, MPG as Sub-Investigator