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Title: Neoadjuvant nivolumab and lirilumab followed by surgery followed by adjuvant nivolumab and lirilumab in SCCHN

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

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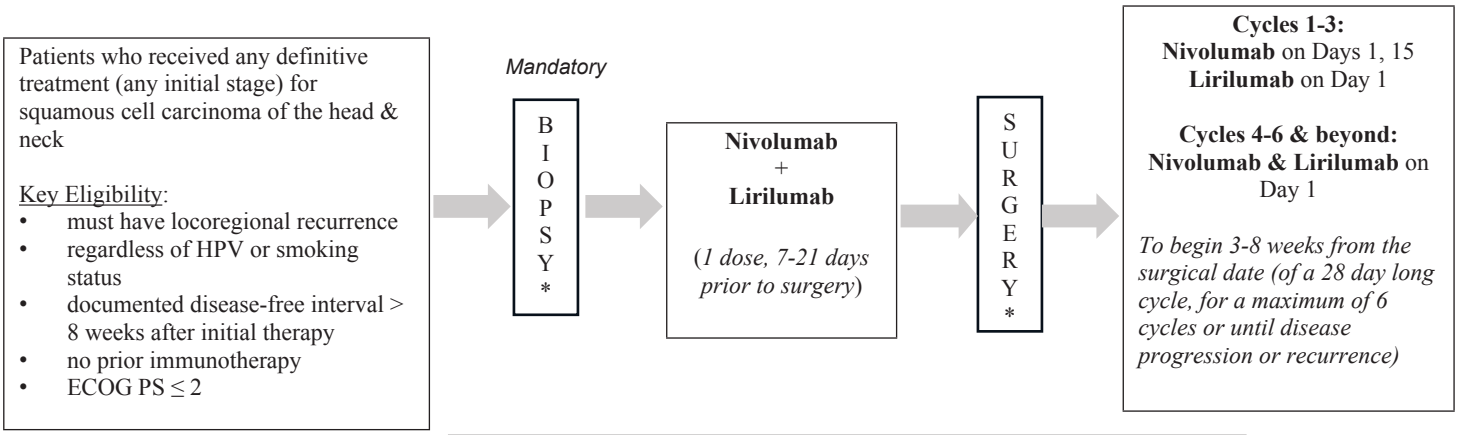
SCHEMA



* Tumor tissue and blood will be collected at the time of biopsy and surgery for correlative studies to include: tumor multiparametric flow cytometry, genomics, immunohistochemistry and circulating immune profiling

** Imaging is required prior to immunotherapy and 1-4 days prior to surgery

Hypothesis: Adjuvant combined immune checkpoint therapy will decrease or delay recurrences and improve survival
Primary endpoint: disease-free survival (DFS^) at 1-year
Secondary endpoints: DFS at 2-years, overall survival at 3-years, immune and genomic correlatives, radiologic response

^ DFS = disease-free survival from date of salvage surgery

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1. OBJECTIVES

1.1 Study Design

This is a phase II, open label, non-randomized, multi-institutional study of nivolumab (anti-PD-1) and lirilumab (anti-KIR) in patients with relapsed, resectable, squamous cell carcinoma of the head and neck (SCCHN). Approximately 58 patients with confirmed locoregionally recurrent squamous cell carcinoma of the head and neck (including any primary site), who are candidates for salvage surgery will be enrolled in this study. A single dose of both study drugs will be given during a window of opportunity phase, before salvage surgery, followed by treatment with both study drugs in the adjuvant setting. Treatment in the adjuvant phase will continue for a maximum of 6 cycles or until disease progression or recurrence. The aim of this study is to improve disease-free survival in this critical SCCHN population. Primary endpoint is to evaluate disease-free survival at 1-year from the time of salvage surgery. Secondary endpoints will include disease-free survival at 2-years, and overall survival at 3-years.

The window phase of this study (from biopsy to surgical salvage) would allow administration of initial doses of immune checkpoint inhibitors facilitating assessment of toxicity and evaluation of early radiologic and clinicopathologic response, as well as immune and molecular correlates.

We hypothesize that the combination of nivolumab and lirilumab used as adjuvant therapy in patients with locoregionally recurrent, resectable SCCHN will improve 1-year disease-free survival compared with standard observation in this high-risk population.

1.2 Primary Objectives

- To estimate disease-free survival (DFS) at 1-year from the time of salvage surgery

1.3 Secondary Objectives

- To evaluate toxicity; radiologic and clinicopathologic responses
- To estimate DFS from the time of salvage surgery
- To estimate overall survival (OS) from the time of salvage surgery
- To characterize distinct tumor immunophentoypes and correlate these findings with outcomes

2. BACKGROUND

2.1 Study Disease(s)

Locoregional recurrence is a major cause of death in patients with squamous cell carcinoma of the head and neck (SCCHN), affecting up to 50% of patients treated with definitive therapy, which may include upfront surgical resection followed by adjuvant therapy or concurrent chemoradiotherapy [1]. Survival outcomes are generally poor for patients with locoregionally

recurrent disease and therapeutic options are limited by prior treatments (radiation and/or chemotherapy) [2]. When possible, salvage surgery is considered in these patients and frequently represents their only remaining chance at possible cure or long-term survival. Retrospective historical data have estimated 3-year overall survival (OS) at 37% among all surgically salvaged, recurrent SCCHN patients [3], with variability based on primary site of disease and interval of disease recurrence [4]. In a prospective single-institution observational cohort of 109 patients who underwent surgical salvage, 2-year disease-free survival (DFS) was 44% for all patients and correlated with stage (stage I, II 67-73%; stage III, IV 22-33%; $p = 0.0005$) and by site of recurrent disease (pharynx: 28%, oral cavity 47%, larynx: 58%, neck: 25%; $p = 0.0645$) [3]. Aside from salvage surgery or reirradiation in select patients, therapeutic options are limited and the standard of care is active surveillance following any salvage approach. A trial of 130 patients with locoregionally recurrent, operable SCCHN randomized patients to receive full-dose reirradiation and concurrent chemotherapy vs. active surveillance following re-resection and demonstrated improved rates of locoregional control (16 vs. 32 events, HR 2.73, 95% CI 1.66-4.51, $p < 0.0001$) in the reirradiation arm but without an improvement in OS ($p = 0.50$) [5] – with an increase in acute and late toxicities observed in the chemoradiotherapy arm. Given these considerations, there is an urgent need to evaluate additional therapies in this critical population.

2.2 IND Agents

2.2.1 Nivolumab

2.2.1.1 Mechanism of action and pharmacology

It has become evident that tumor progression is promoted by immune evasion and abrogation of an effective immune response against cancer cells [6]. Mechanisms of tumor evasion include the development of T cell tolerance, modulation of inflammatory and angiogenic cytokines, downregulation of antigen-processing machinery, and changes in immune checkpoint receptor ligands or receptors that can all facilitate tumor immune evasion [7-9]. These mechanisms serve to define immunotherapy targets for clinical development. Immune checkpoint receptors block normal T cell activation and costimulation to maintain a homeostatic immune response [10]. Programmed cell death protein-1 (PD-1, CD279), one such receptor, is expressed on the surface of immune cells and interact with its cognate ligands on antigen-presenting or tumor cells. High tumor expression of the ligands of PD-1 (PD-L1 or B7-H1/CD274 and PD-L2 or B7-DC/CD273) and/or PD-1 expression by T lymphocytes can attenuate T cell activation and drive T cell exhaustion to favor tumor immune evasion [11]. By modulating these inhibitory immune receptor-ligand interactions, the goal is to overcome tumor mediated immunosuppression and facilitate an anti-tumor response. Preclinical evidence to support the negative regulatory effects of PD-1 comes from murine models. PD-1 knockout mice develop organ-specific autoimmunity which can mimic known autoimmune disease, such as systemic lupus erythematosus and acute graft versus host disease (GVHD) – but this can present at various time points and relies on host genetic factors [12]. Beyond PD-1 deficient models, antibody blockade in several mouse models have demonstrated the emergence of similar autoimmune phenomena [13]. These findings strengthen the argument that PD-1 inhibition permits enhancement of antigen-specific T cell response, but also indicate that responses can be variable and depend largely on underlying host biology.

Efforts have focused on understanding PD-1/L1 expression patterns among various tumor types, in order to predict benefit from PD-1 blocking mechanisms. While estimates of tumor cell PD-L1 expression vary considerably based on tumor type [14, 15], studies have estimated PD-L1 expression in SCCHN at 30–70% with human papillomavirus (HPV) positive tumors more frequently harboring infiltrating immune cells that express PD-1 [16, 17]. Upregulation of PD-L1 expression by tumor cells may offer a strategy for evasion and protect the cell from apoptotic demise mediated by T cells, and itself may facilitate T cell apoptosis [18]. Additionally, elevated PD-L1 expression levels correlate with a poor prognosis in some solid tumor malignancies [19]. However, several studies have demonstrated that even tumors with minimal PD-L1 expression may respond to PD-1 focused inhibitory mechanisms, and thus PD-1:L1 interactions are only one component that dictate response to these inhibitory immune signals in a complex tumor immune microenvironment [20, 21].

Nivolumab (BMS-936558, MDX-1106) is a fully human monoclonal antibody targeting the PD-1 or CD279 cell surface receptor that binds to PD-1 with nanomolar affinity and a high degree of specificity. This therefore precludes binding to cognate ligands, PD-L1 or PD-L2 [22]. In chronic simian immunodeficiency virus (SIV) infection in macaques, studies have shown that PD-1 blockade using an antibody to PD-1 was well tolerated and resulted in rapid expansion of virus-specific CD8 T cells [23]. PD-1 blockade also resulted in proliferation of memory B cells and increases in SIV envelope-specific antibody. These improved immune responses were associated with significant reductions in plasma viral load and also prolonged the survival of SIV-infected macaques. In vitro assays have demonstrated the ability of nivolumab to potently enhance T-cell response and cytokine production (such as interferon alpha release); when later given to cynomolgus macaques at high concentrations, there were no adverse immune-related events, independent of circulating levels of anti-nivolumab antibodies [24]. In intravenous (IV) repeat-dose toxicology studies in cynomolgus macaques, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses.

The pharmacokinetics of nivolumab have been reported in human subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as subsequent doses at 2 or 3 week intervals. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The population pharmacokinetic (PPK) analysis suggested that the following factors had no clinically meaningful effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, and PD-L1 expression. Although patient performance status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment did have a mild effect on nivolumab clearance, the effect was not clinically meaningful [22]. Additionally, PPK and exposure response analyses have been performed to support the use of 240 mg IV flat dosing every 2 weeks in addition to the 3 mg/kg every 2 week regimen. Using the PPK model, exposure to nivolumab at 240 mg IV flat dose was identical to a

dose of 3 mg/kg for subjects weighing 80 kg.

2.2.1.2 Clinical safety

In an early phase I study investigating a single IV infusion of anti-PD-1 (MDX-1106) in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg, followed by a 15-patient expansion cohort at 10 mg/kg (for a total of 39 patients), treatment was well tolerated. There was one serious adverse event, inflammatory colitis, observed in a patient with melanoma who received five doses at 1 mg/kg [25].

