TITLE: A phase II trial of personalized immunotherapy in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M HNSCC) that have progressed on prior immunotherapy.

Corresponding Organization: UPMC Hillman Cancer Center

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Sponsor-Investigator: ***Dan P Zandberg MD***
5150 Centre Avenue, 5th Floor
Pittsburgh PA 15232
412-864-7955
Fax 412-648-6579
zandbergdp@upmc.edu

Biostatistician: *William Gooding, MS*
UPMC Cancer Pavilion Suite 4C
5150 Centre Ave
Pittsburgh, PA 15232
412-383-1583
weg@pitt.edu

Source(s) of Support: Bristol Myers Squibb

Study Monitor: Education and Compliance Office for Human Subject Research
Research Conduct and Compliance Office
University of Pittsburgh
3500 Fifth Avenue, Suite 205
Pittsburgh, PA 15213

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1.0 Protocol Synopsis

Concept and Rationale:
Outcomes with systemic therapy for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) remain poor. For example, treatment with Nivolumab led to increased overall survival compared to investigator's choice chemotherapy in patients with R/M HNSCC that had failed prior platinum based therapy (1), although only a minority (13%) of patients responded. The promise of immune checkpoint blockade with anti-PD-1 mAbs in most solid tumors, including HNSCC, is that while only the minority respond, a proportion of patients that do respond have prolonged response and/or disease control, which has led to greater survival compared to traditional chemotherapy. This has led to two major goals in the field of immuno-oncology. One is to develop novel combinations to try and improve response rates, and the other is the development of better predictive biomarkers of efficacy for these agents. The latter is even more important now that many new combinations are being tested, i.e., how do we select the best drug to be added to Nivolumab to increase efficacy? Additionally, there is currently a great need for better therapeutic options for patients who have progressed on prior immunotherapy. This trial will evaluate a drug selection strategy based on immune gene expression in R/M HNSCC patients who have progressed on prior immunotherapy with anti-PD-1 or anti-PD-L1 mAbs.

Primary Objective(s):

Estimate the probability of objective response to treatment determined by gene expression of LAG3 and CTLA4 per the OmniSeq Immune Report card in R/M HNSCC patients who have progressed on prior immunotherapy.

Secondary Objective(s):

1. Estimate the disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety of treatment determined by gene expression of LAG3 and CTLA4 per the Omniseq Immune Report card for R/M HNSCC patients who have progressed on prior immunotherapy;
2. Estimate the probability of objective response, DCR, PFS, OS and safety of treatment that is randomly assigned instead of determined by gene expression. This will be compared in an exploratory fashion to the objective response of those patients with treatment determined by gene expression.
3. Estimate the probability of objective response, DCR, PFS, OS and safety of treatment determined by gene expression of LAG3 and CTLA4 per the OmniSeq Immune Report card for R/M HNSCC patients who have progressed on trial treatment and undergone a second biopsy and second treatment determined by a second gene expression analysis of LAG3 and CTLA4.

Exploratory Biomarker Studies:

A. Evaluate immune gene expression, immune co-signaling molecule expression by IHC, and immune cell populations over time via paired samples (when available) after exposure to combination immunotherapy;
B. Evaluate co-signaling molecule expression by IHC and correlate with gene expression by RNAseq as well as the predictive value of co-signaling molecule expression by IHC and the efficacy of the combination selected;
C. Evaluate immune cell populations and other potential biomarkers (as per section 14.0) in the peripheral blood at baseline and over time;
D. Evaluate saliva and stool microbiome to determine if any correlation with efficacy of the combination selected.

Primary Endpoint(s):

The primary endpoint is objective response by RECIST 1.1.

Secondary Endpoint(s):

1. Disease control rate
2. PFS
3. OS
4. Adverse events

Exploratory Biomarker Studies:

A. Immune gene expression and immune co-signaling molecule expression by IHC and immune cell populations over time;
B. Co-signaling molecule expression by IHC and correlate with gene expression by RNAseq as well as the predictive value of co-signaling molecule expression by IHC and the efficacy of the combination selected.
C. Evaluation of immune cell populations in the peripheral blood at baseline and over time.
D. Evaluation of saliva and stool microbiome to determine if any correlation with efficacy of the combination selected

Study Design:
This is a phase II trial. Patients who meet eligibility criteria will have tumor tissue obtained (core or excisional/incisional; a FNA is not adequate) for gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card to determine which drug (either Relatlimab or Ipilimumab) will be added to Nivolumab for treatment. The patient will then receive the prescribed therapy continuously for up to 24 cycles (1 cycle = 4 weeks of treatment) with repeat imaging prior to every 3rd cycle until progression of disease. Response, evaluated by RECIST 1.1, with modifications to allow for continued therapy until progressive disease is confirmed if the patient is clinically stable, will be used in the trial. If the patient has confirmed progression and meets eligibility criteria to obtain a second biopsy, he or she will continue on trial and undergo a repeat biopsy for gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card to select another agent to add to Nivolumab. The patient will then be treated with this new combination continuously, with repeat imaging prior to every 3rd cycle as per initial treatment, until progression of disease. (see Schema A).

