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Title: *Window Study of Nivolumab with or without Ipilimumab in Squamous Cell Carcinoma of the Oral Cavity*

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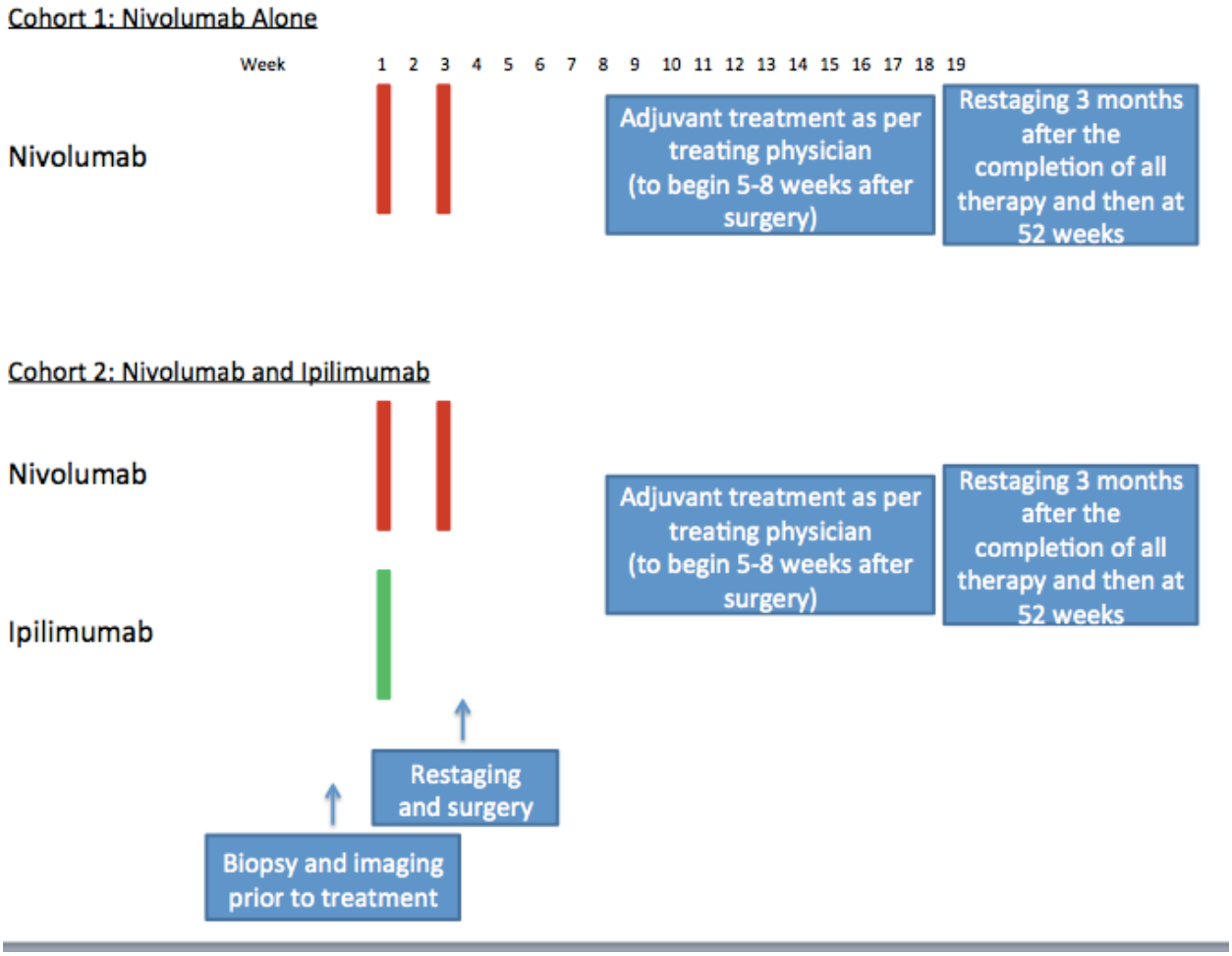
Agents: *Nivolumab and Ipilimumab (Supplied by Bristol-Myers Squibb)*

SCHEMA


Cohort 1: Nivolumab Alone
Week
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Nivolumab
Adjuvant treatment as per treating physician (to begin 5-8 weeks after surgery)
Restaging 3 months after the completion of all therapy and then at 52 weeks
Cohort 2: Nivolumab and Ipilimumab
Nivolumab
Ipilimumab
Adjuvant treatment as per treating physician (to begin 5-8 weeks after surgery)
Restaging 3 months after the completion of all therapy and then at 52 weeks
Restaging and surgery
Biopsy and imaging prior to treatment

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1. OBJECTIVES

1.1 Study Design

This is an open label, randomized, window-of-opportunity trial testing either nivolumab alone, or nivolumab in combination with ipilimumab in patients with locally advanced squamous cell carcinoma of the oral cavity prior to surgical resection. Nivolumab as a single agent was chosen because of preliminary evidence of efficacy of this drug in the metastatic setting in patients with squamous cell carcinoma of the head and neck (SCCHN). The combination of nivolumab and ipilimumab was chosen because of mechanistic rationale, preclinical data and clinical evidence suggesting synergy between these two agents. Indeed, the combination of nivolumab and ipilimumab is now FDA approved as treatment for patients with metastatic melanoma and combinations of CTLA-4 and PD-1 pathway inhibitors have demonstrated promising efficacy across multiple disease types, including melanoma and non-small cell lung cancer. The current study will evaluate response to nivolumab or nivolumab combined with ipilimumab prior to standard of care surgery for patients with locally advanced oral cavity cancers.

1.2 Primary Objectives

- To determine the 1) safety, tolerability; and 2) response rate to window treatment with single agent nivolumab or nivolumab combined with ipilimumab using bidirectional measurements (product of longest 2 diameters of lesions) of primary and nodal lesions to be removed at the time of surgery

1.3 Secondary Objectives

- To determine the radiologic response rate following the window treatment as determined by RECIST v1.1, and burden of disease measurements for each cohort

- To determine pathologic response rates following window treatment and rates of pathologic downstaging as compared to pre-surgical staging

    - To correlate pathologic response with radiologic response

- To estimate the 1-year disease free and overall survival rates

- To explore immunologic changes in the tumor microenvironment (infiltrating immune populations including T-cells, myeloid derived suppressor cells, NK cells, and expression of immune checkpoints such as PD-1, PD-L1, PD-L2, and others) and correlate those markers with radiologic and pathologic response, as well as changes in circulating immune markers such as T-cell subsets, B-cells, and myeloid cells. We will also explore the ability of radiologic parameters to predict response rates as well as immunologic changes in the tumor microenvironment.

2. BACKGROUND

2.1 Study Agents

2.1.1 Nivolumab

2.1.1.1 Mechanism of action and pharmacology

Cancer immunotherapy is based on the premise that the body's immune system can recognize a tumor as foreign and mount an effective antitumor response capable of eliminating that tumor. This likely requires immune recognition of specific tumor antigens, but also effective functioning of activated T-cells capable of eliminating tumor cells as they arise and causing tumor shrinkage where existing tumor deposits are present. Conversely, tumor progression is likely intimately intertwined with mechanisms by which tumors evade immune recognition and attack.

One mechanism by which tumors may evade immune attack is by coopting inherent immune checkpoints that function under normal circumstances to maintain immune homeostasis and prevent harmful autoimmunity. Thus, one strategy that exists for cancer immunotherapy is to modulate these regulatory immune checkpoints that largely exist on the surface of T-cells. This can ideally overcome tumor mediated immune suppression, and potentiate nascent antitumor immune responses that might otherwise have been unable to lead to meaningful tumor regression.

Programmed death receptor-1 (PD-1, CD279), is a 55 kD type I transmembrane protein is a member of the CD28 family of T-cell constimulatory molecules that also includes CD28, CTLA-4, ICOS, and BTLA [1]. PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273) [2]. PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems [2, 3]. PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region [4, 5]. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells [5].

Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus [6-8]. The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes[9, 10]. Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative

for the expression of PD-L1[11-16]. This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies [17-22]. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro [5]. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells[23]. Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by IHC) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness [20, 21]. Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. In addition, in multivariate analysis, high expression of PD-L1 is correlated to have a worse overall survival rate compared to low expression levels of PD-L1[24].

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro [25]. Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1. In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-α release [26].

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, 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. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at <=10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC (0-168 h)] 117,000 μg • h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested

throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice [27].

The PK, clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, and clear-cell renal cell carcinoma (RCC) in addition to other tumor types. Please refer to the 2015 IB for specific details. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

Nivolumab is approved in multiple countries including the US for treatment of previously treated, unresectable or metastatic melanoma, advanced renal cell carcinoma and previously treated, metastatic squamous NSCLC, the EU for treatment of previously treated, unresectable or metastatic melanoma, and Japan for treatment of unresectable melanoma. Please see the IB for more details.

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. 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 Q2W, 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 PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose was identical to a dose of 3 mg/kg for subjects weighing 80 kg, which was the approximate median body weight in nivolumab clinical trials (please see 2015 IB for more details).

2.1.1.2 Clinical safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8,600 subjects treated to date.

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab+ipilimumab, as is proposed in this study. Results to date suggest that the safety profile of nivolumab+ipilimumab combination therapy, described in more detail below, is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

Safety data for nivolumab administered in the context of NSCLC and melanoma are detailed below; additional information for other diseases can be found in the IB.

Safety data for subjects with previously treated advanced or metastatic NSCLC treated with nivolumab monotherapy in CA209017 (131 subjects), CA209057 (287 subjects), and CA209063 (117 subjects) were pooled and safety analyses were performed for these pooled subjects who receiving nivolumab monotherapy (a total of 535 subjects).

Based on the pooled analyses, nivolumab monotherapy at a dose of 3 mg/kg administered IV Q2W has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation. The following were the key safety findings for these pooled subjects:

- The most frequently reported drug-related AEs (reported in ≥ 10% of subjects) were fatigue (19.6%), decreased appetite (12.3%), nausea (12.0%), and asthenia (10.5%). The majority of drug-related AEs were of Grade 1-2 in severity. Drug-related Grade 3-4 AEs were observed in 11.0 % of subjects and included fatigue (1.7%), pneumonitis (1.3%), and diarrhea (0.9%).
- Drug-related SAEs and drug-related AEs leading to discontinuation were reported in 7.9% and 6.0% of subjects, respectively. The most frequently reported event (>=1% of subjects) was pneumonitis (1.9%). The majority of subjects experiencing drug-related SAEs and drug-related AEs leading to discontinuation had an event with worst grade of Grade 3-4 in severity.
- The most frequently reported drug-related select AE categories were skin (15.1%), GI (8.4%), and endocrine disorders (7.3%).
  - The majority of select AEs in each category (described in more detail in the IB) were considered by the investigator to be related to the study drug, except for AEs belonging to the hepatic, and renal select AE categories.
  - Across select AE categories, the majority of events were manageable, with resolution occurring whether or not immunosuppressive medication was needed. Among these medications, corticosteroids were the most common immunosuppressive concomitant medication administered.
- Most deaths (293/339) were due to disease progression. Two deaths (0.4%) were attributed to study drug toxicity: drug-related hypoxic pneumonia reported within 30 days of last nivolumab dose (ie, on-study) and drug-related ischemic stroke within 100 days of last nivolumab dose. One additional death, although reported prior to database lock for CA209057 CSR, had its causality changed after database lock to drug-related paraneoplastic limbic encephalitis.
- Hematology laboratory results, liver function, renal function, and thyroid function remained stable in the majority of subjects. Abnormalities were primarily Grade 1-2 in severity.