In a large registration trial which randomized advanced, platinum-refractory SCCHN patients to either nivolumab or single-agent standard chemotherapy, treatment-related grade 3 or 4 adverse events occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard arm [26]. In the nivolumab treated group, the most common adverse events were fatigue, nausea, rash, decreased appetite, and pruritis. Gastrointestinal events were less common than with standard chemotherapy. Pneumonitis was observed in 2.1% of nivolumab-treated patients and two treatment-related deaths occurred (one from hypercalcemia and one from pneumonitis).

The overall safety experience with nivolumab as monotherapy is based on experience from more than 8,000 subjects treated to-date in patients with varied cancer types. The safety profile appears similar across cancer types [27, 28]. Treatment-related adverse events of grade 3 or 4 were reported in 7% of patients treated with nivolumab in advanced non-small cell lung cancer (NSCLC) of squamous histology and in 16.3% of unresectable, advanced stage melanoma patients.

2.2.1.3 Clinical efficacy

Results from an early phase I trial demonstrated a wide range of clinical activity, including complete, partial and mixed response rates in advanced solid tumor patients; including individuals with colorectal cancer, NSCLC, melanoma, and renal cell carcinoma (RCC) [25]. Thirty-nine patients received a single IV infusion of anti-PD-1 (MDX-1106) in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg, followed by a 15-patient expansion cohort at 10 mg/kg. Patients with evidence of clinical benefit at 3 months were eligible for repeated therapy. One durable complete response (CR) and two partial responses (PRs; melanoma, RCC) were observed. Two additional patients (melanoma, NSCLC) had significant tumor regression not meeting defined PR criteria. Following this early signal, numerous clinical trials emerged to investigate the clinical efficacy of nivolumab in advanced solid tumor and hematologic malignancies – with nivolumab (Opdivo™) now approved in six cancer types owing to its demonstrated clinical efficacy.

In a randomized phase III study (Checkmate-141) of patients with recurrent or metastatic, platinum-refractory SCCHN, 361 patients were assigned to nivolumab or standard chemotherapy in a 2:1 ratio with a primary endpoint of overall survival (OS) [26]. Nivolumab (at a dose of 3 mg/kg body weight IV) every 2 weeks or standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab) was administered. Additional end points included progression-free

survival (PFS), objective response rate (ORR), safety, and patient-reported quality of life (QOL). The median OS was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) in the nivolumab group versus 5.1 months (95% CI, 4.0 to 6.0) in the group that received standard therapy. OS was significantly longer with nivolumab than with standard therapy (hazard ratio [HR] for death, 0.70; 97.73% CI, 0.51 to 0.96; p = 0.01), and the estimates of the 1-year survival rate were approximately 19 percentage points higher with nivolumab than with standard therapy (36.0% vs. 16.6%). Median PFS was 2.0 months (95% CI, 1.9 to 2.1) with nivolumab versus 2.3 months (95% CI, 1.9 to 3.1) with standard therapy (HR for disease progression or death, 0.89; 95% CI, 0.70 to 1.13; p = 0.32). The rate of PFS at 6 months was 19.7% with nivolumab versus 9.9% with standard therapy. The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group. Additionally, individuals in the study who were PD-L1 (≥ 1% of tumor or immune cells by immunohistochemistry [IHC]) or HPV positive appeared to have improved outcomes. This study led to the approval of nivolumab in this setting in April of 2016.

2.3.1 Lirilumab

2.3.1.1 Mechanism of action and pharmacology

IPH-2101 (1-7F9) is a first in class fully human anti-KIR monoclonal antibody that was developed by Innate Pharma. Lirilumab (BMS-986105) is the second anti-KIR antibody and will be the antibody used in this protocol [22]. While lirilumab and IPH-2101 bind to the same KIR subtypes and have similar affinity there are several differences between the two products: IPH-2101 is a non-recombinant protein that is produced by a murine hybridoma cell line, whereas lirilumab is a recombinant product produced in Chinese hamster ovary cells; lirilumab has a single amino acid substitution of a serine to a proline at position 231 of the immunoglobulin-4 heavy chain resulting in greater stability of the compound. Most available preclinical data has utilized IPH-2101, which is a fully human monoclonal anti-KIR antibody that binds specifically and with high affinity to KIR2DL-1, 2 and 3 and KIR2DS-1 and 2, thus preventing interaction between KIR and human leukocyte antigen (HLA)-C. IPH-2101 has been shown to augment NK cell-mediated lysis of HLA-C-expressing tumor cells, including autologous leukemic blasts in vitro, but did not induce killing of normal peripheral blood mononuclear cells, suggesting preferential enhancement of NK-cell cytotoxicity against malignant target cells [29] – and all in vivo treated mice in the experiment survived by day 75 of the study ($p < 0.01$).

Early phase trials evaluating the pharmacokinetic parameters for single-agent IPH-2101 have suggested a half-life of 12-14 days at doses higher than 0.3 mg/kg [30]. At a dose of 0.075 mg/kg, full KIR occupancy (above 90%) was seen for less than 7 days. At a dose of 0.3 mg/kg, KIR occupancy decreased to less than 90% beginning on day 28. Sustained full KIR occupancy (above 90%) was sustained for more than 2 weeks at 1 and 3 mg/kg. There was clear correlation between anti-KIR antibody exposure and KIR occupancy.

2.3.1.2 Clinical safety

A phase I study of IPH-2101 in 23 elderly patients with acute myeloid leukemia (AML) in first complete remission was recently reported. Patients received escalating doses: 0.0003, 0.003, 0.015, 0.075, 0.3, 1 and 3 mg/kg, but a maximally tolerated dose was not reached. At the highest

dose levels (0.3, 1, and 3 mg/kg), transient increases in tumor necrosis factor-alpha (TNF-α) serum concentrations and NK cell CD69 expression were observed. Grade 3 and 4 adverse events were limited to one patient who experienced a transient lipase elevation that resolved spontaneously. The most frequently reported treatment-related effects included pruritis (17%), rash (17%), and fever (13%). A similar trial in 32 patients with relapsed, refractory multiple myeloma used IPH-2101 administered IV every 28 days in 7 dose-escalated cohorts (0.0003 to 3 mg/kg) for up to 4 cycles. Again the highest dose was tolerated without achieving a maximally tolerated dose [31]. In the relapsed, refractory myeloma setting there was one severe adverse event reported (acute renal failure requiring hemodialysis), with no evidence of autoimmunity noted. In the expanded cohort of this trial, the most commonly observed treatment-related effects included fatigue, chills, non-cardiac chest pain and pyrexia.

IPH-2101 has also been evaluated in combination with lenalidomide in the treatment of relapsed, refractory multiple myeloma [32]. In a phase I trial that enrolled 15 patients in three cohorts lenalidomide was given at a standard 10 mg dose in cohort 1 and 25 mg in cohorts 2 and 3 on days 1 to 21 of a 28 day cycle in combination with IPH-2101 given IV on day 1 of each cycle at 0.2 mg/kg in cohort 1, 1 mg/kg in cohort 2, and 2 mg/kg in cohort 3. The biologic endpoint of full KIR occupancy was achieved across the IPH-2101 dosing interval. Pharmacokinetic data of IPH-2101 with lenalidomide were similar to data from a prior single-agent IPH-2101 trial. Five serious adverse events were reported along with five objective responses; with no autoimmunity reported. Grade 3 and 4 adverse events most often included neutropenia and lymphopenia, along with a cytokine release syndrome with elevation in pro-inflammatory cytokines in two patients. After completion of the study, one patient developed therapy-related myelodysplasia.

2.3.1.3 Clinical efficacy

In the above early study utilizing IPH-2101 in elderly, advanced AML patients, overall and relapse-free survival rates compared favorably to reports in comparable patient populations [30]. Twenty evaluable patients had relapse with a median PFS of 7.7 months (95% confidence interval [CI], 1.8-9.5) and a median OS of 12.7 months (95% CI, 10.9-24.2). The 6 patients treated at dose levels 1 and 3 mg/kg showed a significantly improved OS compared with the 16 patients on the previous dose levels (< 0.3 mg/kg): 29.7 months compared with 11.8 months, respectively ($p = 0.03$). In the early phase study of IPH-2101 in relapsed, refractory multiple myeloma, no objective responses were observed while eleven (34%) patients achieved a best response of stable disease [31]. In the combined IPH-2101 and lenalidomide study mentioned above, there were five objective responses: two very good partial responses (VGPR) and three partial responses (PR); out of these, objective responses occurred in 3 patients who had received prior lenalidomide and dexamethasone. The PFS was 24 months (95% CI, 2.5 to not reached).

2.3.2 Nivolumab combined with lirilumab

2.3.2.1 Clinical safety

Across a phase I/II study of the combination of nivolumab and lirilumab in advanced solid tumor patients, treatment-related adverse events of all grades were reported in 71.7% of patients, which was similar to rates observed with anti-PD-1 monotherapy [33]. The most common events

included fatigue (20.8%), pruritis (18.9%), infusion-related reactions (17.6%) and rash (16.4%). Grade 3 and 4 toxicities were observed in 15.1% of patients, with only 2.5% discontinuing treatment.

2.3.2.2 Clinical efficacy

Preclinical studies have evaluated the hypothesis that the combination of anti-KIR and anti-PD-1 would potentiate anti-tumor response in solid tumor models. The rationale was to utilize pharmaceutical manipulation to regulate innate and adaptive immunity and recapitulate what has been observed in post-allogeneic stem cell transplant patients who demonstrate KIR mismatch [34]. Nivolumab and lirilumab are both fully human monoclonal antibodies, and therefore murine specific PD-1 antibody and anti-Ly49 antibody (an F(ab)2 that recognizes Ly49C/I which is the KIR homologue in mice) were utilized. Syngeneic MC38 murine colon carcinoma cell line models were used and mice randomized to one of four cohorts to receive control immunoglobulin (IgG), anti-Ly49 antibody, anti-PD-1 antibody, or both antibodies. Mice treated with a control IgG antibody had rapid tumor growth. While mice treated with anti-Ly49 antibody did not differ significantly from controls, those treated with a murine anti-PD-1 antibody showed latency in tumor progression and 30% of mice continued to be free of tumor. Those treated with both antibodies also had latency in tumor progression and 60% of mice had regression of tumor bulk (referenced from protocol 12-487, DFCI).

In a phase I/II study of 29 patients with advanced SCCHN treated with the combination of nivolumab (3 mg/kg IV every 2 weeks) and lirilumab (in doses ranging from 0.1 to 3 mg/kg IV every 4 weeks – with a phase II established dose of 3 mg/kg IV every 4 weeks) until disease progression, an ORR of 24.1% was observed [33]. Three CRs were reported (10.3%) along with 4 additional PRs (13.8%), of which 2 were near-complete responses with ≥ 80% reduction in the size of tumor burden. Additionally, eight patients had stable disease (overall disease control rate of 51.7%). Six-month OS for the combination was 90% and the 1-year OS rate was 60%. Deep and durable responses were observed in some patients, particularly in PD-L1 positive tumors. Higher levels of PD-L1 expression as measured by IHC resulted in modest increases in ORR (≥ 5%, 54.5%; ≥ 50%, 57.1%). All patients had progressed or were intolerant of at least 1 or more lines of prior therapy.