Each patient's tumor biopsy sample will be analyzed using the OmniSeq Immune Report Card for immune gene expression, which is quantified based on RNA-Seq. The drug to be added to Nivolumab will be based on which relevant gene has the highest expression (CTLA4 or LAG3) assuming that the difference between the relative rank score of two genes are at least 15.2, as per the treatment assignment rule (section 15.0). For example, if analysis shows that LAG-3 is at least 15.2 higher than CTLA-4 based on OmniSeq Immune Report Card then the patient will receive Nivolumab plus Relatlimab. If the difference between CTLA4 and LAG3 relative rank score is less than 15.2, then the patient will be randomized to either Ipilimumab plus Nivolumab or Relatlimab plus Nivolumab. Because the efficacy of the two combinations has not been established in anti-PD-1/PD-L1 failure HNSCC patients, there is equipoise for randomizing if the minimum difference in relative rank score is not met. See Schema B.

Number of Patients: 40 total with an accrual goal of 2 per month.

Main Criteria for Inclusion/Exclusion:

1. Recurrent/Metastatic squamous cell carcinoma of the head and neck that is not amenable to therapy with curative intent. Subjects that refuse salvage surgery or radiation for recurrence are potentially eligible.

2. Failure of prior immunotherapy as defined as:
   a. Progression of disease on anti-PD-1 mAb or anti-PD-L1 mAb treatment in the R/M setting.
   b. Both patients that have received platinum based chemotherapy prior or have not yet received platinum based chemotherapy are eligible.

3. Patients cannot have received more than 3 total lines of prior systemic therapy in the recurrent/metastatic setting

4. ECOG performance status of 0-1

5. Have at least one measurable area of disease (Target Lesion) based on RECIST 1.1.

6. Provide adequate tissue (core or incisional/excisional biopsy) prior to starting study for analysis for gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card. FNA is not adequate. Archival tissue can only be used if it was obtained in the recurrent/metastatic setting and the patient has not received a subsequent systemic therapy.

Intervention and Mode of Delivery:

1. Relatlimab plus Nivolumab: Nivolumab will be dosed 480mg IV q 4 weeks and Relatlimab 160mg IV q 4 weeks. One cycle is defined as 4 weeks of treatment and both drugs are given on the same day.

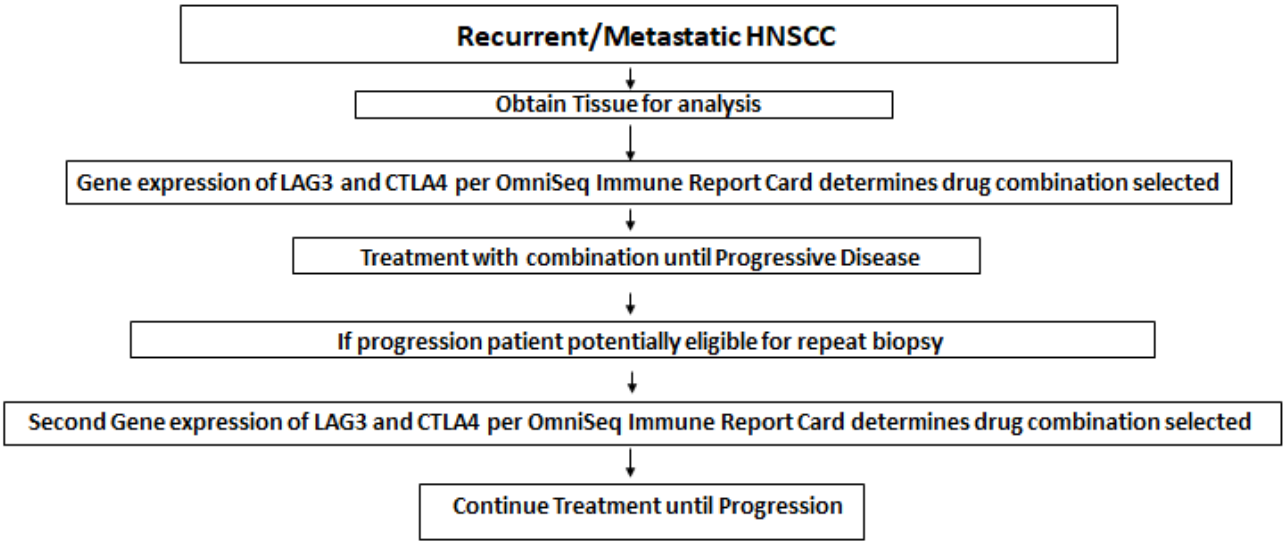
2. Ipilimumab plus Nivolumab: Nivolumab will be dosed at 3mg/kg IV q 2 weeks and Ipilimumab 1mg/kg IV q 6 weeks. Patients will receive four doses of Ipilimumab and the last dosage of Nivolumab 3mg/kg IV q 2 weeks will be given at the time of the 4th dose of Ipilimumab, followed 2 weeks later by Nivolumab 480 mg IV q 4 weeks. A cycle of therapy will be defined as 4 weeks of treatment.