- The immunogenicity of nivolumab was low and not clinically meaningful.

Safety data for subjects with previously treated and untreated unresectable or metastatic melanoma treated with nivolumab monotherapy in CA209037 (268 subjects), CA209066 (206 subjects), and CA209067 (313 subjects) were pooled and safety analyses were performed for these pooled subjects receiving nivolumab monotherapy (a total of 787 subjects).

Based on the pooled analyses, nivolumab monotherapy at a dose of 3 mg/kg administered IV Q2W has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation (summarized in Table 5.5.2.1-1). The following were the key safety findings for these pooled subjects:

- The most frequently reported drug-related AEs (>=10% of subjects) were fatigue (29.2%), pruritus (18.4%), diarrhea (17.2%), rash (16.9%), and nausea (13.7%). No drug-related Grade 3-4 AEs with the exception of lipase increased (2.0%), diarrhea (1.3%), and ALT increased (1.1%) were reported in ≥ 1% of subjects.
- No drug-related SAEs of any grade were reported in ≥ 1% of subjects. The most frequently reported drug-related SAEs of any grade were hyperglycemia (0.6%), colitis, diarrhea, and pneumonitis (0.5% each).
- No drug-related AEs leading to discontinuation of study drug were reported in ≥ 1% of subjects. The most frequently reported drug-related AEs leading to discontinuation of study drug were ALT increased (0.9%), diarrhea (0.8%), AST increased (0.5%), and colitis (0.5%).
- The most frequently reported drug-related select AE categories with nivolumab monotherapy were skin (38.4%), GI (17.7%), endocrine (10.8%), and hepatic (6.9%). The majority of select AEs were considered by the investigators to be related to study treatment.
  - Drug-related select AEs were mostly Grade 1-2.
  - Across categories, the majority of high-grade events subsequently resolved, including those for which immunosuppressive medication was not initiated.
  - The majority of deaths (229/251) were due to disease progression. Only 1 death was attributed to study drug toxicity; this death was due to drug-related neutropenia reported between 31 and 100 days of last nivolumab dose.
  - Abnormalities in select hematology assessments and liver/kidney function tests were primarily Grade 1-2 in severity.
  - The immunogenicity of nivolumab was low and not clinically meaningful.

2.1.1.3 Clinical Efficacy

Nivolumab has demonstrated efficacy across multiple tumor types including NSCLC and melanoma (described below), and other malignancies including renal cell carcinoma, esophageal cancer, and others (described in more detail in the IB). Nivolumab is also currently undergoing testing in patients with metastatic squamous cell carcinoma of the head and neck in a randomized phase 3 trial for which preliminary reports where nivolumab improved survival as compared with chemotherapy following progression on a platinum agent were recently presented at the 2016 AACR Annual Meeting. Other inhibitors of the PD-1 pathway have also demonstrated promising response rates in metastatic head and neck cancer patients [28].

In subjects with previously treated, unresectable or metastatic NSQ NSCLC (CA209057),

nivolumab monotherapy demonstrated superior OS compared with docetaxel, with a clinically meaningful and statistically significant improvement observed (HR=0.73 [95.92% CI: 0.59, 0.89]; stratified log-rank test p-value = 0.0015). In subjects with previously treated, unresectable or metastatic SQ NSCLC (CA209017), nivolumab monotherapy demonstrated superior OS compared with docetaxel, with a clinically meaningful and statistically significant improvement observed (HR=0.59 [96.85% CI: 0.43, 0.81]); stratified log-rank test p-value = 0.0002).

Results of secondary endpoints of ORR, DOR, and TTR further support the antitumor activity of nivolumab in both SQ and NSQ NSCLC subjects. In CA209057, PFS was not statistically different between treatment groups; however, while the median PFS favored docetaxel, the overall HR and 1-year PFS rate favored nivolumab, indicating the potential for long-term PFS benefit from nivolumab in a subset of subjects. In CA209017, nivolumab treatment resulted in a clinically meaningful and statistically significant improvement in PFS with a 38% reduction in the risk of progression as compared with docetaxel.

Nivolumab demonstrated superior OS compared with dacarbazine in previously untreated subjects with BRAF wild-type advanced (unresectable or metastatic) melanoma, with a clinically meaningful and statistically significant improvement observed (HR=0.42 [99.79% CI: 0.25,0.73]; p<0.0001). Results of secondary and exploratory endpoints of PFS, ORR, DOR, and TTR further support the robust and durable antitumor activity of nivolumab in this population.

2.1.2 Nivolumab combined with ipilimumab

2.1.2.1 Preclinical activity and data

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity by activating a more robust anti-tumor immune response compared to either agent alone. In vitro combinations of nivolumab plus ipilimumab increase IFN-gamma production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone [29].

Preclinically, a 4-week toxicity study of nivolumab in combination with ipilimumab conducted in cynomolgus monkeys demonstrated that the combination of nivolumab and ipilimumab resulted in dose-dependent gastrointestinal (GI) toxicity. Histologic findings included inflammatory changes in the large intestine, which increased in incidence and severity in a dose-dependent manner. GI toxicity/colitis was not observed in cynomolgus monkeys administered nivolumab alone, but was observed in monkeys receiving ipilimumab. Nivolumab in combination with ipilimumab was also associated with lymphoid hypocellularity of the cortex and/or medulla of the thymus and with acinar cell degranulation in the pancreas. Additional findings included interstitial mononuclear cell infiltrates in the kidneys, portal mononuclear cell infiltrates in the liver and myeloid hypercellularity in the bone marrow. Nivolumab in combination with ipilimumab at the high-dose level (ie, 50 mg/kg and 10 mg/kg, respectively) was associated with the death of 1

animal, attributed to acute gastric dilatation without histopathological evidence of colitis upon pathology evaluation of the GI tract.

2.1.2.2 Clinical safety of single agent of ipilimumab and pharmacology

Ipilimumab has specificity and a high affinity for human CTLA-4. The calculated dissociation constant value from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by enzyme-linked immunosorbent assay with half-maximal binding at15 ng/mL, whereas saturation was observed at approximately 0.1 µg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of B7.1 and B7.2 to human CTLA-4 at concentrations higher than 6 µg/mL and 1 µg/mL, respectively.

Ipilimumab has a terminal half-life of approximately 15.4 days. The expected in vivo degradation of monoclonal antibodies is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes. The population PK of ipilimumab was studied with 785 subjects and demonstrated that PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time invariant. Upon repeated dosing of ipilimumab, administered every three weeks, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab clearance of 16.8 mL/h from population PK analysis is consistent with that determined by PK analysis. The terminal half-life (T-HALF) and Vss of ipilimumab calculated from the model were 15.4 days, and 7.47 L, which are consistent with that determined by non-compartmental analysis (NCA). Volume of central (Vc) and peripheral compartment were found to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and subsequently into extracellular fluid space. Clearance of ipilimumab and Vc were found to increase with increase in body weight. Nevertheless, there was no significant increase in exposure with increase in body weight when dosed on a mg/kg basis, supporting dosing of ipilimumab based on a weight normalized regimen. Additional details are provided in Appendix E and the Investigator Brochure.

Bristol-Myers Squibb (BMS) and Medarex, Inc. (MDX, acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing more than 19,500 subjects (total number of subjects enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, as well as a compassionate use program. The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

Phase 3 programs are ongoing in melanoma, prostate cancer, and lung cancer. In melanoma, 2 completed Phase 3 studies (MDX010-20 and CA184024) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively. Refer to the IB for additional details.

While the types of safety events observed in subjects receiving ipilimumab do not appear to change, even in combination with other anti-cancer agents, the proportion of subjects experiencing

one type or another irAE may be impacted by the choice of combination partner. For example, skin and GI irAEs predominate in monotherapy studies. In MDX010-20, the ipilimumab monotherapy arm was administered 3 mg/kg ipilimumab every 3 weeks for four doses. In this arm, there were 79% drug related adverse events, with 21% being Grade 3/4 and 3/131 (2%) Grade 5. The most frequent adverse events of interest were rash (30%), pruritis (33%), diarrhea (33%), colitis (8%), endocrine disorders (9%), AST/ALT increased (2%), and hepatitis (1%). Any grade immune related adverse events were 60% and the Grade 3/4 immune related adverse events for the same cohort was 13% with the most frequent adverse events being diarrhea (5%), colitis (5%), rash (2%), and endocrine disorders (3%). Additional details on the safety profile of ipilimumab, including results from other clinical studies, are also available in the ipilimumab IB.

Yervoy TM (ipilimumab) has been approved for use in over 47 countries including the United States (US, Mar-2011), the European Union (EU, Jul-2011), and Australia (Jul-2011). Of note, ipilimumab will be given at a lower dose (1mg/kg) in this trial as compared to many previously conducted trials in order to reduce the rates of ipilimumab induced toxicity.

2.1.2.3 Clinical safety of nivolumab combined with ipilimumab

The safety profile of nivolumab + ipilimumab combination therapy was consistent with the mechanisms of action of nivolumab and ipilimumab. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3 mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD. Of note, this study uses the 3 mg/kg nivolumab/1 mg/kg ipilimumab combination, but only a single dose of ipilimumab, as compared to at least 4 doses which has generally been used in other studies.

In a Phase 1 study, CA209004, ascending doses of nivolumab were studied concomitantly with ascending doses of ipilimumab in subjects with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n = 14), Cohort 2 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16). The following DLTs were observed in Cohort 1 - Grade 3 elevated AST/ALT (1 subject); in Cohort 2 - Grade 3 uveitis (1 subject) and Grade 3 elevated AST/ALT (1 subject) and in Cohort 3 - Grade 4 elevated lipase (2 subjects) and Grade 3 elevated lipase (1 subject). Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

Among the 53 patients in the concurrent-regimen group, adverse events of any grade, regardless of whether they were attributed to the therapy, were observed in 98% of patients. Treatment-related adverse events were observed in 93% of patients, with the most common events being rash (in 55% of patients), pruritus (in 47%), fatigue (in 38%), and diarrhea (in 34%). Grade 3 or 4 adverse events, regardless of attribution, were observed in 72% of patients, and grade 3 or 4 treatment-related events were noted in 53%, with the most common events being elevated levels of lipase (in 13% of patients), aspartate aminotransferase (in 13%), and alanine aminotransferase (in 11%). A total of 6 of 28 patients (21%) had grade 3 or 4 treatment related events that were dose-limiting.

Serious adverse events related to the treatment were reported in 49% of patients in the concurrent regimen group. Common grade 3 or 4 selected adverse events that were related to the therapy included hepatic events (in 15% of patients), gastrointestinal events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were observed, a finding that is consistent with previous experience with monotherapy. A total of 11 patients (21%) discontinued therapy owing to treatment-related adverse events, No drug-related deaths were reported [30].

More recently, the results of a phase 3 trial comparing the combination of nivolumab and ipilimumab to either agent alone in metastatic melanoma were reported [31]. Nivolumab was given at a dose of 1 mg / kg and ipilimumab was given at a dose of 3mg/kg every three weeks for a total a four cycles. After this, nivolumab was continued alone every two weeks. There were 314 patients enrolled on the treatment arm combining nivolumab and ipilimumab. Adverse events of any grade occurred in 95.5% of those in this group. The most common adverse events group were diarrhea (in 44.1% of patients), fatigue (in 35.1%), and pruritus (in 33.2%). The incidence of treatment-related adverse events of grade 3 or 4 was also higher in the nivolumab plus-ipilimumab group (55.0%) than in the nivolumab group (16.3%) or the ipilimumab group (27.3%). Treatment-related adverse events of any grade that led to discontinuation of the study drug occurred in 7.7% of the patients in the nivolumab group, 36.4% of those in the nivolumab-plus ipilimumab group, and 14.8% of those in the ipilimumab group, with the most common events being diarrhea (in 1.9%, 8.3%, and 4.5%, respectively) and colitis (in 0.6%, 8.3%, and 7.7%, respectively). One death due to toxic effects of the study drug was reported in the nivolumab group (neutropenia) and one in the ipilimumab group (cardiac arrest), but none were reported in the nivolumab-plus-ipilimumab group.