In addition to head and neck cancer and other solid tumors, lirilumab is being investigated in combination with nivolumab, as well as with azacitidine and rituximab in certain hematologic malignancy subtypes.

2.4 Rationale

Locoregionally recurrent SCCHN imparts significant morbidity on afflicted patients and results in poor long-term disease outcomes, representing an important population where novel treatments are needed. Mortality rates in this setting approach 50% [1], and it is often very challenging to treat these patients owing to the multifocal and an infiltrative burden of disease. This is further complicated by the fact that prior chemotherapy and radiation treatments may limit potential therapeutic options. The interval in which disease recurs if often of prognostic value: as those with a disease-free interval less than 6 months have poorer outcomes [35]. Also

an important consideration, the site of disease recurrence often dictates available retreatment options and prognosis: laryngeal recurrence can sometimes be salvaged with total laryngectomy (5-year OS approaches 60%) as compared with oropharyngeal or hypopharyngeal tumors (5-year OS in the 16-44% range) which are more difficult to resect [36]. Post-salvage positive resection margins and extracapsular spread of disease also have been reported as predictors of poor outcome [37]. Patient-specific factors also play heavily into decision-making, as prior therapy may have contributed to poor cardiopulmonary or renal reserve, cognitive issues, tobacco and alcohol exposure may be ongoing, and there remain significant quality of life concerns with re-resection. While the morbidity associated with salvage surgery can be substantial depending on the site and extent of disease, it often represents the best therapeutic option for operable patients [38]. For the above reasons, capturing outcomes in this heterogeneous population can be difficult. In a single-center retrospective series of 109 patients undergoing salvage surgery for recurrent SCCHN, 5-year OS was 42% compared with a 5-year DFS of 47% for all patients [36]. Accounting for specific disease sites, 3-year OS in surgically salvaged oropharyngeal tumors has been estimated at 48.7% [39], whereas 5-year OS in laryngeal and hypopharyngeal recurrence treated with surgical salvage is 27-57% [40, 41]. A large multicenter meta-analysis that included over 1000 patients reported a 5-year OS of 39%. Of note, these studies included patients receiving salvage surgery with or without additional 'adjuvant' chemotherapy and/or radiation—the benefit of which remains controversial. Investigating alternative therapeutic strategies that incorporate novel treatment mechanisms is warranted.

It is now widely recognized that tumor cells harbor immune checkpoint receptors to evade immune recognition [11]. Immune checkpoint inhibitors that block inhibitory immune cell signaling have demonstrated efficacy in platinum-refractory and advanced SCCHN [26, 42, 43] prompting clinical trials to explore their potential in various other head and neck cancer populations. Aside from T cells, recent data aimed at understanding the tumor microenvironment has suggested that natural killer (NK) cells are heavily infiltrated in SCCHN tumors and also express immune checkpoint receptors like programmed cell death protein-1 (PD-1) and the killer cell immunoglobulin-like receptor (KIR) [44, 45]. NK cells comprise 15% of peripheral circulating lymphocytes and are crucial in innate immune function: they bind to target via receptors that promote tyrosine kinase phosphorylation and signaling cascades to release preformed perforin and granzyme-containing granules to kill target cells [46]. They also concurrently release chemokines into the surrounding microenvironment to recruit other immune effector cells. While NK cells can mediate cytotoxic activity, they also contain another receptor set that binds major histocompatibility complex (MHC) class I molecules. Binding of human leukocyte antigen (HLA)-A, B or C to KIR leads to downstream signaling which suppresses normal NK cell activation – this KIR:HLA interaction impairs NK cell responsiveness [34]. Additionally, there are seven inhibitory KIRs with some receptors expressed on NK T cells which has implications for activating NK cells via KIRs. Early data about NK cell involvement in anti-tumor response arose from hematopoietic stem cell transplant studies, where leukemia patients transplanted with KIR mismatched donor NK cells (recalling that KIR interacts with specific HLA ligands) had lower rates of relapse [47]. In fact, NK cell activation has been shown to eradicate tumor in the presence of interleukin-15 (IL-15) released by tumor cells in murine models [48]. Moreover, recently published data has suggested higher rates of NK cell presence among SCCHN tumors [44], and our own data suggests higher NK cell abundance among immunologically rich SCCHN tumors [49].

The combination of the KIR inhibitor lirilumab and the PD-1 inhibitor nivolumab resulted in an objective response rate of 24.1% in a phase I/II study that included advanced SCCHN patients – as presented recently in abstract form (NCT01714739) [33]. Among 29 patients, 3 demonstrated a complete response (10.3%) with an additional 4 patients (13.8%) having a partial response – yielding a 1-year overall survival rate of 60% in this cohort. Of the 4 partial responders, half were near-complete responses with > 80% reduction in tumor size. Nivolumab was administered at a standard dose of 3 mg/kg every 2 weeks, while the phase II dose of lirilumab was established at 3 mg/kg every 4 weeks. Treatment-related adverse events of all grades in this group were similar to those with nivolumab monotherapy. These preliminary findings warrant further investigation using this combination in other SCCHN populations, as these patients were often heavily pre-treated and observed responses were usually durable.

Administering systemic therapy prior to surgical re-resection (so-called neoadjuvant treatment) could offer several advantages, including downstaging of tumor burden and nodal disease to decrease the morbidity of salvage surgery and decrease the likelihood of a positive surgical margin. Early systemic therapy may address the risk of distant metastatic spread, and facilitate early evaluation of biomarkers of response to neoadjuvant therapy. The concept of induction therapy in the form of neoadjuvant treatment (prior to surgical resection) has previously been explored in SCCHN in the initial treatment setting. Three cycles of a platinum-based combination followed by surgery in a resectable, locoregionally advanced oral cavity SCCHN population did not improve OS compared with standard resection, but seemed to result in tumor downstaging resulting in fewer patients requiring mandibulectomy and adjuvant radiation [50]. A similar study combining platinum-based therapy with a taxane prior to resection in advanced oral cancer patients failed to improve 5-year OS rates [51]. Recognizing their clinical benefit and favorable toxicity profile in SCCHN, an exciting next step is to investigate neoadjuvant immunotherapeutic approaches to treat resectable SCCHN – and such trials are now underway.

Capitalizing on the window phase of treatment prior to initial surgical resection in SCCHN, several accruing trials using the anti-PD-1 inhibitors pembrolizumab and nivolumab with or without the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab are active [NCT02296684, NCT02641093, NCT02919683, NCT02488759, NCT03021993]. These trials can be distinguished by the number of pre-operative doses of immunotherapy (ranging from one to four) and whether or not adjuvant immunotherapy is continued following resection. Preliminary efficacy and response assessments are eagerly anticipated for these studies to inform future neoadjuvant immunotherapeutic trial designs. Extrapolating from a related disease, non-small cell lung cancer, a neoadjuvant study of two doses of nivolumab prior to definitive surgical resection for resectable non-small cell lung cancer recently reported preliminary results [52]. Seven of 18 (38.8%) evaluable patients had major pathologic regression (defined as < 10% viable tumor remaining at the time of resection) with 1 patient experiencing a pathologic complete response, and all with dense immune cell infiltrates observed on pathology. Importantly, only 1 patient withdrew from the study due to toxicity but there were no delays to surgery. This latter trial indicates that neoadjuvant immunotherapy treatment strategies prior to resection appear feasible and safe.

Recently, an open-label phase II study of pembrolizumab in relapsed, locally recurrent SCCHN

opened with a primary endpoint of 1-year DFS (NCT02769520). The study includes a window of opportunity phase which randomizes patients 3:1 to pembrolizumab and placebo for a maximum of 2 doses prior to salvage surgery. Following surgery, pembrolizumab (or placebo) at standard dosing will be administered every 3 weeks up to 12 months or until disease progression. Given the favorable preliminary response signal observed with combined anti-PD-1 and anti-KIR immunotherapy in an advanced SCCHN cohort, studies utilizing this regimen in the neoadjuvant and/or adjuvant treatment setting are warranted. Here we propose a single arm, non-randomized phase II study for patients with relapsed, resectable SCCHN using the combination anti-KIR and anti-PD-1 therapy both in a window of opportunity phase prior to resection and in the adjuvant setting following salvage surgery in hopes of improving the 1-year DFS in this critical population. The use of this novel neoadjuvant combination of immune checkpoint inhibition offers early systemic therapy with a favorable side effect profile in a high-risk population in hopes of downstaging tumor burden and addressing the risk of distant disease spread, while permitting a window phase in which to explore immune correlatives. Additionally, the adjuvant phase of therapy seeks to continue immune checkpoint inhibition exposure post-resection to potentially address remaining microscopic disease and improve both disease-free and overall survival while minimizing toxicity.

2.5 Correlative Studies Background

Given that response rates to PD-1 blockade in the advanced, platinum-refractory SCCHN setting approach 20%, there is strong interest in identifying biomarkers that predict clinical benefit. In a NSCLC population, PD-L1 expression in at least 50% of tumor cells yielded a response rate of 45.2%, compared with an objective response rate of 19.4% among all treated patients [53]. More recently, whole-exome sequencing of NSCLC tumors treated with PD-1 blockade revealed that higher mutational burden correlated with improved objective response rates [54]. Somatic alterations in tumor cells yield neoantigens which are thought to facilitate antigen-specific CD8+ T cell responses – suggesting that the genomic landscape of the tumor impacts PD-1 response. In SCCHN, stromal or tumor PD-L1 expression does appear to partially impact response, but even PD-L1 negative patients may respond to treatment – suggesting important mechanisms beyond PD-1:L1 interactions [42, 43]. Moreover, NK cell infiltration is thought to be increased among SCCHN tumors, and our own work has suggested that NK cell populations may be higher in immunologically rich SCCHN tumors [44, 49].

More recent work has sought to use more comprehensive immune-based metrics to characterize the tumor microenvironment. Cytometric profiling has identified immunologically ‘hot’ and ‘cold’ immunophenotypes which may identify tumors more likely to respond to immunotherapies [55, 56]. Studies confirming these findings in head and neck cancer patients are not yet published, although our own preliminary work has shown that a robust CD8+ T cell infiltrate and pattern of immune checkpoint co-expression may predict clinical benefit to PD-1 blockade in an advanced SCCHN population [57]. The window phase of treatment proposed in this study will allow evaluation of pre- and post-immunotherapy tumor samples, permitting investigation of immune microenvironment alterations to potentially identify mechanisms of response and resistance. Additionally, whether the circulating peripheral immune environment recapitulates the tumor immune microenvironment remains an unanswered question. By evaluating both the tumor and circulating immune profile, we hope to evaluate whether early

peripheral blood changes in immune parameters could parallel an early indication of treatment response, avoiding the cost and risk of sequential tumor biopsies. Understanding the genomic determinants which drive immunophenotype appear crucial and therefore whole exome and bulk RNA sequencing are also planned. Finally, we will attempt to correlate changes in tumor and lymph node radiologic measurements with immune microenvironment alterations and circulating immune parameters.