Duration of Intervention and Evaluation: Patients will be treated with up to 24 cycles or until progression or adverse events requiring discontinuation, whichever occurs first. Repeat imaging will be done prior to every 3rd cycle

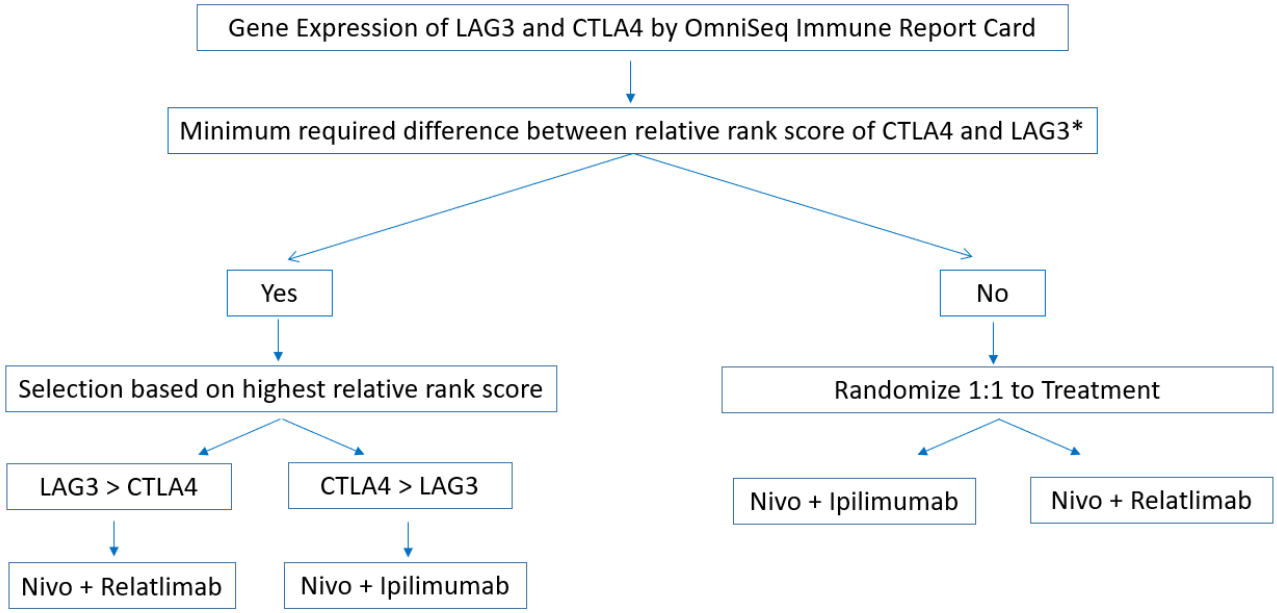
of therapy. If a patient completes 24 cycles without progression, repeat imaging will continue to be done every 3 months until progression.
Patient Acceptability/Ethics and Consent Issues: Both Relatlimab plus Nivolumab as well as Ipilimumab plus Nivolumab have been studied in recurrent/metastatic solid tumors with combination dosage established already and overall have been well tolerated. All patients will sign informed consent before screening commences on trial.

SCHEMAS

A. Trial Schema



B. Selection of drug to be combined with Nivolumab



* Minimum difference between relative rank score of CTLA4 and LAG3 is 15.2.