Preliminary experience in lung cancer as part of the Checkmate-012 study has evaluated the combination of nivolumab and ipilimumab in patients with advanced non-small cell lung cancer. Preliminary data was presented at the 2015 World Conference on Lung Cancer. Four administration/dosing schedules for the combination of nivolumab and ipilimumab were explored. In arm A, both agents were administered at a dose of 1 mg/kg every 3 weeks (Q3W, N = 31). In arm B, nivolumab was administered at 1 mg/kg every 2 weeks (Q2W) plus ipilimumab 1 mg/kg every 6 weeks (Q6W; N = 40). Arm C and D dosed nivolumab at 3 mg/kg Q2W and ipilimumab 1 mg/kg every 12 weeks (Q12W; N=38) or Q6W (N = 39). Treatment-emergent grade 3/4 adverse AEs occurred in 28% to 35% of patients in each group but led to discontinuation in just 3% to 10% of cases. All grade treatment-related AEs occurred in 77%, 73%, 74%, and 69% of patients in groups A, B, C, and D, respectively. The safety profile was consistent with previous studies of the combination, and the discontinuation rate associated with AEs was similar to rates observed with nivolumab alone. The only grade 3/4 adverse events that occurred in as many as 10% of patients were hepatic in arm B (10%) and skin-related in arm C and D (13%). Grade 3/4 pulmonary AEs occurred in no more than 3% of patients in any of the groups. There were no treatment-related deaths in the trial.

This data suggests that delivering fewer doses of ipilimumab at a lower dose of 1mg/kg will reduce the toxicity of this agent combined with nivolumab. This study will use only a single administration of ipilimumab at the lower dose of 1mg/kg, in a cohort that will open only after nivolumab single agent treatment has been deemed tolerable in this population.

2.1.2.4 Clinical efficacy of nivolumab combined with ipilimumab

The combination of nivolumab and ipilimumab has been studied most extensively in melanoma, where combination therapy is now FDA approved.

In the Phase 1 study CA209004, ascending doses of nivolumab were studied concomitantly with ascending doses of ipilimumab in subjects with unresectable or metastatic melanoma. In each arm of this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n=14), Cohort 2 (nivolumab 1.0 mg/kg plus ipilimumab 3 mg/kg; n = 17) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a that evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 16). In the concurrent-regimen cohorts, across all dose levels, confirmed objective responses according to modified WHO criteria were observed in 21 of 52 patients (40%; 95% confidence interval [CI], 27 to 55) who had a response that could be evaluated. In addition, 4 patients had an objective response according to immune-related response criteria and 2 had an unconfirmed partial response. These patients were not included in the calculation of objective response rates.

After noting that several patients had major responses (approaching complete response), a post hoc analysis of the number of patients with tumor reduction of 80% or more was conducted. This depth of response was uncommon in published studies of checkpoint blockade [32]. A total of 16 patients had tumor reduction of 80% or more at 12 weeks, including 5 with a complete response. In the concurrent-regimen group, overall evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for >24 weeks) was observed in 65% of patients (95% CI, 51 to 78). Responses were ongoing in 19 of 21 patients who had a response, with the duration ranging from 6.1 to 72.1 weeks at the time of data analysis [30].

More recently, the results of a phase 3 trial comparing the combination of nivolumab and ipilimumab to either agent alone in metastatic melanoma were reported [31]. Nivolumab was given at a dose of 1 mg / kg and ipilimumab was given at a dose of 3mg/kg every three weeks for a total a four cycles. After this, nivolumab was continued alone every two weeks. The median progression-free survival was 6.9 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, 11.5 months (95% CI, 8.9 to 16.7) in the nivolumab-plus-ipilimumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. Significantly longer progression-free survival was observed in the nivolumab plus-ipilimumab group than in the ipilimumab group (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001) and in the nivolumab group than in the ipilimumab group (hazard ratio, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001).

The tumor-burden change was assessed as the change from baseline in the sum of the longest diameters of the target tumor lesions. The median change was −34.5% (interquartile range, −75.4 to 15.4) in the nivolumab group, −51.9% (interquartile range, −75.8 to −10.2) in the nivolumab plus-ipilimumab group, and 5.9% (interquartile range, −28.0 to 33.3) in the ipilimumab group.

Preliminary experience in lung cancer as part of the Checkmate-012 study has evaluated the combination of nivolumab and ipilimumab in patients with advanced non-small cell lung cancer. Preliminary data was presented at the 2015 World Conference on Lung Cancer. Four

administration/dosing schedules for the combination of nivolumab and ipilimumab were explored. In arm A, both agents were administered at a dose of 1 mg/kg every 3 weeks (Q3W, N = 31). In arm B, nivolumab was administered at 1 mg/kg every 2 weeks (Q2W) plus ipilimumab 1 mg/kg every 6 weeks (Q6W; N = 40). Arm C and D dosed nivolumab at 3 mg/kg Q2W and ipilimumab 1 mg/kg every 12 weeks (Q12W; N=38) or Q6W (N = 39). All four regimens demonstrated activity, with the arms containing nivolumab at 3 mg/kg showing the best objective response rate (ORR). In arm C, the ORR was 39% and in arm D the ORR was 31%. The ORRs were 25% and 13%, in arm B and arm A, respectively.

2.2 Study Disease

SCCHN is the 6th most common type of cancer with an incidence of approximately 550,000 new cases worldwide each year. Approximately two thirds of these patients have non-metastatic advanced disease (stage III/IV), and are candidates for curative treatment using either upfront chemoradiation or surgery followed by radiation-based therapy. Patients with locally advanced SCCHN who are treated non-surgically, receive chemotherapy and radiation therapy. Surgical resection is also a common treatment for participants with resectable SCCHN. Postoperative radiotherapy (PORT) is the standard of care for most resected stage III/IV with the addition of chemotherapy for participants at high risk of recurrence [33]. Yet local-regional recurrence is common among such participants.

Locally advanced squamous cell carcinoma of the oral cavity has a particularly poor prognosis, with a 5-year survival of approximately 30-50% [34]. Initial management with surgical resection is standard, but is associated with significant morbidity and impacts on quality of life[35]. These impacts are somewhat dependent on the size of the tumor, with larger tumors requiring removal of more tissue and the subsequent use of grafts to maintain functional integrity.

Preoperative treatment has previously been investigated as treatment for tumors of the oral cavity. Licitra et al. evaluated 3 cycles of cisplatin and fluorouracil as compared with proceeding to surgery directly in a randomized multicenter trial of 198 patients [36]. Although survival was not improved, preoperative therapy may have reduced the number of patients who needed manibulectomy or adjuvant radiation therapy. More recently, Zhong et al. randomized 256 patients with oral cavity cancer to preoperative chemotherapy with TPF compared with proceeding directly to surgery [37]. Induction chemotherapy did not increase the perioperative morbidity and was associated with a clinical response rate of 80%; however, there was no benefit in terms of disease-free or overall survival with extended follow up.

2.3 Rationale

The rationale of the current study is based on the premise that patients with squamous cell carcinoma of the oral cavity fare poorly overall with standard treatments, and thus, new approaches are needed to improve outcomes in this disease.

As described above, immunotherapy represents a promising potential treatment strategy for patients with metastatic squamous cell carcinoma of the head and neck, with likely efficacy in the

metastatic setting based on several promising preliminary studies [28]. As has been the case in other malignancies, head and neck patients who respond to immune checkpoint blockade could potentially demonstrate durable responses, even after immune checkpoint blockade treatment is stopped [38].

Evidence obtained from patients treated with immune checkpoint therapy for non-small cell lung cancer suggests that patients who have received fewer previous lines of therapy may derive a greater benefit from immune checkpoint blockade then heavily pretreated patients[39]. Thus, it is rational to explore the use of immune checkpoint blockade in the upfront setting in treatment naïve patients with relatively lower overall burden of disease to potentially obtain a more favorable response. Squamous cell carcinomas of the oral cavity, in particular, are often related to tobacco use, and therefore harbor a significant number of mutations that may render them intrinsically more sensitive to immune checkpoint blockade. Additionally, a significant number of oral cavity tumors may express PD-L1 on the surface of tumor cells [40], which has been suggested as a potential predictive biomarker of response to PD-1 inhibiting therapy in SCCHN as well as other malignancies.

As described above, the addition of CTLA-4 blockade to PD-1 blockade with nivolumab has demonstrated synergy in preclinical models and is now FDA approved for the treatment of metastatic melanoma. The benefit of combined PD-1 / CTLA-4 inhibition may be particularly apparent in patients whose tumors don't express significant levels of PD-L1 and/or have relatively few tumor infiltrating lymphocytes, which would include a significant number of oral cavity tumors [40]. The combination of CTLA-4 and PD-1/PD-L1 blockade is actively being pursued in a number of malignancies including head and neck cancer, and there is reason to think that the combination may improve response rates across a variety of disease types including SCCHN.

Because of the preliminary activity seen with PD-1 inhibition in SCCHN in the metastatic setting and potential for synergistic benefit with combined CTLA-4/PD-1 blockade, a window of opportunity study is well-suited to begin to explore these strategies in the upfront setting. Patients typically undergo a relatively brief period of at least several weeks before definitive surgery for oral cavity cancer due to a variety of medical and logistic issues; during this period of time they are typically not receiving active treatment that could potentially be of benefit, both symptomatically as well as in regards to disease-specific and overall survival. Surgery with or without adjuvant treatment for oral cavity cancers can be significantly morbid. Therefore, treatments that can potentially reduce the burden of disease may be able to decrease the side effects associated with these procedures. Finally, a window of opportunity study would allow for pathologic confirmation of response seen to nivolumab monotherapy or the combination of nivolumab and ipilimumab, helping to guide further evaluation of these agents in this setting. The tissue obtained before and after treatment will also be of great value exploring predictors of response and effects of checkpoint blockade on the tumor microenvironment.