3. PARTICIPANT SELECTION

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

3.1 Inclusion Criteria

3.1.1 Subject must have histologically or cytologically confirmed locoregionally recurrent squamous cell carcinoma of the head and neck (including any primary site, such as oral cavity, oropharynx, larynx or hypopharynx, and nasopharynx carcinoma)

3.1.2 Must be a candidate for salvage surgery

3.1.3 Willing to provide blood and tissue from diagnostic biopsy and at the time of surgery

3.1.4 Has documented disease-free interval (DFI) > 8 weeks after completion of initial therapy; DFI is from the time of completion of initial treatment (from date last known disease-free at end of initial treatment) to the diagnosis of local or locoregional recurrence

3.1.5 Any HPV status or smoking history is permitted. Oropharyngeal cancer patients are required to undergo HPV testing with p16 immunohistochemistry and/or confirmatory HPV PCR or ISH testing

3.1.6 Age 18 years or older

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

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

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin ≤2.0 g/dL
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- creatinine within normal institutional limits

OR

- creatinine clearance ≥60 mL/min/1.73 m^2 (calculated using the Cockcroft-

Gault equation) for participants with creatinine levels above institutional normal

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

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

3.1.11 Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 iu/l or equivalent units of hcg) within 24 hours prior to the start of nivolumab

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

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

See Appendix B for further guidance on contraception.

3.2 Exclusion Criteria

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

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

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

3.2.4 Subject with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. However, baseline brain imaging is not required prior to enrollment in the study if patients are asymptomatic.

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

3.2.6 Known human immunodeficiency virus carrier or a diagnosis of immunodeficiency. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

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

3.2.8 Receipt of a live vaccine within 30 days of start of study treatment.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

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

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

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

4.2 Registration Process for DF/HCC Institutions

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

4.3 General Guidelines for Other Investigative Sites

See DSMP appendix

4.4 Registration Process for Other Investigative Sites

See DSMP appendix

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than nivolumab (BMS-936558) and lirilumab (BMS-986015) may be administered with the intent to treat the participant's malignancy during the course of treatment.

5.1 Pre-Treatment Criteria

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

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

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

5.2 Treatment Regimen

Patients will be premedicated with diphenhydramine, famotidine, and acetaminophen before lirilumab doses unless otherwise directed by treating investigator. Each treatment cycle will be 28 days long. On the days when both nivolumab and lirilumab are administered, nivolumab will be administered first, followed by lirilumab, with a 30-minute minimum duration time between the administration of nivolumab and lirilumab. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the lirilumab infusion. Participants should be carefully monitored for infusion reactions during nivolumab and lirilumab administration. If an acute infusion reaction is noted, participants should be managed according to the algorithm described in Appendix C or in Nivolumab IB.

Nivolumab infusion time should be 30 (+/-10) minutes. A volumetric pump with a 0.2 - 0.22 micron in-line filter through an IV transfer set will be used.

Lirilumab infusion time should be 60 (+/-15) minutes. A volumetric pump with a 0.2 micron in-line filter through an IV transfer set will be used.

Window phase: Seven to twenty-one days prior to salvage surgical resection, a single dose of each study drug will be administered. Nivolumab 240 mg IV flat dosing will be administered through IV infusion, followed by lirilumab 240 mg IV flat dosing.

Salvage surgical resection: Each participant should be a candidate for salvage surgical resection to be able to participate in this study. Surgery should be performed no later than 4 weeks after study enrollment. Patients remain eligible to continue on study regardless of post-salvage surgery excisional margin status. Following salvage surgery, re-irradiation or additional chemotherapy is not permitted during the study period.

Adjuvant phase: Three to eight weeks after salvage surgery, treatment will restart. If additional surgery is required after the initial salvage surgery (e.g., for completion, reconstruction), treatment will restart after the additional surgery. In Cycle 1-3: Nivolumab will be administered on Days 1 and 15 and lirilumab will be administered on Day 1 of each 28 day long cycle. In Cycle 4-6 and beyond: Nivolumab and lirilumab will be administered on Day 1 of each 28 day long cycle. Treatment with both study drugs will continue for a maximum of 6 cycles or until disease progression or recurrence, unacceptable toxicity or withdrawal of consent. Nivolumab 240 mg IV flat dosing will be administered through IV infusion, followed by lirilumab 240 mg IV flat dosing.

5.2.1 Cycle 1, Day 1

If screening assessments occur within a week before start of study treatment, then they may serve as the baseline cycle 1 day 1 visit and cycle 1 day 1 labs do not need to be performed. Laboratory evaluations do not need to be repeated to meet eligibility criteria on cycle 1 day 1, if they were done within 3 days of the first treatment dose.

5.3 Pharmaceutical Properties and Formulation for Lirilumab:

5.3.1 Description of the Dosage Form

Lirilumab Injection 100 mg/Vial (10 mg/mL): Lirilumab injection has been developed to be used as an intravenous (IV) infusion for clinical studies. The drug product is a clear to opalescent, colorless liquid, which may contain few particles.

The 100-mg/vial presentation is contained in a 10-cc Type I flint glass vial, closed with 20-mm stoppers, and sealed with aluminum seals. Each vial of the drug product contains the labeled amount of lirilumab drug substance, sucrose, sodium phosphate monobasic, sodium phosphate dibasic, polysorbate 80 (PST), and water for injection. Diluted sodium hydroxide and/or hydrochloric acid solution may be added to adjust the pH to 7.0. A sufficient overfill is included in each vial to account for vial, needle, and syringe holdup.

5.3.2 Drug Product Preparation

Lirilumab injection is administered IV either undiluted (10 mg/mL) or diluted in NS to lirilumab concentrations as low as 0.5 mg/mL. The dosing solution is to be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a non-di-2-ethylhexyl phthalate (DEHP) or DEHP IV infusion set with a 0.2 micron polyethersulfone in-line filter. The drug product is not to be administered as an IV push or bolus injection.

Care must be taken to ensure the sterility of the prepared solutions, as the drug product does not contain anti-microbial preservatives or bacteriostatic agents.

5.3.3 Recommended Storage and Use Conditions

Lirilumab injection should be stored refrigerated at 2°C to 8°C and protected from light and freezing. The administration of lirilumab infusions must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 20 hours, and at room temperature (20°C to 25°C, 68°F to 77°F) and room light for a maximum of 4 hours. The maximum 4-hour period under room temperature and room light conditions includes the product administration period. The solution in IV bag (diluted or undiluted) should not be shaken or frozen. Equilibration to room temperature is recommended for the infusion bag, drug product, or their combination prior to administration.

5.4 Pharmaceutical Properties and Formulation for Nivolumab:

5.4.1 Description of the Dosage Form

Nivolumab injection, 100 mg/10 mL (10 mg/mL): Nivolumab injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween 80), at pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

5.4.2 Drug Product Preparation

Nivolumab Injection, 100 mg/10 mL (10 mg/mL): Nivolumab injection is to be administered as an IV infusion through a 0.2 - 0.22 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with

polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

5.4.3 Recommended Storage and Use Conditions

Nivolumab Injection, 100 mg/10 mL (10 mg/mL): Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container: The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

5.5 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of IND Agents with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect CYP450 isoenzymes.

5.5.1 Prohibited and/or Restricted Treatments

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

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

5.5.2 Other Restrictions and Precautions

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

5.5.3 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

5.6 Criteria for Taking a Participant Off Protocol Therapy

The following stopping rule will be used to monitor delays in salvage surgery due to excessive nivolumab and/or lirilumab-related toxicity: if 3 or more of the first 10 patients who begin protocol treatment experience treatment related toxicities which cause delays in definitive surgery, accrual to the trial will be suspended to further evaluate the events and decisions made regarding the overall status of the trial. If the true delay in surgery rate due to toxicity is 10% then the probability of suspending accrual is 7%; if the true rate is 20%, then the probability of suspending accrual is 32.2%; if the true delay in surgery rate due to toxicity is 30% then the probability of suspending accrual is 62%. Adverse events will be continuously monitored throughout the trial by the study team with decisions made accordingly regarding the study status and patient entry throughout the duration of the trial.

Any adverse event(s) (as outlined in Section 6.1) attributed to the study medication that result in a delay in the planned date of salvage surgery exceeding 14 days warrants removal of the patient from the study protocol treatment. Otherwise, therapy can be resumed in the adjuvant phase at the discretion of the treating physician or PI. Duration of therapy will depend on individual response, evidence of disease progression or recurrence and tolerance. In the absence of treatment delays in the adjuvant phase due to adverse event(s), treatment may continue for six cycles or until one of the following criteria applies:

- Disease progression or recurrence
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) (see Section 6.2)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition rendering the participant unacceptable for further treatment in the judgment of the treating investigator

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

An ODQ Treatment Ended Form will be filled out when a participant is removed from protocol therapy. This form can be found on the DF/HCC website at http://www.dfhcc.harvard.edu/research/clinical-research-support/document-library-forms-sops-etc/.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, ***Glenn Hanna, MD at 617-632-3696 or 617-632-3090.***

5.7 Duration of Follow Up

Participants, regardless if they receive the adjuvant therapy, will be followed for response (at the end of the window phase of the trial) and until first disease progression/recurrence and for survival for 5 years from point of salvage surgery (or from study registration if no salvage surgery was performed). Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.8 Criteria for Taking a Participant Off Study

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

- Patient completed required follow-up
- 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).

For "Centralized Subject Registrations", the research team submits a completed Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

There will be no dose reductions for nivolumab or lirilumab permitted. Doses of nivolumab or lirilumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. If a lirilumab dose is delayed beyond four weeks from the prior lirilumab dose, then subsequent lirilumab doses should be rescheduled, if needed, such that the patient receives both nivolumab and lirilumab at next visit

6.1 Administration both study drugs should be delayed for the following adverse events:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
  Note: see Appendix C for guidelines on managing immune-related toxicities

Participants who require delay of nivolumab or lirilumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab or lirilumab dosing when re-treatment criteria (as described below) are met. Participants with a delay in dosing beyond 8 weeks should be considered for discontinuation of protocol treatment and discussed with the Overall PI.

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

6.2 Administration of both study drugs should be permanently discontinued for the following adverse events:

- A grade 3 pneumonitis and grade 3 uveitis will require permanent discontinuation.
- Any grade 4 adverse event will require permanent discontinuation with the following exceptions:
  - Grade 4 electrolyte abnormalities that < 72 hours in duration
  - Grade 4 neutropenia < 5 days in duration
  - Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis
  - Grade 4 lymphopenia < 5 days in duration

The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall benefit/risk profile and in consultation with the Overall PI.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Adverse Event Characteristics:

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.

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

7.2 Serious Adverse Events

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

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

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

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

7.3 Expected Toxicities

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

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

The most common adverse reactions (>5%) related to lirilumab alone were: asthenia, fatigue, pruritus, infusion-related reaction, chills, and neutropenia.

The most common adverse reactions (>10%) related to nivolumab in combination with lirilumab were: fatigue, pruritus, infusion-related reaction, and rash.

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

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

7.4 Routine Adverse Event Reporting

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

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

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE version 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.

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

IRB, FDA, etc.) must also be reported in routine study data submissions.

7.4.1 Routine Adverse Event Reporting to BMS

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

The Adverse Event information required to be sent to BMS is noted in the 'Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan' spreadsheet and submitted to BMS via the mailbox: MG-RD-GPVE-PHARMACOVIGILANCE@bms.com

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

Sites other than Dana-Farber must fill out the ISR spreadsheet to Dana-Farber every three months and Dana-Farber will include information from other sites in their submissions to BMS.

7.5 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing. All SAEs should be followed to resolution or stabilization.