2.0 BACKGROUND

2.1 RATIONALE FOR THE STUDY

Squamous cell carcinoma of the head and neck (HNSCC) is the 6th most common cancer worldwide and includes cancers that involve the nasopharynx, larynx, hypopharynx, oropharynx and oral cavity (2). While smoking and alcohol intake are still traditional risk factors for HNSCC, in recent decades it has become apparent that the human papillomavirus (HPV) also has an etiological role in squamous cell carcinoma of the oropharynx, and these tumors are associated with an improved prognosis compared to HPV negative HNSCC (3-6). However, prognosis remains poor in the recurrent/metastatic setting for all HNSCC patients, including HPV positive oropharyngeal cancer, with a median survival with systemic therapy alone of 10-12 months.

Anti-PD-1 monoclonal antibody Nivolumab is currently approved for R/M HNSCC patients that have failed prior platinum based chemotherapy. This approval was as a result of the phase III Checkmate 141 trial where Nivolumab significantly improved overall survival compared to investigator choice chemotherapy (1). While this is the first drug in a randomized trial to ever prolong overall survival in R/M disease after platinum failure, the response rate was only 13% with an additional 20% achieving SD. Therefore, the majority of patients will progress through nivolumab. There is no defined standard of care after failure of immunotherapy and while various chemotherapy agents can be tried, outcomes are poor.

The promise of immune checkpoint blockade with anti-PD-1 mAbs in most solid tumors, including HNSCC, is that while only the minority respond, a proportion of patients that do respond have prolonged response and/or disease control, which has led to greater survival compared to traditional chemotherapy. This has led to two major goals in the field of immuno-oncology. One is to develop novel combinations to try and improve response rates, and the other is the development of better predictive biomarkers of efficacy for these agents. The latter is even more important now that many new combinations are being tested, i.e how do we select the best drug to be added to Nivolumab to increase efficacy. It is unlikely that one combination will work in the majority of HNSCC patients; rather that personalized biomarker selection of the right immunotherapy agent to add to Nivolumab will lead to the majority of HNSCC benefiting from combination immunotherapy.

Predictive biomarkers for immunotherapy strive to characterize the functional state of immune cells in the tumor microenvironment. Towards this goal, immune gene expression profiles (GEP) via analysis of extracted RNA, characterize the “T cell activation status” in the tumor microenvironment, and have been observed to be predictive of efficacy with treatment with anti-PD-1 mAbs across various solid tumor types, including HNSCC, with more accuracy than with co-signaling molecule expression by immunohistochemistry (7-10). A composite score based on six Interferon gamma related genes (CXCL9, CXCL10, IDO1, IFNG, HLA-DRA, and STAT1) significantly correlated with response rate as well as progression free survival (PFS) in R/M HNSCC patients treated with anti-PD-1 mAb Pembrolizumab in Keynote 012. Specifically, patients with a score above the Youden index had a response rate of 40% compared to 5% for those below (95% negative predictive value) (9). Furthering these results, in a cohort of 258 R/M HNSCC patients treated with Pembrolizumab in Keynote 012 and 055, a high 18 gene expression profile score (GEP) was significantly and independently associated with increased response, PFS, and OS (11).

In this Phase II trial of personalized immunotherapy in R/M HNSCC, we will use on gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card to select the appropriate agent (Ipilimumab or Relatlimab) to add to Nivolumab in patients with R/M HNSCC patients that have failed prior immunotherapy with anti-PD-1 or PD-L1 mAb therapy. The agent, either Ipilimumab or Relatlimab will be chosen based on the highest relevant immune gene expression (CTLA4 or LAG-3) as long as the minimum difference required is met (detailed in protocol). Importantly, as is detailed in sections 2.2-2.5 below, the safety of combination of Ipilimumab and Nivolumab as well as Relatlimab and Nivolumab has already been established with efficacy results in some solid tumors and ongoing trials in biomarker unselected R/M HNSCC patients. Additionally, as discussed in background sections below, both CTLA-4 and LAG-3 upregulation on immune cells has been associated with resistance to anti-PD-1 blockade (12, 13). In mouse models for example when LAG3 is expressed in addition to PD-1, dual blockade of LAG3 and PD-1 is more efficacious than PD-1 alone(14). Currently there is no established standard of care for R/M HNSCC patients that have failed prior anti-PD-1/PD-L1 therapy and their great need for better therapeutics

for these patients. This patient population is growing as anti-PD-1 mAb is currently being used in trials in the upfront locally advanced setting as well as first line R/M setting. This trial has immediate implications not only for HNSCC patients that have failed prior immunotherapy and also in furthering our knowledge of the mechanisms of immunotherapy resistance, but also this strategy has the potential to be applied to any immunotherapy drug combination in any solid tumor.