2.4 Correlative Studies Background

There is great interest in identifying tumor markers that may predict response to PD-1 blockade or combined blockade of both PD-1 and CTLA-4 receptors. Based on prior studies conducted in patients across several disease types, expression of PD-L1 on tumor cells and tumor infiltrating

immune cells could potentially serve as a predictor of response, at least in patients treated with PD-1 therapy alone [41, 42]. Tumor infiltrating lymphocytes at baseline and / or mutational burden may also serve as a predictive marker in patients treated with either PD-1 or CTLA-4 blockade, although this has not yet been demonstrated in head and neck cancer [43-45]. Additionally, it is currently unknown whether therapy with either PD-1 or CTLA-4 will impact expression of PD-L1 or the immunologic composition of the tumor microenvironment. Given the amount of tissue that will be available in this window study as per standard of care resection, we will be able to investigate these changes and potentially identify mechanisms of resistance to immune checkpoint blockade in SCCHN patients, including upregulation of other targetable checkpoint receptors such as PD-L2. Evaluating these changes in patients who don't respond to PD-1 or combined PD-1/CTLA-4 therapy will facilitate the design of future combination therapy that seeks to further increase the number of responding patients. Additionally, we will attempt to correlate changes in the tumor microenvironment with radiologic changes as well as circulating immune biomarkers to facilitate non-invasive monitoring of immune responses in future studies.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

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

1. Pathologically confirmed squamous cell carcinoma of the oral cavity. Clinical stage >=T2 (primary tumor greater than 2 cm in size) and/or evidence of regional nodal involvement by clinical exam or imaging

2. Only patients 18 years and older are eligible. There is no upper age limit but the patients must be able to medically tolerate the regimen. Adverse event data are currently unavailable on the use immune checkpoint blockade for participants < 18 years of age, and thus children are excluded from this study
3. ECOG performance status <=1 (see Appendix A)

4. Patients much be a surgical candidate (e.g. their disease must be considered resectable before any treatment and must have no serious medical contraindications that definitively preclude undergoing general anesthesia)
   Ability to understand and the willingness to sign a written informed consent document
5. Women of childbearing potential (WOCBP) must agree to use appropriate method(s) of contraception (see Appendix B). WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug. WOCBP is defined as any woman or adolescent who has begun menstruation and is not post- menopausal. A post-menopausal woman is defined as a woman who is over the age of 45 and has not had a menstrual period for at least 12 months

6. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be scheduled within 24 hours prior to the start of nivolumab

7. Men who are sexually active with WOCBP must agree to use any contraceptive method (see Appendix B) with a failure rate of less than 1% per year. 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 Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception)

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

Laboratory parameters: WBC $\geq$ 2000/uL, Absolute neutrophil count (ANC) $\geq$ 1500/mm^3; Platelets $\geq$ 100,000/mm^3; Hemoglobin (Hgb) $\geq$ 9 g/dL; Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 3 $\times$ upper limit of normal (ULN); Bilirubin $\leq$ 2.5 $\times$ ULN ($\leq$ 4 $\times$ ULN for subjects with Gilbert's disease); Alkaline phosphatase $\leq$ 2.5 $\times$ ULN; Creatinine $\leq$ 1.5 $\times$ ULN

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

1. Pathologically proven, radiologic or clinical evidence of distant metastatic disease (this includes all disease below the clavicles, as well as disease metastatic to the bone, brain, or in the spinal canal)

2. Any prior immunologic cancer therapy with systemic inhibitors of the PD-1 or CTLA-4 pathway

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

4. Individuals with a history of a different malignancy are ineligible except for the following circumstances: if they have been disease-free for at least 2 years and are deemed by the investigator to be at low risk for recurrence of that malignancy; or if diagnosed and treated within the past 2 years for cervical cancer in situ or basal cell or squamous cell carcinoma of the skin

5. Prior radiation to the head and neck region

6. Prior chemotherapy within the last 2 years

7. History of pneumonitis or interstitial lung disease

8. Has evidence of active, noninfectious pneumonitis that required treatment with steroids.

9. Active, suspected or prior documented autoimmune disease that has required systemic treatment in the last 2 years with immune modifying agents (e.g. replacement therapy such as thyroxine, insulin or physiologic corticosteroids is not an exclusion criteria). This does not include patients with vitiligo or type 1 diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger

10. The subject is known to be positive for the human immunodeficiency virus (HIV), HepBsAg, or HCV RNA.These tests do not have to be resulted prior to registration if patient is low risk.

11. Lack of availability for follow up assessments

12. Concurrent administration of other cancer specific therapy during the course of this study is not allowed

13. Patients who require systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease

14. History of allergy to study drug components

15. History of severe hypersensitivity reaction to any monoclonal antibody

16. The investigator's belief that the subject is medically unfit to receive nivolumab, and/or ipilimumab or unsuitable for any other reason

17. Has received a live vaccine within 28 days of planned start of study therapy

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Women, minorities and other underrepresented populations are all at risk to develop squamous cell carcinoma of the oral cavity, with smoking and alcohol use as the critical risk factors for the disease. Socioeconomically-deprived populations tend to have higher rates of smoking and potentially higher risks of alcohol use, and therefore it is possible this study will be more likely to enroll these individuals. However, there is no reason to think that immune checkpoint blockade will have a differential effect on these populations. The eligibility criteria should not substantially differentially affect their enrollment in the trial, although some minority populations are more likely to have certain comorbid conditions such as heart failure, which may preclude them from the trial.

4. REGISTRATION/ENROLLMENT PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

Following registration/enrollment, 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.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at DF/HCC by the study coordinator. All sites should reach the study coordinator to verify the dose level availabilities. The required forms can be found in Appendix D. Following registration, participants should begin protocol therapy within 7 days. Issues that would cause treatment delays should be discussed with the overall PI. If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and faxed (617-582-8911) or e-mailed to the study coordinator:

- Copy of screening test results, including imaging and pathology results
- Signed participant consent form
- HIPAA authorization form
- Eligibility checklist
- Clinic note, covering screening requirements and baseline AEs

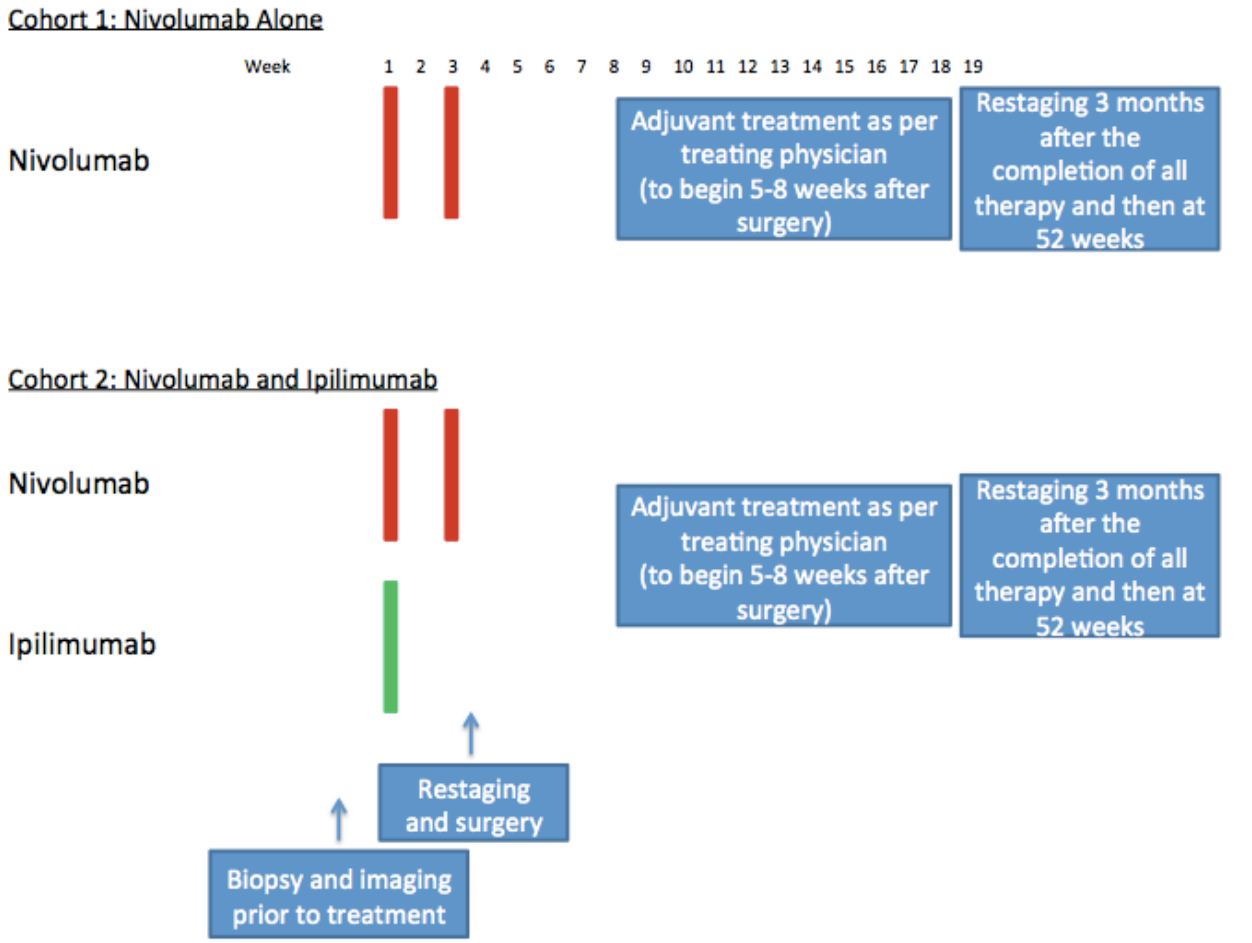
The participating site will then call 617-582-8939 or e-mail the study coordinator to verify eligibility. The study coordinator will follow DF/HCC policy (SOP #: REGIST-101) and register the participant on the protocol. The study coordinator will fax or e-mail the study participant number, and the Cohort assignment, to the participating site.

5. TREATMENT PLAN

5.1 Treatment regimen

Treatment will be administered on an outpatient basis. Expected toxicities and potential risk as well as management of these toxicities are described in Appendix D and E. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy during the course of treatment.

The treatment schema is shown below:



The initial window treatment regimen prior to surgery is described below:

Cohort 1: Nivolumab to be delivered at a dose of 3mg/kg two weeks (weeks 1 and 3)
Cohort 2: Nivolumab to be delivered at a dose of 3mg/kg two weeks (weeks 1 and 3); ipilimumab to be delivered at a dose of 1mg/kg once (week 1, same day as nivolumab).

5.2 Pre-treatment Criteria

5.2.1 Screening for trial eligibility

Day -21 to Day 1: Screening Visit
Eligibility and exclusion criteria are provided in Section 3. These criteria will be assessed within 21 days of the first dose of study treatment (nivolumab +/- ipilimumab) 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. If screening assessments occur within 3 days 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.

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, medical histories, and prior and concomitant medications. P16 / HPV status will also be collected when available.

Additionally, given the potential difficulty with radiologic measurements in the oral cavity, photo documentation of the tumor size along with bidirectional clinical measurements is strongly encouraged in all patients.

Additional testing required, as per Section 3, is: hematology panel (see Table 1), chemistry panel (see Table 1), coagulation panel, urine or serum HCG (in women of childbearing potential; see Section 3 for when serum HCG testing is required), TSH (with reflexive Free T4 and Free T3), Mg, LDH, amylase, lipase.

Archival tumor sample should be collected (block or if not possible, 20 unstained slides). If unavailable, a baseline tumor biopsy is also recommended.

Table 1: Clinical Laboratory tests.

Category	Tests
Hematology panel	
	• Hematocrit, hemoglobin, platelet count, WBC with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), ANC
Chemistry Panel	
	• Chloride, potassium, sodium, BUN, serum creatinine, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, total bilirubin, glucose

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; WBC = white blood

cells

5.2.2 On treatment visits

Reasonable effort should be made to conduct study visits on the day scheduled (+/- 3 days).

Any changes from screening clinical evaluation findings that meet the definition of an AE will be recorded on the AE page of the eCRF.

Cycle 1, Day 1
If screening assessments occur within 3 days before start of study treatment, then they may serve as the baseline cycle 1 day 1 visit and screening tests do not need to be repeated. Pharmacy is allowed to follow the DFCI dosing weight practice which is to use the weight from baseline or the previous dose if it has not changed more than >/= 5%.≥ 5%.
Draw blood sample for:
-Hematology panel (Table)
-Chemistry panel (Table)
-Mg, LDH, amylase, lipase, LFTs

Record:
-ECOG PS
-Weight
-Vital signs
-Physical exam
-Concomitant medication use

Review all laboratory results before administering study treatment.