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

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

7.6 Expedited Adverse Event Reporting to Overall PI

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs following the subject's written consent, during treatment, or within 100 days of the last dose of treatment on the local institutional SAE form.

In the event of an unanticipated problem or life-threatening complications, treating investigators must immediately notify the overall PI.

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

7.7 DF/HCC Expedited Reporting Guidelines

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.

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

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

Report any unexpected fatal or life-threatening suspected adverse reactions no later than 7 calendar days after initial receipt of the information. Submit 7-day reports by a rapid means of communication (preferably fax). Each submission should be address to the Regulatory Project Manager and/or to the Chief, Project Management Staff.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/. Send the SAE forms as follows:

By fax:
301-796-9849

OR

By mail:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

7.9 Expedited Adverse Event Reporting to Hospital Risk Management

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

7.10 Expedited Adverse Event Reporting to BMS

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804

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

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

7.11 Multi-Center Trial Specifications

For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in section 7.3.

Product information table: please also see respective product investigator brochures

Table	**Product Description**				
Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	10 mL vial	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Lirilumab (BMS-986015-01) Solution for Injection	100 mg (10 mg/mL)	10 mL vial	5 vials per carton/Open-label	Clear to opalescent, colorless liquid. Essentially free of particles	2 to 8°C. Protect from light and freezing

8.1 Storage and Stability

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

For additional details on prepared drug storage and use time of nivolumab or lirilumab under room temperature/light and refrigeration, please refer to section 5 of this protocol.

8.2 Handling

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

8.3 Availability

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

8.4 Ordering

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

8.5 Accountability

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

8.6 Destruction and Return

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Correlative studies are planned as part of this study. At the time of biopsy to demonstrate recurrence, tumor tissue will be sent for multiparametric flow cytometry (Belfer Center for Applied Cancer Science, DFCI), a portion of fresh-frozen, paraffin-embedded (FFPE) tissue will be obtained for genomic sequencing and for immunohistochemistry (IHC) for immune marker staining (e.g. PD-1, PD-L1/L2) and/or multiplexed immunofluorescence (MIF). Flow cytometry, sequencing and IHC/MIF data will be gathered to characterize distinct tumor immunophentoypes and these findings will be correlated with outcomes.

9.1 Biomarker Studies

Biopsy confirmed squamous cell carcinoma of the head and neck is a requirement to be enrolled on this study. A separate, fresh research biopsy is mandatory prior to starting treatment on study if tumor is accessible, otherwise archival tissue will be accepted. At the time of definitive surgical resection, after adequate tumor for pathological assessment has been harvested as deemed appropriate 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 research purposes.

Tumor biopsies and/or surgery should not generally be performed on Friday afternoons, as there may not be time for processing of fresh tissue samples. If a biopsy or surgical resection is performed on Friday morning, Dr. Patrick Lizotte of the Belfer Center for Applied Cancer Science should be notified ahead of time to ensure that there will be adequate time for processing fresh tissue or serum samples, since these should not be stored over the weekend.

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

will be cryopreserved and stored in secure locked freezers. Once all research is complete, the link between the coded samples and patient identifiers will be destroyed.

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

1. 2 tubes drawn in 8 mL whole blood, purple top tubes for circulating immune profiling
2. 2 tubes drawn in 8 mL whole blood, purple top tubes for neoantigen T cell profiling

Multiparametric flow cytometry

At the time of pre-treatment biopsy and surgical resection, two cores of fresh tissue will be allocated to two 1.5 mL centrifuge tubes (one core in each tube) in RPMI containing 10% fetal bovine serum (FBS). Additionally, at the time of pre- and post-treatment biopsy and at specified time points during and after treatment, two tubes of peripheral blood (obtained at a minimum of 3 time points during the study) will be obtained per standard collection protocols – drawn in phlebotomy or clinic and captured in 8 mL whole blood, purple top tubes. The volume of blood to be collected per blood draw for study purposes will not exceed 40 mL. All specimens will be de-identified and labeled with the participant's initials, study ID number and the date of acquisition. After collection, the tissue and blood collection tubes should be delivered immediately to the lab of Dr. Patrick Lizotte and Megan Cavanaugh [office: LC-4315J, Robert and Renee Belfer Center for Applied Cancer Science, 360 Longwood Avenue, Boston, MA 02215, phone: 207-423-0958 or 631-487-6573]. The specimen must arrive in a timely fashion to facilitate processing for evaluation of immune cells. Tissue will be prepared as a cell suspension that will be stained using fluorescently-conjugated antibody cocktails for human immune markers (surface antibodies include: CD45, CD3, CD4, CD8, CD69, CD38, CCR7, LAG-3, TIM-3, PD-1, CD45RA, HLA-DR, CTLA-4, CD16, CD56, CD31, CD33, PD-L1, PD-L2, GITR, CD15, CD19, and CD14). Cells will be analyzed within 72 hours of fixation on a BD Fortessa cell analyzer with FACSDiva software v8.0.1 (BD Biosciences) and gated using FlowJo software v10.

Immunohistochemistry

At the time of pre-treatment biopsy and surgical resection, one core of fresh tissue will be allocated to a standard orange-top specimen cup containing 10% neutral buffered formalin. The specimen will be labeled with the participant's initials, medical record number and the date of acquisition. After collection, the specimen will be sent to the Brigham & Women's Hospital (BWH) pathology division for processing. Following standard tissue processing, sectioning and slide preparation for histopathologic review, the specimen will be stored in accordance with BWH protocols (both tissue blocks and tissue slides). At a later time, we will then request tissue block retrieval through the Pathology Specimen Locator Core with preparation of 5 unstained slides through the Specialized Histopathology (SHP) Core service at BWH. SHP will then prepare 1 stained hematoxylin & eosin slide, 1 slide stained for PD-1, 1 slide stained for PD-L1 and 2 unstained slides will be stored for additional studies. These slides will be retrieved from the SHP in Thorn Building, 6th floor, room 603 at the BWH by the study principal investigator. In collaboration with an oral histopathologist, Dr. Sook-Bin Woo of the BWH Department of Oral Medicine and Dentistry, the slides will be analyzed and scored based on stained immune parameters.

Genomic sequencing

At the time of pre-treatment biopsy and surgical resection, one core of fresh tissue will be allocated to 5 mL of RPMI media in a 15 mL conical tube for the purposes of DNA and RNA sequencing efforts. Once prepared, aliquoted core material for sequencing will be delivered immediately to the laboratory of Dr. Ravindra Uppaluri at the DFCI [Dana Building, 8th floor, room 819, 450 Brookline Avenue, Boston, MA 02215, office: 617-632-3091].

9.2 Multi-center Guidelines

Non-DF/HCC sites will be responsible for shipping samples to Dana-Farber on the day of collection. Specific shipping instructions will be provided separately.

10. STUDY CALENDAR

Screening evaluations are to be conducted within 3 weeks prior to study registration. Procedures done within a week of study registration don't need to be repeated to establish baseline. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. Laboratory evaluations do not need to be repeated to meet eligibility criteria on cycle 1 day 1, if they were done within 3 days of the first treatment dose. In an event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Each treatment cycle in this study is 28 days long.

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

	Screening	Window Phase	Pre-surgery	Surgery	Adjuvant phase							End of Treatment	Follow up visit 30 days after last dose
					Cycle 1		**Cycle 2**		**Cycle 3**		**Cycle 4-6**		
					Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1		
Informed consent	X												
Medical History	X												
Concomitant Medicines	X												
Physical exam (Ht, Wt, VS, PS) [a]	X	X			X	X	X	X	X	X	X	X	X
Routine labs [b]	X	X			X	X	X	X	X	X	X	X	X
FSH (if female <55 years old)	X												
HPV testing (oro-pharyngeal only)	X												
B-HCG (WOCBP only) [c]	X											X	X
ECG	X											X	X

Radiologic evaluation [d, g]	X		X		X								
Biopsy sample [e, f]	X											X[h]	
Correlative biopsy [f]	X											X[h]	
Correlative blood [i]	X[i]						X					X	
Nivolumab		X			X	X	X	X	X	X	X		
Lirilumab		X			X		X		X		X		
Adverse event evaluation		X			X	X	X	X	X	X	X	X	X

a) Physical exam is symptom directed. Height measured at screening only.
b) Routine labs include: CBC, LFTs, CMP, Mg, TSH, Free T4. Baseline HCV antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody testing is required. TSH and free T4 are required less frequently according to the following schedule: screening, window phase (D1 of pre-surgery immunotherapy dosing), D1 of each adjuvant cycle, and at the 30-day post protocol treatment visit.
c) Serum or urine within 24 hours prior to first dose.
d) PET-CT or contrast-enhanced CT imaging of the chest, abdomen and pelvis will be obtained at baseline to rule out distant disease. Contrast-enhanced neck CT or MRI at the time of screening or registration and will be repeated 1-4 days prior to salvage surgery. Interval scans (contrast-enhanced neck CT or MRI) will be performed every 8 weeks following salvage surgery or as clinically indicated while on treatment. Follow-up imaging will be performed at the end of treatment (see footnote g).
e) Archival tissue is acceptable. Some of this tissue will also be used for correlative study.
f) Fresh biopsy is mandatory if tumor is accessible. Fresh tissue is also collected at the time of surgery. Biopsy will also be obtained at the time of progression or recurrence, if safe to perform.
g) Participants, regardless if they receive the adjuvant therapy, will be followed for response (at the end of the window phase of the trial) until first disease progression or recurrence and for survival throughout the trial for a total of 5 years from time of salvage surgery (or from study registration if no salvage surgery was performed). Post-end of protocol treatment, if first disease progression or recurrence has not been confirmed, tumor assessments (contrast-enhanced neck CT or MRI and PET-CT) are to continue every 3 months (+/- 1 month) until first disease progression or recurrence, death, or 2 years post-date of salvage surgery (or from study registration if no salvage surgery was performed), then every 6 months until 5 years post-date of salvage surgery (or from study registration if no salvage surgery was performed). After first disease progression or recurrence has been confirmed, patients will be followed for survival by phone only, every 3 months (+/- 1 month) until death or 5 years post-date of salvage surgery (or from study registration if no salvage surgery was performed), whichever occurs first.
h) Recommended in the setting of disease recurrence or progression only.
i) Screening correlative blood collection may occur at screening or at pre-surgery. Pre-surgery correlative blood collection may occur any time from the day following neoadjuvant drug administration until surgery. EOT blood draw may occur after the EOT visit.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for recurrence every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained (not less than 4) weeks following initial documentation of objective response. Timelines are described in section 10.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

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

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

11.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable)

since they are, by definition, simple cysts.

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

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

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

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST

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

MIBG (meta-iodobenzylguanidine). The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

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

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete

pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria (for the window phase of the study)

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

short axis).

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.1.4.3 Evaluation of New Lesions (for the window phase and adjuvant phase)

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 (for example, some 'new' bone lesions may be simply 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.

11.1.4.4 Evaluation of Best Overall Response (for the window phase of the study)

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

For Participants with Measurable Disease (*i.e.*, Target Disease)

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

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

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

11.1.5 Duration of Response (for the window phase of the study)

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

11.1.6 Disease-Free Survival and Overall Survival

Overall Survival: Overall Survival (OS) is defined as the time from salvage surgery (or from study registration if no salvage surgery was performed) to death due to any cause, or censored at date last known alive.