2.2 BACKGROUND OF LAG3,CTLA4, AND PD-1

2.2.1 LAG3 AND RELATLIMAB/BMS-986016 (ANTI-LAG3 ANTIBODY)

Lymphocyte activation gene 3 (LAG3, CD223) is a negative regulatory T-cell receptor that is implicated in the control of T-cell function in conventional and regulatory T cells. LAG3 is a member of the immunoglobulin (Ig) superfamily and displays high homology to CD4. It is over 500 amino acids in length and consists of 4 extracellular domains, D1 to D4. D4 is followed by a connecting peptide region and a transmembrane and intracellular domain of 75 amino acids. LAG3 is related to CD4 in domain organization (D1 to D4), and their genes are adjacent to one another in the genome, reflecting a common origin(15). Both CD4 and LAG-3 bind to major MHC Class II, but LAG3 binds with a higher affinity (60 nM) as a LAG3-immunoglubulin fusion protein(16). LAG3 is expressed on the surface of activated T cells, T regulatory cells, and a subpopulation of NK cells but not on resting peripheral blood lymphocytes.

In human T cells, LAG3 is upregulated upon activation; when activated T cells were bound by LAG3 antibody and then exposed to immobilized antibody cross-linking reagents, a reduction in proliferation and cytokine secretion was observed(16). A subset of T cells known as T-regulatory (Treg) cells suppress the activity of conventional T cells. LAG3 transcripts have been detected in Treg cells in humans and mice, and LAG3 expression contributes to Treg suppressive function. LAG3 expression on Tregs may also mediate T-cell suppression via engagement of MHC Class II on dendritic cells (DCs), which results in suppression of DC maturation and immunostimulatory potential. Adoptive transfer of antigen-specific T cells into mice expressing cognate antigen resulted in the appearance of regulatory cells that promoted tolerance. LAG3 was expressed on these induced Tregs, and anti-LAG-3 antibody C9B7W reversed in vitro suppression activity of these cells. Naturally occurring CD4+CD25+ Tregs express LAG3 upon activation, and the same cells from LAG3 (-/-) mice exhibit reduced regulatory activity.

Relatlimab (also referred to as BMS-986016, BMS-986016-01, and anti-LAG3) is a fully human LAG3-specific antibody that was isolated following immunization of transgenic mice expressing human immunoglobulin (Ig) genes. It is expressed as an immunoglobulin G4 (IgG4) isotype antibody and includes a stabilizing hinge mutation (S228P). Relatlimab binding inhibits the negative regulatory function of LAG3 in vitro.

2.2.2 BACKGROUND OF CTLA4 AND IPILIMUMAB/BMS-734016

Full activation of naïve T cells requires not only stimulation of the antigen receptor by peptide/major histocompatibility complexes but also co-stimulatory signals mediated by engagement of CD28 by B7 molecules. T cells constitutively express CD28, and expression of B7 molecules is limited to antigen-presenting cells (APCs), such as dendritic cells, activated macrophages, and activated B cells. CD28-B7 co-stimulatory signals are critical for the induction of T-cell proliferation, cytokine secretion, and effector functions(17).

CTLA4 is an activation-induced T-cell surface molecule that also binds CD80 and CD86, but with greater affinity than CD28. CTLA4-mediated signals are inhibitory and turn off T-cell-dependent immune responses. Disrupting CTLA4 interaction with its ligands B7.1 (CD80) and B7.2 (CD86), which are expressed on APCs, augments T-cell-mediated immune responses. In vivo blockade of CTLA4, utilizing anti-CTLA4 mAb, induced regression of established tumors and enhanced anti-tumor immune responses in several murine tumor models.