Criteria to treat:
-WBC ≥ 2000/ul
-ANC ≥ 1500ul
-Hgb > 9g/dL
-Platelets ≥100,000/ul
-ALT/AST ≤ 3x ULN
-Total bilirubin ≤ 1.5 ULN (or 3 in a patient with well documented Gilbert's syndrome
-Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

- *Female* CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL

- *Male* CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL

Every-2-week assessments, day 1 of cycle 2 (within 3 days of treatment):

Draw blood/collect urine sample for:

-Hematology panel
-Chemistry panel
-Mg, LDH, amylase, lipase, TSH (with reflexive Free T4 and Free T3), LFTs

Record:
-ECOG PS
-Weight
-Vital signs
-Physical exam
- Given the potential difficulty with radiologic measurements in the oral cavity, photo documentation of the tumor size along with bidirectional clinical measurements is strongly encouraged in all patients around the time of cycle 2 treatment

-Concomitant medication use
-AEs or SAEs

Review all laboratory results before administering study treatment.

Criteria to treat:
-WBC ≥ 2000/ul
-ANC ≥ 1500ul
-Hgb > 9g/dL
-Platelets ≥100,000/ul
-ALT/AST ≤ 3x ULN
-Total bilirubin ≤ 1.5 ULN (or 3 in a patient with well documented Gilbert's syndrome
-Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

- *Female* $\text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$

- *Male* $\text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$

5.2.3 Additional On-Treatment Assessments

Tumor Assessments
Tumor assessments will be performed using volumetric criteria, and RECIST 1.1 (see Section 11). Response evaluations will be performed at baseline and then following window treatment.

Research Blood Sample Collection
Three research blood sample collections should be collected at the following time points:
1. At baseline, within 21 days prior to cycle 1 day 1 of protocol therapy (ideally as close to administration of cycle 1 day 1 therapy as possible)
2. At week 2-4 prior to surgery, and then again following surgery before adjuvant therapy (if indicated).

Specific instructions for research blood draw handling are described in Section 7 and appendices.

Tumor biopsy.
Tumor biopsy should be performed when feasible at baseline, although archival tissue is acceptable.

Further details about collection and handling of tumor biopsy specimens and archival tissue can be found in Section 7 and appendices.

5.3 Agent Administration

5.3.1 Nivolumab

5.3.1.1 Storage and dispensing

Please refer to the current version of the Investigator Brochure for complete storage, handling, dispensing, and infusion information. It is acceptable to prepare and administer nivolumab per institutional practice.

5.3.1.2 Dosing

Pharmacy is allowed to follow the DFCI dosing weight practice which is to use the weight from baseline or the previous dose if it has not changed more than ≥ 5%. Other investigative sites should also follow this practice. All doses should be rounded to the nearest milligram. There are no premedications recommended for nivolumab for the first cycle. If an acute reaction is noted, it should be managed according to 5.3.1.5. Subjects may be dosed no less than 12 days from the previous dose.

Antiemetic premedications

Antiemetic premedications should not be routinely administered prior to dosing of nivolumab. See 5.3.1.9 for premedication recommendations following an infusion related reaction.

5.3.1.3 Criteria to resume treatment

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade <=1 or baseline value, with the following exceptions:
-Subjects may resume treatment in the presence of Grade 2 fatigue.
-Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
-Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin. Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (5.3.1.5) should have treatment permanently discontinued
-Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
-Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement

may resume treatment.

If the criteria to resume treatment are met, the subject may receive treatment, as long as they have not yet reached week 4 of the protocol calendar. If week 4 has been reached, the patient should proceed with surgery when feasible and medically appropriate. Any remaining doses of nivolumab will not be given.

5.3.1.4 Discontinuation criteria

Tumor assessments should continue as per protocol even if study drug is discontinued.

Treatment should be permanently discontinued for the following:

Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.

Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, and infusion reactions:

Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.

Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:

AST or ALT > 8 x ULN

Total bilirubin > 5 x ULN

Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:

Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.

Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

5.3.1.5 Treatment of infusion reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on exact clinical circumstances as appropriate.

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated). Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for <= 24 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; presser or ventilator support indicated).

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. The patient should be treated for therapy induced anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

5.3.2 Ipilimumab

5.3.2.1 Storage and dispensing

Please refer to the current version of the Investigator Brochure for complete storage, handling, dispensing, and infusion information. It is acceptable to prepare and administer ipilimumab per institutional practice.

5.3.2.2 Dosing

Pharmacy is allowed to follow the DFCI dosing weight practice which is to use the weight from baseline or the previous dose if it has not changed more than ≥ 5%. Other investigative sites should also follow this practice. All doses should be rounded to the nearest milligram. There are no premedications recommended for ipilimumab. If an acute reaction is noted, it should be managed according to 5.3.2.6.

5.3.2.3 Antiemetic premedications

Antiemetic premedications should not be routinely administered prior to dosing of ipilimumab. See 5.3.2.9 for premedication recommendations following an infusion related reaction.

5.3.2.4 Criteria to resume treatment

N/A as only a single dose of ipilimumab is administered in this trial.

5.3.2.5 Treatment of infusion reactions

Since ipilimumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on exact clinical circumstances as appropriate.

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated). Remain at bedside and monitor subject until recovery from symptoms. For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for <= 24 hours).

Stop the ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; presser or ventilator support indicated).

Immediately discontinue infusion of ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

5.3.3 Standard of care treatment following window treatment with nivolumab with or without ipilimumab

5.3.3.1 Surgery

Surgery will be scheduled following restaging imaging either during week 3 or week 4 of treatment (no sooner than 72 hrs and no longer than 7 days following administration of the 2nd cycle of

nivolumab when tolerated). The exact surgical procedure and perioperative care is at the discretion of the treating surgeon as per standard of care, but should in general include resection of the primary lesion and an ipsilateral or bilateral neck dissection with or without a reconstruction or graft.

As evidenced by patients with melanoma treated with checkpoint blockade, patients who derive clinical benefit from these agents may, in some cases, experience a transient tumor "flare" prior to a prolonged systemic response. It is unknown whether this will occur in patients treated on this trial. Since this transient flare could potentially be indicative of an anti-tumor immune response, investigators are encouraged to proceed with treatment as per protocol; however, if there is symptomatic progression with significantly increased pain, airway compromise, or any other symptoms or exam findings deemed concerning by the treating physician then the patient may proceed to surgery early. As long as the patient has received experimental treatment he/she will be monitored and considered similar to other patients enrolled in this protocol.

5.3.3.2 Adjuvant treatment

The need for adjuvant treatment will be determined by the treating physicians based on the initial clinical staging in conjunction with pathology at the time of surgery and the patient's performance status and medical comorbidities. If indicated, adjuvant treatment (radiotherapy with or without concurrent chemotherapy) will begin approximately 5-8 weeks following surgery as per standard of care.

5.4 Definition of Dose-Limiting Toxicity

Nivolumab, ipilimumab, and the combination of these two agents have been evaluated in prior phase I protocols and are being evaluated specifically in patients with SCCHN. However, although this is not a phase I protocol, the use of these drugs and the combination in the preoperative 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 each cohort. As described in detail Section 14, the safety run-in will first be performed in the nivolumab single agent cohort, using the definitions and window period defined in this section. Once the safety run in has completed successfully with single agent nivolumab, patients will be enrolled to the nivolumab/ipilimumab cohort safety run-in.

The DLT window for this study will be the period between the first treatment and the time of surgery. We will also closely monitor toxicities in the post operative period and during adjuvant treatment; however, given the significant variability in surgical procedure and adjuvant treatment and significant toxicities associated with this when administered as SOC, these will not be considered DLTs. Dose-limiting toxicity (DLT) is based on the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.0). A DLT will be defined as follows:

A patient in either cohort that is medically unable to undergo planned surgery because of toxicities deemed to be the result of experimental treatment or where surgery is delayed by >1 month beyond the originally scheduled date.

Other DLTs will be graded according to the National Cancer Institute's CTCAE version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). A DLT is any event that: a) occurs during the DLT evaluation period; and b) is possibly, probably, or definitely related to the administration of nivolumab and/or ipilimumab; and c) fulfills any of the following criteria:

1. Any Grade ≥ 3 pneumonitis, neurological event or uveitis.
2. Any Grade 2 pneumonitis, neurological event or uveitis, with the *following exception*:

- Grade 2 pneumonitis, neurological event or uveitis that downgrade to Grade ≤ 1 within 3 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.

3. Any *other* Grade ≥ 3 toxicity, with the *following exceptions*:

- Grade 3 irAEs that downgrade to Grade ≤ 2 within 3 days, or to Grade ≤ 1 or baseline within 14 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.

- Grade 3 colitis that downgrades to Grade ≤ 2 within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.

- Grade 3 asymptomatic endocrinopathy, managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.

- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).

- Grade 3 fatigue for ≤ 7days.

- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.

- Liver transaminase elevation ≤ 8 times ULN that downgrades to Grade ≤ 2 (≤ 5 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.

- Total bilirubin ≤ 5 times ULN that downgrades to Grade ≤ 2 (≤ 3 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.

- Grade ≥ 3 neutropenia that (1) is not associated with fever or systemic infection, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.

- Grade 3 and 4 lymphopenia.

- Grade 3 thrombocytopenia that (1) is not associated with clinically significant bleeding, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.

- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.

- Any pre-existing laboratory abnormality that deteriorates to Grade 3/4, but where the increment of deterioration is considered not clinically significant by both investigator and sponsor.

Immune-related AEs (irAEs) are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

While rules for adjudicating DLTs are specified above, an AE that is Grade < 3 or listed as exempt above may also be defined as a DLT after consultation with the sponsor and Investigators, based on the emerging safety profiles of nivolumab and ipilimumab. Likewise, subjects who become not evaluable for DLT because they discontinued or interrupted treatment due to toxicities other than DLTs may be counted as DLT subjects.

5.5 General Concomitant Medication and Supportive Care Guidelines

The treating physicians may deliver supportive care as indicated or as specified above in section 5.2, 5.3 and the IB.

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

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

All concomitant medications received within 28 days before the first dose of study treatment should be recorded. Relevant concomitant medications administered after the last dose of trial treatment should be recorded for SAEs as specified in Section 11.1.2.

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol

- Investigational agents other than nivolumab with or without ipilimumab

- Any systemically active oral, injected, or implanted hormonal method of contraception except for progesterone coated intrauterine devices (IUDs) that had been previously implanted.

- Live vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

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

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

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

The following treatments are permitted throughout the duration of the study treatment phase and during follow-up:

- Standard therapies for pre-existing medical conditions unless listed as prohibited therapy below. Any medication intended solely for supportive care (e.g., analgesics, anti-diarrheal, anti-depressants) may be used at the investigator's discretion. Antiemetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drugs. At the discretion of the investigator, prophylactic antiemetic and anti-diarrheal medication(s) may be used as per standard clinical practice before subsequent doses of study drugs or before, during or after radiation treatment.
- Anticoagulants - Anticoagulation with heparin, heparin derivatives, and/or warfarin may be given at the discretion of the treating physician. Coagulation parameters should be checked at least once monthly, or more frequently at discretion of treating physician.
- Pain medications administered per standard clinical practice are acceptable while the patient is enrolled in the study.

Patients who experience toxicities should be treated symptomatically as clinically indicated. Medications that are considered necessary for the subject's welfare and that are not expected to interfere with the evaluation of study treatment or be restricted may be given at the discretion of the investigator. Ancillary treatments will be given as medically indicated.