Disease-Free Survival: Disease-Free Survival (DFS) is defined as the time from salvage surgery (or from study registration if no salvage surgery was performed) to first progression or recurrence or invasive non-head-and-neck second primary or death from any cause, whichever occurs first. Participants alive without disease progression or recurrence are censored at date of last disease evaluation.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

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

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30

days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter 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 B.

- 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.

12.4 Data Sharing Agreement

Data are planned to be transferred to BMS a the following 2 proposed timepoints:

1) When n=27 patients (50% of the total sample size) have been accrued and undergone the response assessment during the window phase and proceeded to salvage surgery.
2) When those same n=27 patients have first disease progression or date last know disease-free and/or follow up information to 1 year post salvage surgery.

To be compliant with HIPAA:

a) Variables such as age will be transferred as needed rather than patient identifying information such as names, date of birth, etc
b) Patient specific dates will be replaced with times in days or months from date of salvage surgery to date of progression/date last know disease-free and/or to date of most recent follow-up.
c) The case number from the trial database will be replaced with a unique case identifier and will be the only assigned identifier in the dataset(s) upon transfer (note the study statistician generates this random number and keeps a mapping of this identifier to the original case number).

Closer to data transfer itself, decisions will be made as to whether the study statistician or ODQ staff (or a combination) prepare the dataset(s) and BMS preference to receive excel or SAS dataset(s). Documentation will also be included with the dataset(s) (i.e. variables names with corresponding descriptions and/or definition). Once the dataset(s) is prepared, it will be reviewed by the study statistician (if they did not prepare it) and the study chair, data will be archived and then transferred (by study statistician or ODQ) in a secure manner (method to be determined at time of transfer).

No party may report and/or publish on outcome data while the trial is ongoing. After closure of trial the usual follow up and preparation of reports and/or manuscript will resume.

13. STATISTICAL CONSIDERATIONS

This is a one arm phase II trial. The primary endpoint is 1-year disease-free survival (DFS) from point of salvage surgery. A 1-year DFS of 57% [36, 39-41] is the basis of the null hypothesis. Based on a 1-year DFS of 57%, the hazard is .5621 DFS events/person-year of follow up. A 30% reduction in that hazard would lead to a hazard of .3935. When 37 DFS events are observed among n=54 patients who receive salvage surgery and begin adjuvant treatment, this design has 81% power to detect a 30% reduction in the DFS hazard (using a one-sided 10% type I error rate, Wald's test). Assuming an exponential distribution, this corresponds to improving 1-year DFS from 57% to approximately 67.5% from using the adjuvant treatment.

Allowing for patients who may fail prior to salvage surgery, not receive the adjuvant portion of treatment, or for patients who are declared ineligible, n=58 patients will be registered to the trial.

The primary efficacy population includes all eligible patients who receive salvage surgery and begin adjuvant treatment. The Kaplan-Meier method will be used to estimate time-to-event endpoints.

For secondary objectives: Best overall response (at the end of the window phase of the trial) will be summarized as a proportion with a corresponding exact 95% confidence interval (CI) (noting that a 'modified' version (no confirmation of initial CR or PR) of RECIST will be used for patients whose disease initially achieves a CR or PR: the patients' tumor will be resected prior to confirming the CR or PR at least 4 weeks after initial response). Adverse events will be classified and graded according to the CTCAE v.4.0. Frequencies of adverse events will be summarized. The distributions of n-year DFS and survival will be estimated using a Kaplan-Meier method with corresponding 95% confidence intervals for time-specific event time. Several correlative studies are also planned. Given the small sample size of this trial, these studies are exploratory. Samples will be collected at baseline and at post-baseline timepoints as outlined in the protocol. Markers from the samples (cluster differentiation markers from both tumor and circulating peripheral blood, see Section 9.1) will be summarized descriptively and graphically. Within subject changes in markers will also be analyzed. Assuming n=50 patients with useable baseline and post baseline markers, there is 81% power to detect .42 SD mean difference (Wilcoxon sign rank test two-sided 0.05 alpha level.

The following stopping rule will be used to monitor delays in salvage surgery due to excessive nivolumab and/or lirilumab-related toxicity: if 3 or more of the first 10 patients who begin protocol treatment experience treatment related toxicities which cause delays in definitive surgery, accrual to the trial will be suspended to further evaluate the events and decisions made regarding the overall status of the trial. If the true delay in surgery rate due to toxicity is 10% then the probability of suspending accrual is 7%; if the true rate is 20%, then the probability of suspending accrual is 32.2%; if the true delay in surgery rate due to toxicity is 30% then the probability of suspending accrual is 62%. Adverse events will be continuously monitored

throughout the trial by the study team with decisions made accordingly regarding the study status and patient entry throughout the duration of the trial.

Assuming accrual of approximately 2.2 patients per month, 2 years of accrual and 2 years of follow up are needed for the operating characteristics for the primary endpoint. Analysis of primary endpoint is estimated to take place therefore approximately 4 years after the trial opens to accrual (approximately 2 years of accrual and 2 years follow up) or when 38 DFS events have been observed. Due to possible delays in initiation of approval at other sites, in initiation of accrual itself, the accrual period could take longer and due to possible delays in data submission and processing, the actual analysis time for the primary endpoint could be later. Analysis of secondary endpoints will require more follow-up. Assuming that the stated accrual assumptions hold, if at any time within 4 years >37 DFS events are observed, the study will not have met its primary endpoint.

See also Data Sharing Agreement in section 12.

14. PUBLICATION PLAN

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

15. REFERENCES

1. Brockstein B, H.D., Rademaker AW, Kies MS, Stenson KM, Rosen F, Mittal BB, Pelzer H, Fung BB, Witt ME, Wenig B, Portugal L, Weichselbaum RW, Vokes EE, *Patterns of failure, prognostic factors and survival in locoregionally advanced head and neck cancer treated with concomitant chemoradiotherapy: a 9-year, 337-patient, multi-institutional experience.* Ann Oncol, 2004. **15**(8): p. 1179-86.
2. Ho AS, K.D., Ganly I, Lee NY, Shah JP, Morris LG, *Decision making in the management of recurrent head and neck cancer.* Head Neck, 2014. **36**(1): p. 144-51.
3. Jr, G.W., *Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means?* Laryngoscope, 2000. **110**(3 Pt 2 Suppl 92): p. 1-18.
4. M, Z., *Surgical salvage of recurrent cancer of the head and neck.* Curr Oncol Rep, 2014. **16**(5): p. 386.
5. Janot F, d.R.D., Benhamou E, Ferron C, Dolivet G, Bensadoun RJ, Hamoir M, Géry B, Julieron M, Castaing M, Bardet E, Grégoire V, Bourhis J, *Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma.* J Clin Oncol, 2008. **26**(34): p.

5518-23.
6. Galon J, C.A., Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, Tosolini M, Camus M, Berger A, Wind P, Zinzindohoué F, Bruneval P, Cugnenc PH, Trajanoski Z, Fridman WH, Pagès F, *Type, density, and location of immune cells within human colorectal tumors predict clinical outcome.* Science, 2006. **313**(5795): p. 1960-4.
7. Duffy SA, T.J., Terrell JE, Islam M, Li Y, Fowler KE, Wolf GT, Teknos TN, *Interleukin-6 predicts recurrence and survival among head and neck cancer patients.* Cancer, 2008. **113**(4): p. 750-7.
8. M, S., *Immunobiology of HPV and HPV vaccines.* Gynecol Oncol, 2008. **109**(2 Suppl): p. S15-21.
9. O'Brien PM, S.C.M., *Evasion of host immunity directed by papillomavirus-encoded proteins.* Virus Res, 2002. **88**(1-2): p. 103-17.
10. AG, R., *Immune checkpoint blockade immunotherapy to activate anti-tumour T-cell immunity.* Br J Haematol, 2013. **162**(3): p. 313-25.
11. Leach DR, K.M., Allison JP, *Enhancement of antitumor immunity by CTLA-4 blockade.* Science, 1996. **271**(5256): p. 1734-6.
12. Nishimura H, N.M., Hiai H, Minato N, Honjo T, *Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor.* Immunity, 1999. **11**(2): p. 141-51.
13. Blazar BR, C.B., Panoskaltsis-Mortari A, Carter L, Iwai Y, Yagita H, Nishimura H, Taylor PA, *Blockade of programmed death-1 engagement accelerates graft-versus-host disease lethality by an IFN-gamma-dependent mechanism.* J Immunol, 2003. **171**(3): p. 1272-7.
14. Cooper WA, R.P., Cherian M, Duhig EE, Godbolt D, Jessup PJ, Khoo C, Leslie C, Mahar A, Moffat DF, Sivasubramaniam V, Faure C, Reznichenko A, Grattan A, Fox SB, *Intra- and Inter-Observer Reproducibility Assessment of PD-L1 Biomarker in Non-Small Cell Lung Cancer (NSCLC).* Clin Cancer Res, 2017. **Apr 18. pii: clincanres.0151.2017. doi: 10.1158/1078-0432.CCR-17-0151**([Epub ahead of print]).
15. Powles T, S.K., Stenzl A, Bedke J, *Immune Checkpoint Inhibition in Metastatic Urothelial Cancer.* Eur Urol, 2017. **Apr 13. pii: S0302-2838(17)30278-6. doi: 10.1016/j.eururo.2017.03.047**([Epub ahead of print]).
16. Feldman R, G.Z., Knezetic J, Reddy S, Nathan CA, Javadi N, Teknos T, *Molecular profiling of head and neck squamous cell carcinoma.* Head Neck, 2016. **38**(Suppl 1): p. E1625-38.
17. Lyford-Pike S, P.S., Young GD, Taube JM, Westra WH, Akpeng B, Bruno TC, Richmon JD, Wang H, Bishop JA, Chen L, Drake CG, Topalian SL, Pardoll DM, Pai SI, *Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma.* Cancer Res, 2013. **73**(6): p. 1733-41.
18. Azuma T, Y.S., Zhu G, Flies AS, Flies SJ, Chen L, *B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells.* Blood, 2008. **111**(7): p. 3635-43.
19. Hino R, K.K., Kato Y, Yagi H, Nakamura M, Honjo T, Okazaki T, Tokura Y, *Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma.* Cancer, 2010. **116**(7): p. 1757-66.
20. Iwai Y, I.M., Tanaka Y, Okazaki T, Honjo T, Minato N, *Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade.* Proc Natl Acad Sci USA, 2002. **99**(19): p. 12293-7.