5.6 Duration of Therapy

In the absence of DLTs study treatment is expected to continue until the second dose of nivolumab is administered. At that time, all subsequent cancer treatment will be administered as per standard of care.

5.7 Criteria for Taking a Participant Off Protocol Therapy

Participants should also be removed from protocol therapy if any of the following occurs:

- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply
- 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
- Intercurrent illness that prevents further administration of treatment and/or would affect the assessment of the subject's clinical status to a significant degree
- Pregnancy

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.

Information will be entered in OnCore when a participant is removed from protocol therapy.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Jonathan Schoenfeld, MD, MPH at 617-632-3591 or at Partners pager 18874.

5.8 Duration of Follow Up

5.8.1 The patient will be followed at least every other week during the window phase of this trial (weeks 1-4)

5.8.2 First restaging will be performed after window treatment and prior to surgery (week 3 or week 4)

5.8.3 Following surgery on week 3 or 4, patients will be followed as per standard of care. This may include radiation with or without concomitant chemotherapy at the discretion of the treating physicians. As per standard of care, patients will have restaging exam and scans between 10 and 16 weeks following the completion of all cancer directed therapy or earlier if clinically indicated. The scans at the 3 month follow up time point are optional, but highly encouraged.

5.9 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).

The research team will update the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE version 4.0) which is identified and located on the CTEP website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit 1 year after enrollment. Participants continuing to experience toxicity at the last scheduled study visit may be kept on the study until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

Adverse events (both non-serious and serious) associated with nivolumab with or without ipilimumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. Please refer to Appendix D and E and the current versions of Investigator's Brochures for expected toxicities related to nivolumab and ipilimumab.

As there is potential for hepatic toxicity with nivolumab or nivolumab/ipilimumab combinations, drugs with a predisposition to hepatoxicity should be used with caution in patients treated with nivolumab-containing regimen.

6.2 Toxicity Management

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological. (Please see Appendix C).

Early recognition and intervention are recommended according to the management algorithms; and in addition include ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab or ipilimumab related uveitis.

The recommendations are to follow the algorithms in the nivolumab investigator brochure for immune related events; while the ipilimumab investigator brochure contains similar algorithms, the algorithms in the nivolumab brochure have been aligned to accommodate combinations as well as nivolumab monotherapy.

For subjects expected who require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider the following recommendations

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.

- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.

- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab and ipilimumab, including results from clinical studies, are available in the Appendix D and E and the IB.

6.2.1.1 Management algorithms for nivolumab (Please see Appendix C)

Immuno-Oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, renal, pulmonary, hepatic, endocrinopathies, skin, neurological. The algorithms recommended for utilization in this protocol are found in the Investigator Brochure.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in the IB.

Because of the potential for clinically meaningful nivolumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity.

6.2.1.2 Management algorithms for ipilimumab (Please see Appendix C)

Immuno-Oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Ipilimumab is considered an immuno-oncology agent in this protocol. Early recognition and management of adverse events

associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, renal, pulmonary, hepatic, endocrinopathies, skin, neurological.

The algorithms recommended for utilization in this protocol are found in the Investigator Brochure.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in the IB.

Because of the potential for clinically meaningful ipilimumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity.

6.3 Dose Modifications/Delays

Dose modifications to nivolumab and ipilimumab are not permitted in this study.

6.3.1 Delays in nivolumab administration

Study drug administration should be delayed for the following:

-Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions: Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.

-Any Grade 3 skin, drug-related adverse event.

-Any Grade 3 drug-related laboratory abnormality, with the following exceptions: Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.

- If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
- If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity

-Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Note: If any treatment delay would extend the second cycle beyond the planned surgical date, it is suggested that the second cycle be held and the patient proceed to surgery as scheduled or as soon as medically indicated.

7. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Biopsy confirmed squamous cell carcinoma is a requirement to be enrolled on this study. Tissue will be obtained prior to any treatment for research purposes whenever possible. If diagnostic biopsy was performed prior to enrollment on study (archival sample) and extra specimen is available from this biopsy, then this tissue may be obtained for use. A separate research biopsy is also strongly recommended – this can be a core biopsy of a lymph node or an in office biopsy. At the time of definitive surgical resection, after adequate tumor for pathological assessment has been harvested as deemed by the surgeon, remaining tissue will also be obtained for research purposes. If relevant, tissue may also be obtained at the time of first recurrence after surgery for study.

Biopsies/surgery should not generally be performed on Friday afternoons, as there may not be time for processing of tissue. However, specimens in formalin may be stored over the weekend and transported on Monday. Specimens in formalin should be stored at room temperature until shipment. Other investigative sites should follow institutional procedures for collecting and processing biopsy specimens.

When archival tissue is used for the pretreatment tissue specimen, formalin-fixed paraffin embedded block(s) and or unstained/unbaked slides (15-20 recommended, although fewer are acceptable), stored at room temperature and tissue scrolls should be obtained to facilitate correlative analyses.

In the case of fresh biopsies / surgical specimens, ideally at least 2-4 core biopsies / pieces of tumor tissue will be obtained:

- Half of the cores / specimens should be placed in 10% neutral buffered formalin tube.
- Half of the cores / specimens should be processed fresh for molecular analyses in media, snap frozen or frozen in RNAlater.

After being obtained, processing of the specimens is as follows:

- All samples should be de-identified and labeled with the Participant initials, Participant Study ID number, anatomical location from which tissue was obtained (e.g. lymph node, primary oral cavity tumor) and date of procedure.
- Specimens in formalin should be should be transferred to a pathology laboratory, placed in fixative at a 10:1 ratio and fixed for at least 24-48 hours. Thicker tissue samples may require longer fixation to create a formalin-fixed, paraffin embedded block.
- Specimens to be processed immediately for molecular analyses should be transferred to the lab of Ravindra Uppaluri, MD PhD or Kai Wucherpfennig PhD with 1.5 hours of collection.
- Snap frozen or specimens in RNA later should frozen in liquid nitrogen and then stored at -70 to -80.

Slides / tissue blocks will then be sent to / collected by:

Shana Criscitiello | Clinical Research Coordinator
Department of Radiation Oncology
Brigham and Women's Hospital/Dana-Farber Cancer Institute
E-mail: scriscitiello@bwh.harvard.edu
Phone: (617) 582-8919

Fax: (617) 582-8911
Pager: BWH 33150
Location: Dana L1, Room 51

If slides / blocks are shipped, a specimen inventory including the Participant initials, Participant Study ID number, anatomical location from which tissue was obtained (e.g. lymph node, primary oral cavity tumor) and date of procedure should be included with all samples and also emailed to scriscitiello@bwh.harvard.edu with shipment tracking number. Site specific shipping policies should be observed to ensure safe handling, travel and arrival.

Frozen / RNAlater samples can be batched and shipped overnight on dry ice to the lab of Mariano Severgnini at:
Center for Immuno-Oncology
Dana-Farber Cancer Institute
450 Brookline Ave, JF0406
Boston, MA 02215
Phone: (617) 632-2421
DFCI pager: 617-632-3352 pager: 42093
Email: **mariano_severgnini@dfci.harvard.edu**

If frozen specimens are shipped, a specimen inventory including the Participant initials, Participant Study ID number, anatomical location from which tissue was obtained (e.g. lymph node, primary oral cavity tumor) and date of procedure should be included with all samples and also emailed to mariano_severgnini@dfci.harvard.edu with shipment tracking number. Site specific shipping policies should be observed to ensure safe handling, travel and arrival.

We will perform comprehensive immune profiling on all tissue obtained in the context of this trials as allowed by the amount of tissue obtained. The purpose of these analyses will be to analyze the expression select biomarkers (PD-L1, PD-L2, PD1, CD3, CD68, CD8, Ki67) and to determine the p16 status from samples collected from patients with oral cavity cancer treated with nivolumab with or without ipilimumab and analyze the effect of treatment on these parameters. These analyses will include, H&E stain, immunohistochemistry and multiplex immunofluorescence to evaluate multiple biomarkers in tandem.

Additional tissue, if available, will be used to stain for additional markers including other checkpoint ligands and receptors, RNA analyses including RNA profiling, whole exome sequencing to determine mutational burden and neoantigen detection, T-cell receptor sequencing to determine intratumoral TCR diversity (in conjunction with Adaptive Biotechnology) mouse xenograft studies, and flow cytometry to quantify immune populations. De-identified specimens be processed and analyzed by outside facilities as appropriate to perform these analyses.

Peripheral blood samples will be collected for use in studies by the study team and Adaptive Biotechnology to investigate immune functioning and anti-tumor immunity before and after window

treatment and then again after surgery and before adjuvant treatment, if indicated. The volume of blood to be collected per blood draw for study purposes will not exceed 40 cc.

Each 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 lab 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.

Research blood samples will be drawn in phlebotomy and will be captured in three 8-cc whole blood or EDTA tubes, and 1 red top tubes.

Blood samples will be processed by the lab of Kai Wucherpfennig PhD, the Center for Immuno Oncology laboratory at the Dana-Farber Cancer Institute, or at other investigative sites. Two components will be stored from the tubes: serum/plasma and mononuclear cells. Each red tube should yield about 3 cc of serum. Blood for serum will be spun (3000 g x 10 minutes at 4C) within 5 hours of collection and serum removed by pipetting. Serum will be maintained in 1-cc aliquots in vials at -80C. Isolation of mononuclear cells and plasma will be collected from whole blood tubes after centrifugation at 1500 RCF for 20 minutes or by using similar standard institutional protocols. Plasma will be removed by pipetting and maintained in 1-cc aliquots in vials at -80C. Mononuclear cells will be pipetted into a 15 mL centrifuge tube and washed twice with PBS, spinning the cells at 300 RCF and aspirating the PBS in between each wash. The resulting cell pellet will be resuspended in 10% DMSO-containing media and stored in cryovials at -80C.
Sites other than the DFCI may either process PBMCs on site, following standard protocols and ship frozen pellets and plasma separately (**preferred method**) or immediately express ship unprocessed vacutainer tubes using an overnight courier, ex. Fed Ex. **The integrity of the blood samples requires they be processed within 24 hours of collection.**

Shipping information from sites other than DFCI:

- Unprocessed tubes must be shipped on the day of collection. Samples are to be shipped overnight Mon-Thurs ONLY, at ambient temperature by overnight carrier such as FedEx or UPS
- Processed samples – it is suggested to batch ship these samples at a time agreed by the collection site and DFCI.
    - Plasma/ Serum: Ship overnight, Monday-Thursday ONLY, using a styrofoam box containing dry ice, using appropriate labels, following all safety/shipping regulations. Shipments must be made by an overnight carrier, such as FedEx or UPS.
    - PBMCs: ship overnight, Monday-Thursday ONLY, using cryotanks containing liquid nitrogen, using appropriate labels, following all safety/shipping regulations. Shipments must be made by an overnight carrier, such as FedEx or UPS. Cryotanks have temperature monitors

connected to an alarm system at Cryoport headquarters. Shipping temperature should be around -150C.
Cryoport, Inc
17305DaimlerSt.
Irvine, CA 92614
+1 949.470.2300
cs@cryoport.com

All blood samples will be shipped to the lab of Mariano Severgnini at:
Center for Immuno-Oncology
Dana-Farber Cancer Institute
450 Brookline Ave, JF0406
Boston, MA 02215
Phone: (617) 632-2421
DFCI pager: 617-632-3352 pager: 42093
Email: **mariano_severgnini@dfci.harvard.edu**

When specimens are shipped, a specimen inventory including the Participant initials, Participant Study ID number, and date of collection should be included with all samples and also emailed to mariano_severgnini@dfci.harvard.edu with shipment tracking number. Site specific shipping policies should also be observed to ensure safe handling, travel and arrival.

Once collected, samples will be coded to maintain patient confidentiality and then transferred to the center for Immuno Oncology at the DFCI for use in studies of immune functioning.

Studies of immune function performed on blood will include:
-Analysis of antibody response (both quantitative antibody titer and qualitative antibody binding and functionality)
-Study of T-cell composition and functioning
-Analysis of cytokine response
-Identification of circulating antigen, DNA or tumor cells
-Comparison of immune responsiveness in serum
-Analysis of blood cell composition using flow cytometry
-Effect of immune status on circulating tumor cells
-Analysis of genomic or protein polymorphisms that may affect immune functioning and inflammation
-Analysis of inflammatory status in correlation to toxicity response
-Analysis of intracellular signaling pathways

Blood will be collected according to standard clinical protocol. Blood samples will only be requested during a regularly scheduled clinic visit, and no more than 40 cc will be collected during a single visit, and no more than 80 ml in a four-week period. Patient identifiers will be removed from patient samples, and each sample will be given a unique identifier. Discarded samples will be completely de-identified, and all samples will be de-identified at the end of the study. Samples should be stored in a locked freezer.

Standard imaging (CT neck and/or PET/CT or CT chest) will be performed before and after window treatment. Although not required – a before and after PET/CT is strongly encouraged in all patients. In addition to monitoring response and correlating with pathologic response, we will analyze various radiologic parameters [46] to correlate with pathologic response, outcome as well as immunologic parameters such as degree of lymphocyte infiltration.

8. PHARMACEUTICAL INFORMATION

Drug Ordering

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

Product information

PRODUCT INFORMATION TABLE 2: Please also see respective Product Investigator Brochures

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	5-10 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
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

*Nivolumab may be labeled as BMS-936558-01 Solution for Injection

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

For additional details on prepared drug storage and use time of nivolumab or ipilimumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) and Ipilimumab Investigator Brochure section for “Recommended Storage and Use Conditions”

Dose calculations and administration

The first dose of nivolumab with or without ipilimumab will be administered week 1 of the study treatment. Preparation and administration details are described in the investigational brochure.

Nivolumab and ipilimumab will be given together week 1 for subjects enrolled in cohort 2.

Nivolumab dose = 3 mg/kg

Ipilimumab dose = 1 mg/kg

When study drugs (ipilimumab or nivolumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. It is recommended that nivolumab be administered first. The second infusion will always be ipilimumab, and will start approximately 30 minutes after completion of the nivolumab infusion.

BMS-936558 (nivolumab) is to be administered as a 60 (+/- 15) minute IV infusion. Ipilimumab should be administered as a 90 (+/- 15) minute IV infusion following.

Ipilimumab and nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

Pharmacy is allowed to follow the DFCI dosing weight practice which is to use the weight from baseline or the previous dose if it has not changed more than ≥ 5%. All doses should be rounded up or to the nearest milligram per institutional standard.

Cohort 1 patients will receive a total of two nivolumab doses (Week 1 and 3). Cohort 2 patients will receive a total of two nivolumab doses (Week 1 and 3) and one ipilimumab dose (Week 1).

Following the first dose of nivolumab with or without ipilimumab, nivolumab will be given on week 3 at a dose of 3mg/kg. Patients may not be dosed with nivolumab less than 12 days apart; and may be dosed up to 3 days after the scheduled date, if necessary.

Dose Modifications
There will be no dose modifications permitted. Dose reductions or dose escalations are not permitted.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 3 weeks prior to start of protocol therapy (except for pregnancy test and baseline tumor biopsy, as detailed). If these screening assessments occur within 3 days before start of study treatment, then they may serve as the baseline cycle 1 day 1 values. Each treatment cycle will be 14 days long. Subjects may be dosed no less than 12 days between doses.

As detailed in the Study Calendar, a negative pregnancy test in women of child-bearing potential must be documented within 24 hours before the first dose of study medication.

Correlative tissue collection obtained before starting protocol therapy, should be performed if archival tissue is not available.

In the 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.

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.

Scans must be done ≤4 weeks prior to the registration.

	Screening	Week 1	Week 3	Presurgery/surgery (week 3-4)	Week 10-20	3 months after all treatment	3 months to 1 year[l]	1 year visit[l]	Survival follow up by phone[m]
Informed consent	X								
Medical History	X								
Physical exam (Ht, Wt, VS, PS)[a]	X	X	X			X[i]	X[i]	X[i]	
B-HCG[b]	X								
Routine labs[c, d]	X	X[c]	X	X					Xi
Screening labs/ECG[e]	X								
Adverse event evaluation[f]	X	X	X			X[i]	X[i]		
Radiologic evaluation[g]	X			X					
Correlative blood collection[h]	X			X	X		X		X
Correlative tissue collection	X[j]			X[k]					
Study Agent - Nivolumab		X	X						
Study Agent - Ipilimumab(cohort 2 only)		X							

a. Height is taken only at screening.
b. Serum or urine pregnancy test (women of childbearing potential), within 24 hours of the first dose of nivolumab.
c. Not needed if pre-study labs performed within 3 days of Day 1.
d. CBC with differential, comprehensive chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea, Cre, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, phosphorus, albumin, and total protein as well as TSH, Free T4, and Free T3.
e. Routine labs as per D, and also HBVsAg, HCV Ab or HCV RNA. EKG is required only at screening and as clinically indicated. If patient is not high risk, negative tests results don't need to be resulted for study enrollment.
f. In addition to specified time points, adverse effects will also be continuously monitored.

g. Imaging will include CT neck/chest and/or PET-CT. MRI neck may be performed instead of CT neck. h. Correlative blood collections will be timed to coincide with blood drawn for other reasons, but will in general be scheduled at baseline, week 3-4 and then after surgery and before adjuvant treatment (week 10-20), if indicated. Additional optional research blood draws may be taken during routine follow up to year 3. i. Not performed if patient receiving care at outside institution. All efforts will be made to obtain outside medical records. j. Archival tissue may be used. k. Obtained at the time of surgery (week 3-4). l. Visits will occur approximately every 2-3 months over the first year. Medical records from local evaluations may be provided if patient is unable to follow up at study site. m. 1 year after enrollment (+/-2 weeks), patients will be restaged with a clinical exam, CT neck/chest and/or PET-CT as per standard of care. This is optional, but highly encouraged. Medical records from local evaluations may be provided if patient is unable to follow up at study site. n. After the 1 year visit, follow up for survival will continue by phone. Patients will be contacted by phone, every 3 +/- 1 month, for up to 3 years from enrollment.	

10. MEASUREMENT OF EFFECT

The main focus of this trial is to determine safety and response in the window period where the two investigational agents will be investigated. Thus patients will be examined and staged as part of the screening process and then again following window treatment prior to surgery. Pathologic evaluation will also be performed at the time of surgery. Following surgery (and adjuvant therapy, if indicated), follow up will be as per standard of care, with an emphasis on monitoring of disease-free and overall survival.

10.1 Antitumor Effect– Solid Tumors

For the purposes of this study, participants should be re-evaluated for response at week 3-4 following window treatment and prior to definitive surgery.

There is currently some uncertainty about how best to monitor response to immunotherapy [47], as well as how best to monitor response in the preoperative window setting [48, 49]. Additionally, assessing radiologic response in the oral cavity can be complicated by dental artifact and head position. Therefore, response will be assessed in multiple ways using clinical, radiologic and pathologic data. Thus, although our primary endpoint will utilize volumetric measurements (obtained either radiologically, clinically or pathologically) that have been previously investigated in this setting [48], international RECIST criteria will also be measured as a secondary endpoint. Changes in the diameter (unidimensional axial measurement) of the tumor lesions are used in the RECIST criteria. We will also evaluate pathologic response defined below.

10.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

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

10.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one lesion that can be accurately measured in at least one dimension with longest diameter $\geq$20 millimeters (mm) using conventional techniques (CT, MRI, x-ray, PET-CT or clinical exam) or $\geq$10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). In the oral cavity, imaging modalities may be obscured by dental artifact, or normal mucosa; therefore, clinical exam or pathologic measurements may suffice.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease.

Target lesions. All measurable lesions up to a maximum of 10 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the RECIST objective tumor response. Volumetric measurements may also be made using imaging software using contouring software or by obtaining measurements in at least 2 dimensions or by multidimensional measurements obtained from clinical exam.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 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 or absence of each should be noted at each follow-up.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital 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. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial or mucosal (e.g., skin nodules, oral cavity primaries and palpable lymph nodes). In these cases, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously.

10.1.4 FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (L.K. Shankar, J.M. Hoffman, S. Bacharach, M.M., et al. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med, 47(6):901-903, 2006 or http://www.ncbi.nlm.nih.gov/pubmed/16741317). Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose

of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients.

10.1.5 **Response Criteria**

10.1.5.1 Evaluation of Target Lesions

Volumetric Analysis

As previously described [48], volumetric response will be determined by measuring measurable and non measurable primary and nodal disease in at least two dimensions as determined by scan, clinical exam or pathology. If measurement in two dimensions is not possible due to irregular shape of the lesion, comparison of the single largest dimension measured may be used. In all cases, serial photographs are strongly recommended to help assess response. Responders will have demonstrated any decrease in overall tumor volume. Primary and nodal volume will also be assessed separately in terms of response.

RECIST Criteria

Complete Response (CR): Disappearance of all target lesions.

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

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

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

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

10.1.5.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

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

Progressive Disease (PD): Appearance of one or more new lesions* (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time by review of the Principal Investigator. Additionally, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is mandatory to differentiate between stable and progressive disease.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e., not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. 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 scan on which the lesion was discovered.

10.1.6 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 recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

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 recurrent disease is objectively documented.

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

10.1.7 Local failure is defined as the presence of biopsy-proven recurrent cancer at the original site of the primary tumor or radiologic scans that demonstrate progression at that site. Local progression-free survival (LPFS) is defined as the duration of time from enrollment to time of local failure or death.

10.1.8 Regional failure is defined as the presence of biopsy-proven recurrent cancer within the head and neck region outside of the area of the primary lesion or radiologic scans that

demonstrate progression at that site. Regional progression-free survival (RPFS) is defined as the duration of time from enrollment to time of regional failure or death.

10.1.9 Disease-free survival is defined as the time between first study treatment and either recurrent disease or death. Recurrent disease includes a local failure, regional failure, or distant metastasis.

10.1.10 Response Review

Central review is not going to be performed.

10.2 Other Response Parameters

Pathologic response should be assessed qualitatively and quantitatively (e.g. percent viable cells) [36, 37] when possible. This will take into account immune infiltration with or without tertiary lymph node structures, evidence of tumor death and subsequent tissue repair – these features should be documented and recorded when observed.

Pathologic staging will also be compared with clinical staging performed at study entry.

For patients that have a PET performed before and after treatment, the maximum SUV of the primary lesion and of the most avid nodal disease with in the neck should be recorded before and after study therapy.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry, are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned). Surgery to remove the primary oral cavity lesion and/or nodal disease, or any additional surgery performed as a result of this surgery is also not considered an SAE.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions. This does not include expected side effects of planned surgery.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.3.1 Expected adverse event

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, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

11.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, or the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- 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.

11.2 Procedures for AE and SAE Recording and 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 4.0) will be utilized for AE reporting. The CTEP Active Version of the CTCAE version 4.0 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.