21. Strome SE, D.H., Tamura H, Voss SG, Flies DB, Tamada K, Salomao D, Cheville J, Hirano F, Lin W, Kasperbauer JL, Ballman KV, Chen L, *B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma.* Cancer Res, 2003. **63**(19): p. 6501-5.
22. Brochure, B.-a.-K.a.I.s.
23. Velu V, T.K., Zhu B, Husain S, Pladevega A, Lai L, Vanderford TH, Chennareddi L, Silvestri G, Freeman GJ, Ahmed R, Amara RR, *Enhancing SIV-specific immunity in vivo by PD-1 blockade.* Nature, 2009. **458**(7235): p. 206-10.
24. Wang C, T.K., Han M, Wang XT, Huang H, Feingersh D, Garcia C, Wu Y, Kuhne M, Srinivasan M, Singh S, Wong S, Garner N, Leblanc H, Bunch RT, Blanset D, Selby MJ, Korman AJ, *In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates.* Cancer Immunol Res, 2014. **2**(9): p. 846-56.
25. Brahmer JR, D.C., Wollner I, Powderly JD, Picus J, Sharfman WH, Stankevich E, Pons A, Salay TM, McMiller TL, Gilson MM, Wang C, Selby M, Taube JM, Anders R, Chen L, Korman AJ, Pardoll DM, Lowy I, Topalian SL, *Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates.* J Clin Oncol, 2010. **28**(19): p. 3167-75.
26. Ferris RL, B.G.J., Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW, Gillison ML, *Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck.* N Engl J Med, 2016. **375**(19): p. 1856-67.
27. Brahmer J, R.K., Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR, *Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer.* N Engl J Med, 2015. **373**(2): p. 123-35.
28. Larkin J, C.-S.V., Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD, *Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.* N Engl J Med, 2015. **373**(1): p. 23-34.
29. Romagné F, A.P., Spee P, Zahn S, Anfossi N, Gauthier L, Capanni M, Ruggeri L, Benson DM Jr, Blaser BW, Della Chiesa M, Moretta A, Vivier E, Caligiuri MA, Velardi A, Wagtmann N, *Preclinical characterization of 1-7F9, a novel human anti-KIR receptor therapeutic antibody that augments natural killer-mediated killing of tumor cells.* Blood, 2009. **114**(13): p. 2667-77.
30. Vey N, B.J., Boissel N, Bordessoule D, Prebet T, Charbonnier A, Etienne A, Andre P, Romagne F, Benson D, Dombret H, Olive D, *A phase 1 trial of the anti-inhibitory KIR mAb IPH2101 for AML in complete remission.* Blood, 2012. **120**(22): p. 4317-23.
31. Benson DM Jr, H.C., Padmanabhan S, Suvannasankha A, Jagannath S, Abonour R, Bakan C, Andre P, Efebera Y, Tiollier J, Caligiuri MA, Farag SS, *A phase 1 trial of the anti-KIR antibody IPH2101 in patients with relapsed/refractory multiple myeloma.* Blood, 2012. **120**(22): p. 4324-33.

32. Benson DM Jr, C.A., Jagannath S, Munshi NC, Spitzer G, Hofmeister CC, Efebera YA, Andre P, Zerbib R, Caligiuri MA, *A Phase I Trial of the Anti-KIR Antibody IPH2101 and Lenalidomide in Patients with Relapsed/Refractory Multiple Myeloma.* Clin Cancer Res, 2015. **21**(18): p. 4055-61.
33. Leidner R, K.H., Haddad R, et al, *Preliminary efficacy from a phase 1/2 study of the natural killer cell–targeted antibody, lirilumab, in combination with nivolumab in squamous cell carcinoma of the head and neck. Presented at: 2016 SITC Annual Meeting.* 2016: p. November 9-13, 2016; National Harbor, MD. Abstract 456.
34. Murphy WJ, P.P., Miller JS, *NK cells--from bench to clinic.* Biol Blood Marrow Transplant, 2012. **18**(1 Suppl): p. S2-7.
35. Spencer SA, H.J., Wheeler RH, Machtay M, Schultz C, Spanos W, Rotman M, Meredith R, Ang KK, *Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck.* Head Neck, 2008. **30**(3): p. 281.
36. Hamoir M, H.E., Ambroise J, Lengelé B, Schmitz S, *Salvage surgery in recurrent head and neck squamous cell carcinoma: Oncologic outcome and predictors of disease free survival.* Oral Oncol, 2017. **67**(Epub 2017 Jan 28): p. 1-9.
37. Tan HK, G.R., Auperin A, Bourhis J, Janot F, Temam S, *Salvage surgery after concomitant chemoradiation in head and neck squamous cell carcinomas - stratification for postsalvage survival.* Head Neck, 2010. **32**(2): p. 139-47.
38. Jr, G.W., *Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means?* Laryngoscope, 2000. **110**(3 Pt 2 Suppl 93): p. 1.
39. Zafereo ME, H.M., Rosenthal DI, Sturgis EM, Lewin JS, Roberts DB, Weber RS, *The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx.* Cancer, 2009. **115**(24): p. 5723-33.
40. Putten L, B.R., Doornaert PA, Buter J, Eerenstein SE, Rietveld DH, Kuik DJ, Leemans CR, *Salvage surgery in post-chemoradiation laryngeal and hypopharyngeal carcinoma: outcome and review.* Acta Otorhinolaryngol Ital, 2015. **35**(3): p. 162-72.
41. Sandulache VC, V.L., Skinner HD, Cata J, Hutcheson K, Fuller CD, Phan J, Siddiqui Z, Lai SY, Weber RS, Zafereo ME, *Salvage total laryngectomy after external-beam radiotherapy: A 20-year experience.* Head Neck, 2016. **38 Suppl 1**: p. E1962-8.
42. Chow LQ, H.R., Gupta S, Mahipal A, Mehra R, Tahara M, Berger R, Eder JP, Burtness B, Lee SH, Keam B, Kang H, Muro K, Weiss J, Geva R, Lin CC, Chung HC, Meister A, Dolled-Filhart M, Pathiraja K, Cheng JD, Seiwert TY, *Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort.* J Clin Oncol, 2016. **[Epub ahead of print]**.
43. Seiwert TY, B.B., Mehra R, Weiss J, Berger R, Eder JP, Heath K, McClanahan T, Lunceford J, Gause C, Cheng JD, Chow LQ, *Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial.* Lancet Oncol, 2016. **17**(7): p. 956-65.
44. Mandal R, S.Y., Desrichard A, Havel JJ, Dalin MG, Riaz N, Lee KW, Ganly I, Hakimi AA, Chan TA, Morris LG, *The head and neck cancer immune landscape and its immunotherapeutic implications.* JCI Insight, 2016. **1**(17): p. e89829.

45. Norris S, C.A., Kuri-Cervantes L, Bower M, Nelson M, Goodier MR, *PD-1 expression on natural killer cells and CD8(+) T cells during chronic HIV-1 infection.* Viral Immunol, 2012. **25**(4): p. 329-32.
46. Purdy AK, C.K., *Natural killer cells and cancer: regulation by the killer cell Ig-like receptors (KIR).* Cancer Biol Ther, 2009. **8**(23): p. 2211-20.
47. Ruggeri L, M.A., Capanni M, Urbani E, Carotti A, Aloisi T, Stern M, Pende D, Perruccio K, Burchielli E, Topini F, Bianchi E, Aversa F, Martelli MF, Velardi A, *Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value.* Blood, 2007. **110**(1): p. 433-40.
48. Liu RB, E.B., Arina A, Schreiber K, Hyjek E, Schietinger A, Binder DC, Butz E, Krausz T, Rowley DA, Jabri B, Schreiber H, *Densely granulated murine NK cells eradicate large solid tumors.* Cancer Res, 2012. **72**(8): p. 1964-74.
49. Hanna GJ, L.H., Jones RE, Bacay AF, Lizotte PH, Ivanova EV, Bittinger MA, Cavanaugh ME, Rode AJ, Schoenfeld JD, Chau NG, Haddad RI, Lorch JH, Wong KK, Uppaluri R, Hammerman PS, *Defining an inflamed tumor immunophenotype in recurrent, metastatic squamous cell carcinoma of the head and neck.* Oral Oncol, 2017. **67**: p. 61-69.
50. Licitra L, G.C., Guzzo M, Mariani L, Lo Vullo S, Valvo F, Quattrone P, Valagussa P, Bonadonna G, Molinari R, Cantù G, *Primary chemotherapy in resectable oral cavity squamous cell cancer: a randomized controlled trial.* J Clin Oncol, 2003. **21**(2): p. 327-33.
51. Zhong LP, Z.C., Ren GX, Guo W, William WN Jr, Sun J, Zhu HG, Tu WY, Li J, Cai YL, Wang LZ, Fan XD, Wang ZH, Hu YJ, Ji T, Yang WJ, Ye WM, Li J, He Y, Wang YA, Xu LQ, Wang BS, Kies MS, Lee JJ, Myers JN, Zhang ZY, *Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma.* J Clin Oncol, 2013. **31**(6): p. 744-51.
52. Forde PM, S.K., Chaft JE, Hellmann M, Merghoub T, Wolchok JD, Yang SC, Battafarano RJ, Gabrielson E, Georgiades CS, Verde F, Rosner GL, Naidoo J, Cottrell TR, Taube JM, Anagnostou V, Velculescu VE, Topalian SL, Pardoll DM, Brahmer JR *Neoadjuvant anti-PD1, nivolumab, in early stage resectable non-small-cell lung cancer.* Ann Oncol, 2016. **27**(6): p. 1-36.
53. Garon EB, R.N., Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Soria JC, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki GM, Roach C, Emancipator K, Gandhi L; KEYNOTE-001 Investigators, *Pembrolizumab for the treatment of non-small-cell lung cancer.* N Engl J Med, 2015. **372**(21): p. 2018-28.
54. Rizvi NA, H.M., Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN, Chan TA, *Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.* Science, 2015. **348**(6230): p. 124-8.
55. Gajewski TF, S.H., Fu YX, *Innate and adaptive immune cells in the tumor microenvironment.* Nat Immunol, 2013. **14**(10): p. 1014-22.

56. Lizotte PH, I.E., Awad MM, Jones RE, Keogh L, Liu H, Dries R, Almonte C, Herter-Sprie GS, Santos A, Feeney NB, Paweletz CP, Kulkarni MM, Bass AJ, Rustgi AK, Yuan GC, Kufe DW, Janne PA, Hammerman PS, Sholl LM, Hodi FS, Richards WG, Bueno R, English JM, Bittinger MA, Wong KK, *Multiparametric profiling of non–small-cell lung cancers reveals distinct immunophenotypes.* JCI Insight, 2016. **1**(14): p. e89014.
57. Hanna GJ, L.H., Jones RE, Bacay AF, Lizotte PH, Ivanova EV, Bittinger MA, Cavanaugh ME, Rode AJ, Schoenfeld JD, Chau NG, Haddad RI, Lorch JH, Wong KK, Uppaluri R, Hammerman PS, *Defining an inflamed tumor immunophenotype in recurrent, metastatic squamous cell carcinoma of the head and neck.* Oral Oncol, 2017. **Apr;67:61-69. doi: 10.1016/j.oraloncology.2017.02.005. Epub 2017 Feb 14**.

APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B GUIDANCE ON CONTRACEPTION

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

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

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

For male subjects with partners that are WOCBP
• Condom

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

Women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of nivolumab.

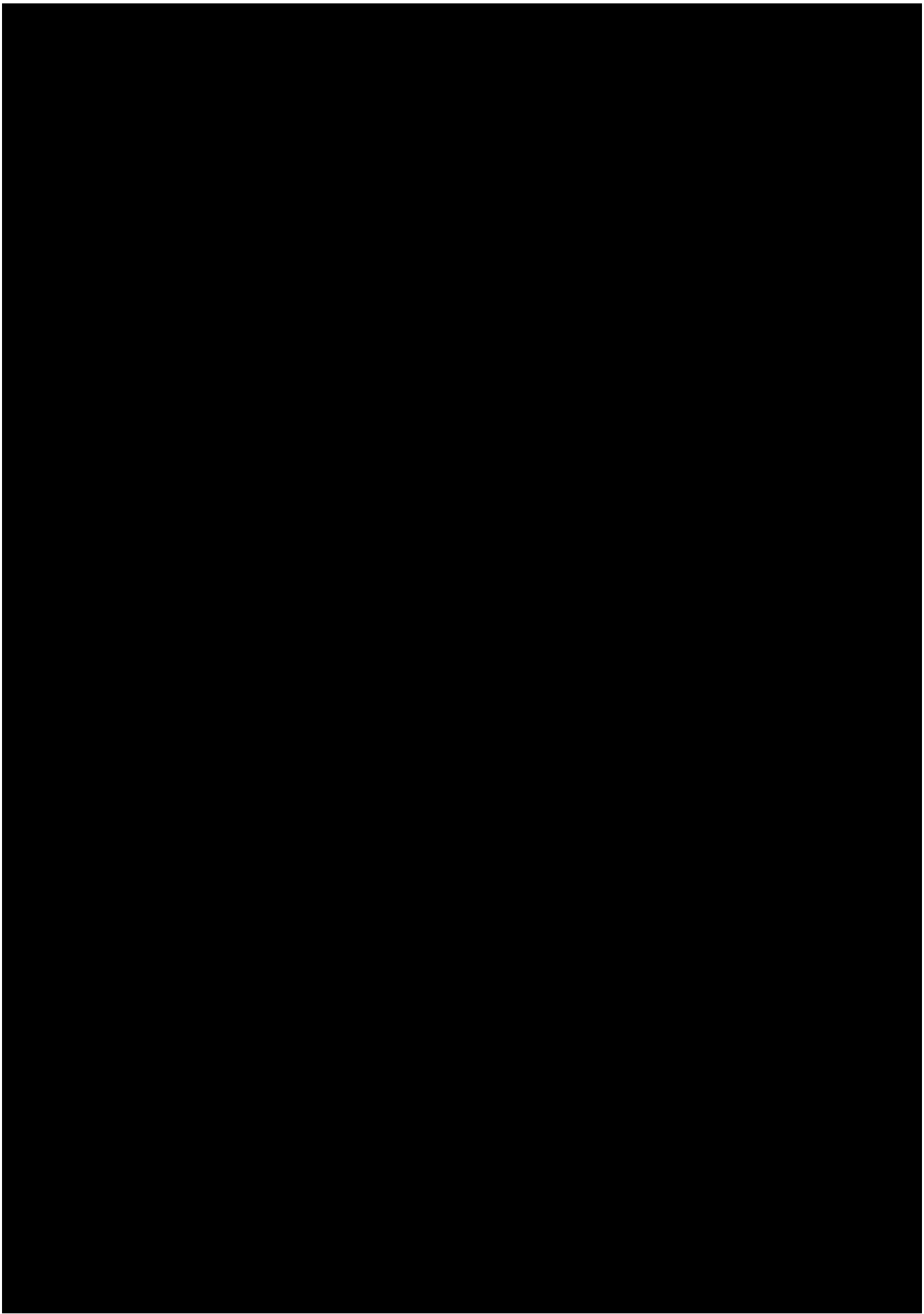
APPENDIX C MANAGEMENT ALGORITHMS

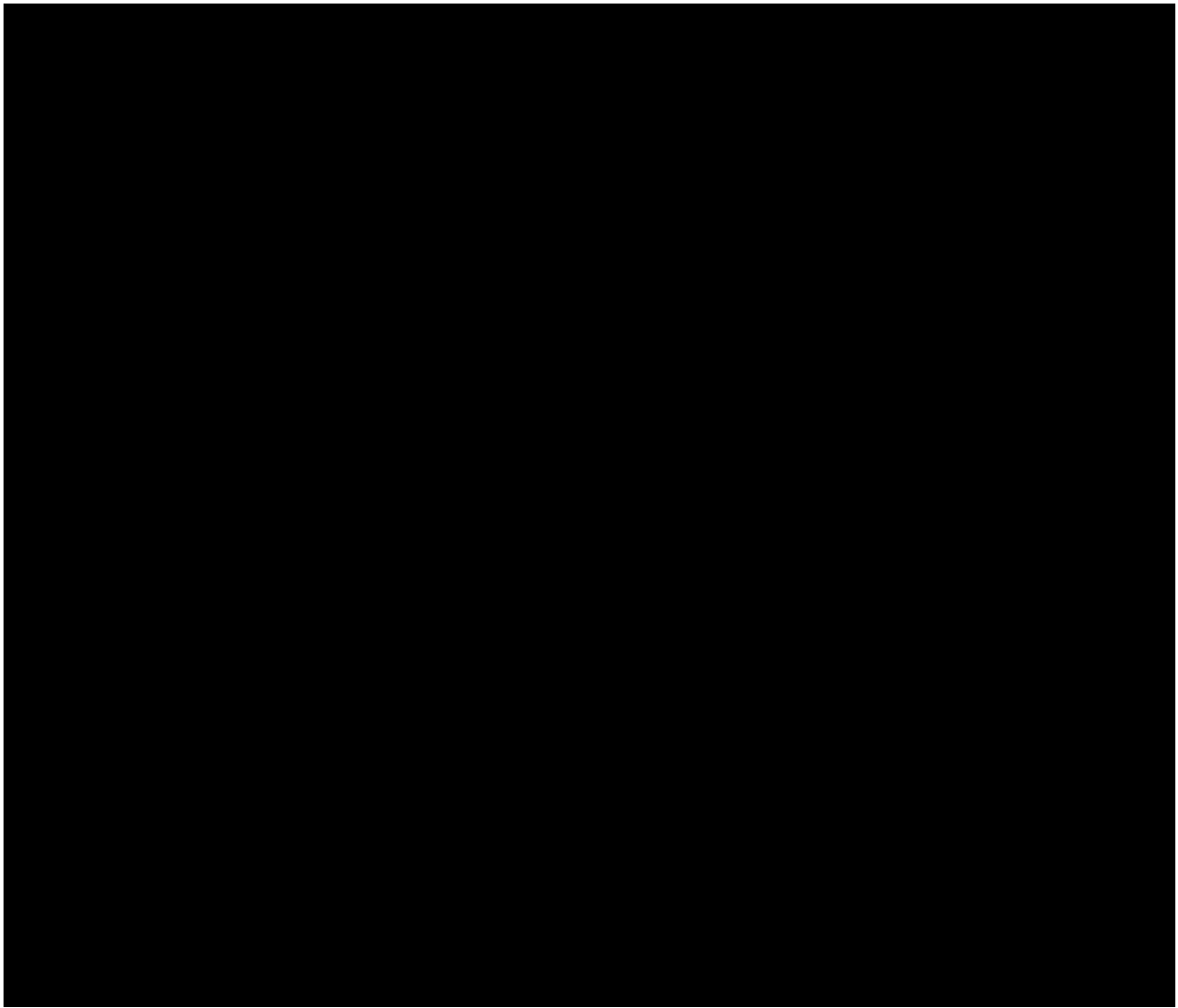
- These general guidelines constitute guidance to the Investigator. The guidance applies to all immuno-oncology (I-O) agents and regimens.
- A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be 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

DFCI IRB Protocol #: 17-411

APPENDIX *D*

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





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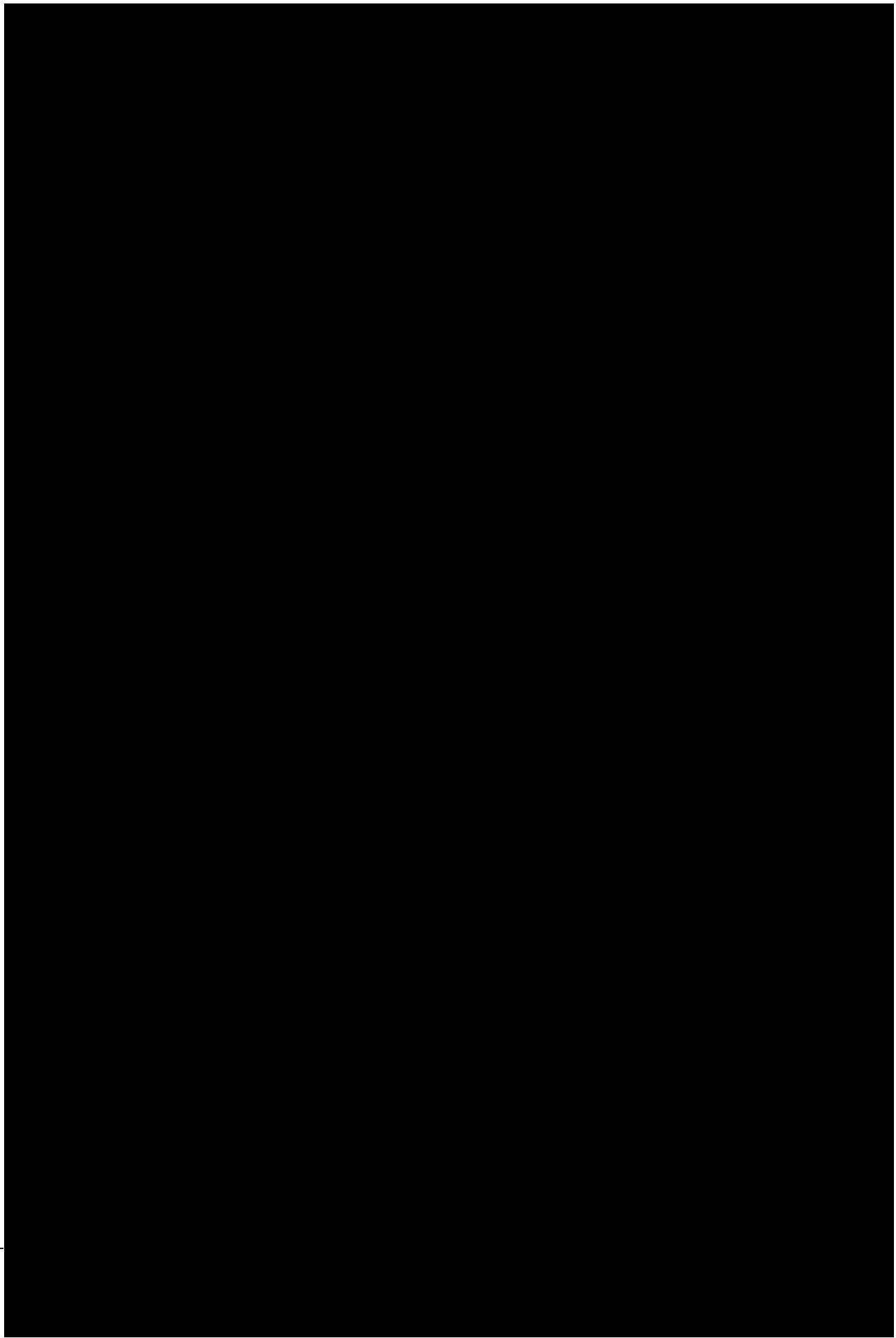

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