11.3 Reporting Requirements for Participating Investigators

Each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

It is the responsibility of each participating investigator to report adverse events within 48 hours to the Overall PI, Dr. Jonathan Schoenfeld, MD, MPH (at the contact given below), or representative personnel; and submit to DFCI IRB within 10 working days.

Jonathan Schoenfeld, MD, MPH
617-632-3591
jdschoenfeld@partners.org

11.4 Reporting Requirements for DFCI IRB

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 30 days of the last dose of treatment (C2D1) on the local institutional SAE form.

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.
.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

11.5 Expedited Reporting to Hospital Risk Management

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

11.6 Reporting Requirements for FDA

There will be no submissions to the FDA as this protocol is deemed IND exempt.

11.7 Reporting Requirements for BMS

The Overall PI, or representative personnel; as soon as possible under the circumstances, will notify BMS of any serious adverse events (within 48 hours of learning about the event).

A report will be sent for any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment (C2D1).

BMS contact for SAE reports:

Email: Worldwide.Safety@BMS.com
Fax: +01-609-818-3804

11.8 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention through the study intervention period and up to 30 days after the last study intervention (C2D1) should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and monitor data for this study.

Note: **All** adverse events that have occurred on the study, including those reported through AdEERS, must be reported via CTMS or CDUS.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the ODQ is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to enrollment with ODQ
On Study Form	Within 21 days of enrollment

Baseline Assessment Form	Within 21 days of enrollment
Treatment Form	Within 14 days of the last day of the cycle
Adverse Event Report Form	Within 14 days of the last day of the cycle
Response Assessment Form	Within 14 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 21 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 21 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. 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 Principal Investigator and study team.

The DSMC will meet quarterly and/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 within 30 days for Phase I or II protocols; 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.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant enrollment and will continue during protocol performance and completion.

12.4 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix D.

- *The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.*

- *Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.*

- *Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.*

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator will disseminate protocol amendment information to all participating investigators.

All IRB decisions concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

    - Title 21 Part 56 – Institutional Review Boards
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

    - Title 21 Part 312 – Investigational New Drug Application
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

14. STATISTICAL CONSIDERATIONS

This sequential biomarker driven screening design is designed to identify promising treatments worthy of additional study.

Co Primary Endpoint
The primary endpoints for this trial is safety and tolerability defined as the number of DLTs and volumetric response as defined in section 10.1.

Secondary Endpoints:
Secondary endpoints include disease response according to RECIST 1.1, pathologic response, local failure rate, regional failure rate, local and regional progression free survival, disease-free survival, and overall survival. All are defined in Section 10.1.

Sample Size and Study Duration:

Because the use of nivolumab with or without ipilimumab is relatively novel in this setting, we will complete a safety run-in prior in each cohort prior to enrolling additional patients. If a single patient in either cohort is permanently unable to undergo surgery as a result of investigational treatment, enrollment to that cohort will close other DLTs are defined in Section 5.4. If this occurs in the nivolumab cohort then the study will close. The safety run in will begin and complete for nivolumab cohort before enrollment begins on the safety-run in ipilimumab cohort. Once both safety run-ins are complete, patients will be randomizedrandomized to one of the two cohorts. If at any point during the study only one cohort is open for enrollment, all patients will be assigned to that cohort.

The safety run in for each cohort will follow a typical 3+3 design in each cohort. Initially 3 patients will be entered. If 0 out of 3 patients experiences dose-limiting toxicity (DLT), the safety run in will end and the study will proceed. If exactly 1 out of 3 patients has a DLT, an additional 3 patients will be entered in the safety run in. If none of the next 3 patients experiences a DLT, the study will proceed. If at any time 2 (or more) patients experience DLT, the study will terminate. Either arm will be considered promising if the safety run in is successfully completed.

Additionally, either arm (nivolumab or nivolumab combined with ipilumumab) will be considered promising and worthy of further evaluation if there is strong evidence that the response rate in either arm evaluated independently may be at least 15% (number of patients with volumetric response versus total number of patients treated in that arm). Response rates will also be correlated with RECIST and pathologic response and changes in lymphocyte infiltration of primary tumor deposits.

The decision rule will be based on the lower bound of the one-sided, 90% exact binomial confidence interval. With this criteria, the treatment will be considered promising if 6 or more of the 20 patients (including patients in the safety-run in) in either arm demonstrate a response. This

would correspond to a lower confidence bound that is at least 15%. If none of the first 10 patients in either arm have a response, then enrollment will stop. Analyses of response rates will be presented by treatment arm within disease accompanied by exact 80% confidence intervals. For a sample of size 20 per arm, each confidence interval will be no wider than 0.32. We will also estimate an aggregated response rate for each treatment modality and present with 80% exact confidence intervals.

Correlative studies will be largely exploratory in nature. We will attempt to correlate PD-L1 expression, mutational burden, T-cell infiltration and initial tumor burden with volumetric, RECIST and pathologic response. We will measure changes in radiologic and pathologic parameters and IHC staining over the course of therapy and correlate these with response and changes in immune markers present in the peripheral circulation.

The accrual goal for this study is 40 patients. We anticipate enrolling approximately 2 patients per month. Therefore, we expect to completely accrue to this study in approximately 20 months. 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 reported or after the outcome data are sufficiently mature for analysis, as defined above.

Analysis of Endpoints:

The primary endpoint is volumetric response, which will be assessed among all patients who initiate protocol therapy. Response will be assessed as defined in section 10.1. The response rate will be reported with 90% exact confidence intervals.

All patients who initiate protocol therapy will also be evaluated for response using RECIST v1.1, pathologic response at the time of surgery, safety and tolerability, local failure rate, regional failure rate, local and regional progression free-survival and overall survival. PFS and OS will be analyzed using Kaplan–Meier product-limit estimates and will be plotted using Kaplan-Meier plots. PFS is defined as the time from study randomization to disease progression according RECIST 1.1, medical judgment or death due to any cause, whichever occurred first. Patients alive without disease progression are censored at the date of last disease evaluation. The hazard ratio for each time-to-event endpoint will be estimated with 95% confidence intervals derived from the Cox proportional hazard model, but no hypothesis testing will be conducted. Other definitions are provided in section 10.1.

All patients will be evaluable for toxicity from the time of their first treatment with any study agent. Toxicity will be graded according to NCI CTCAE, Version 4.0. Toxicities will be summarized by maximum grade and by treatment arm. Incidence rate of each toxicity will be reported with 95% exact CI.

15. PUBLICATION PLAN

We expect this study to produce at least 1 abstract that will be presented at a national meeting, as well as a publication reporting the final results of the study. We will plan on submitting the study results approximately 2 years after the accrual is complete, allowing additional time for toxicity.

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APPENDICES

Appendix A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	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: Methods of Contraception

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

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. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure

Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

6. Intrauterine hormone-releasing system (IUS).
7. Complete abstinence

Complete abstinence is defined as the complete avoidance of heterosexual intercourse.

Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).

It is not necessary to use any other method of contraception when complete abstinence is elected.

Subjects who choose complete abstinence must continue to have pregnancy tests

Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Less Effective Methods Of Contraception

1. Diaphragm with spermicide
2. Cervical cap with spermicide
3. Vaginal sponge with spermicide
4. Male or female condom with or without spermicide*
5. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

* A male and a female condom must not be used together.

Unacceptable Methods Of Contraception

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)
3. Spermicide only

4. Lactation amenorrhea method (LAM)

Appendix C: 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

Investigators should refer to the most current version of the nivolumab or ipilimumab IB for current recommendations for management of a specific Adverse Event of interest.


I-O Safety Algorithm_GI.pdf


I-O Safety Algorithm Renal.pdf


I-O Safety Algorithm_Pulm.pdf


IO Safety Algorithm_Hepatic.pd


I-O Safety Algorithm_Endocrine.


I-O Safety Algorithm_Skin.pdf


I-O Safety Algorithm_Neuro.pdf

Appendix D: MULTICENTER GUIDELINES

Appendix D
Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies [17-22]. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro [5]. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells[23]. Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by IHC) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness [20, 21]. Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. In addition, in multivariate analysis, high expression of PD-L1 is correlated to have a worse overall survival rate compared to low expression levels of PD-L1[24]. 6
Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. 7
OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014). 7
Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro [25]. Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1. In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-α release [26]. 7
In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, 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. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.....7
In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at <=10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC (0-168 h)] 117,000 µg • h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice [27]. 7
The PK, clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, and clear-cell renal cell carcinoma (RCC) in addition to other tumor types. Please refer to the 2015 IB for specific details. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies. 8
Nivolumab is approved in multiple countries including the US for treatment of previously treated, unresectable or metastatic melanoma, advanced renal cell carcinoma and previously treated, metastatic squamous NSCLC, the EU for treatment of previously treated, unresectable or metastatic melanoma, and Japan for treatment of unresectable melanoma. Please see the IB for more details.....8
The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. 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 Q2W, 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 PPK analysis suggested that the following factors had no clinically important

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA, OHRP, etc.). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e.

CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Jonathan Schoenfeld, MD will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Require all DFCI and Participating Institution Institutional Review Boards' (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor and as approved by Janssen.

- Identify and qualify Participating Institutions and obtain accrual projections prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.

- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center.
- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.
- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB will provide a consent template, with information regarding authorization for the use and disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be

de-identified. It is recommended that the assigned unique subject number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the research nurse or data manager and e-mailed to the Coordinating Center or study coordinator:

- Copy of screening test results, including imaging and pathology results
- Signed participant consent form
- HIPAA authorization form
- Eligibility checklist
- Clinic note, covering screening requirements and baseline AEs

The research nurse or data manager at the participating site will send the registration packet via email to the project manager at DFCI CTO. To complete the registration process, the coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101A) and register the participant on the protocol. The coordinator will e-mail the participant study number and treatment assignment to the participating site.

Subjects will be randomized by HCRN DF/HCC Office of Data Quality (ODQ) in a 1:1 ratio to either Cohort 1 or Cohort 2. Following registration and randomization, subjects may begin protocol treatment. Issues that would cause treatment delays should be discussed with the sponsor-investigator.

Randomization can only occur during ODQ's normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Time.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.9 Protocol Deviations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.9.1 Definition

Protocol Deviation: Any departure from the defined procedures set forth in the IRB approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol deviations occurring at their site. The DF/HCC Sponsor will also be responsible for ensuring that all protocol deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring is outlined in the protocol.

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol Section 11.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy IRB of record's Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the protocol requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.11 Data Management

Data will be handled and recorded in accordance with Section 12 of the protocol and from Section 3.10.1 of the DSMP.

Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of

electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

3.11.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

- All visits must be checked in and all data entered within 15 business days of the visit occurring. Any visit data not entered within 15 business days is considered overdue. Sites will be notified of delinquent data in an escalating series of contacts until data is complete.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institutions may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

5.1.1 Remote Monitoring

DFCI CTO will virtually monitor sites throughout the study. On-site monitoring visits will be supplemented with virtual monitoring visits. The DF/HCC Lead Institution will request source documentation from Participating Institutions as needed to complete virtual monitoring activities. Participating Institutions will be asked to forward de-identified copies of participants' medical

record and source documents to the DF/HCC Lead Institution to aid in the source documentation verification process.

5.1.2 On-Site Monitoring

On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for verification during on-site visits. Upon request, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the Participating site. If there are protocol compliance concerns, issues that impact subject safety or the integrity of the study, or trends identified based on areas of need, additional monitoring visits may occur.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The minimum accrual requirement is 3 patients per site annually because this is a Phase II trial.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited. The DF/HCC Sponsor may request that an audit be performed by the ODQ if instances of serious non-compliance are found during routine monitoring.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this

protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor, DFCI IRB is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.