In addition to being expressed on activated effector T cells, CTLA4 is constitutively expressed on the surface of Tregs(18). Conditional knockout mice lacking CTLA4 in the CD4+ forkhead box P3 (FOXP3+) T-regulatory cellular compartment are characterized by systemic lymphoproliferation and impaired Treg function in vitro, suggesting that CTLA4 is critical for the maintenance of Treg suppressive function. Tumor rejection mediated by anti-CTLA4 antibodies is associated with selective intratumoral Treg depletion. In mouse melanoma and colon carcinoma models, anti-mouse CTLA4 antibodies, which bind to activating Fc-gamma receptors (FcγRs), depleted intratumoral Tregs in an FcγR-dependent mechanism, resulting in increased intratumoral T-effector/Treg cell ratio and effective anti-tumor immunity(19, 20). Depletion of Tregs was observed within the tumor

microenvironment but not in the periphery. The preferential depletion of intratumoral Tregs was consistent with an antibody-dependent cellular cytotoxicity (ADCC) mechanism since it was associated with the presence of cells expressing activating FcγRs and higher levels of CTLA-4 surface expression on intratumoral Tregs relative to peripheral Tregs and CD4 and CD8 tumor-infiltrating T effectors.

Ipilimumab is a fully human monoclonal antibody (mAb) that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. In cancer patients, reduction of Treg frequency has been reported in tumor tissues following ipilimumab therapy. As might be expected for an IgG1 antibody, ipilimumab showed strong binding to the activating FcγRI and low to moderate ability to produce ADCC in vitro. In a clinical study in which 6 bladder cancer patients received 2 doses of ipilimumab at 3 mg/kg, intratumoral Tregs (CD4+ FOXP3+) measured 4 weeks after the last dose of ipilimumab were significantly lower than in bladder cancer tissues from untreated patients(21). In a neoadjuvant translational study of ipilimumab (10 mg/kg; N = 10) with locally and/or regionally advanced melanoma, a trend towards lower intratumoral Treg frequency (CD4+ CD25hi+ FOXP3+) was observed in patients who benefited from therapy (CR/partial response [PR]/standard deviation [SD] mean change = -0.64, SD = 1.83 versus progressive disease [PD]; mean change = 1.5; SD = 1.46; p = 0.09). Finally, melanoma patients responding to ipilimumab displayed lower Treg counts within the tumor microenvironment 3 to 4 weeks post-ipilimumab treatment compared with nonresponders(22). Since FOXP3+ tumor- infiltrating Treg counts at baseline were similar in both responders and nonresponders, and the decrease in Treg count post-ipilimumab therapy was also associated with greater infiltration of cells able to induce ADCC (CD68+CD16+), the authors concluded that ipilimumab may induce Treg depletion.

2.2.3 BACKGROUND OF PD-1 AND NIVOLUMAB/BMS-936558 (ANTI-PD-1 ANTIBODY)

Programmed Cell Death 1 (PD1) is a cell surface signaling receptor that plays a critical role in the regulation of T cell activation and tolerance. PD1 is primarily expressed on activated T cells, B cells, and myeloid cells(23). It is also expressed on NK cells. Binding of PD1 by its ligands PD-L1 and PD-L2, results in phosphorylation of the tyrosine residue in the proximal intracellular immune receptor tyrosine inhibitory domain, followed by recruitment of the phosphatase SHP-2, eventually resulting in down-regulation of T cell activation (24-26). PD1 is highly expressed on tumor infiltrating lymphocytes, and its ligands are up-regulated on the cell surface of many different tumors (27-29). Multiple murine cancer models have demonstrated that binding of ligand to PD1 results in immune evasion (30-32). In addition, blockade of this interaction results in antitumor activity. These findings provided the rationale for testing PD1 pathway blockade in clinical trials.

Nivolumab is a fully human monoclonal antibody that blocks the interaction between PD1 and its ligands, PD-L1 and PD-L2. Nivolumab does not bind other related family members, such as BTLA, CTLA4, ICOS or CD28.

2.2.4 PRECLINICAL STUDIES UTILIZING ANTI-PD1 AND ANTI-LAG3 ANTIBODIES

The importance of LAG3 as an immunotherapy target was validated in murine in vivo models using 2 surrogate antibodies specific for LAG3. These studies evaluated tumor growth inhibition in syngeneic tumor models (Sa1N fibrosarcoma and MC38 colon adenocarcinoma) and monitored acceleration of autoimmunity in the non-obese diabetic (NOD) model. Anti-LAG3 antibody administration resulted in both overall tumor growth inhibition and an increase in the number of tumor-free (TF) mice in those treatment groups (Figure 1). Anti-LAG3 antibody administered in combination with anti-PD1 antibody provided enhanced antitumor activity above the activity of either agent alone. For example, in multiple Sa1N tumor models, anti-LAG3 antibody resulted in 20%-30% TF mice compared to control and anti-PD1 antibody-treated mice (0%-10% TF mice), while the combination of anti-LAG3 and anti-PD1 antibodies resulted in 60%-90% TF mice. In the MC38 model, anti-LAG3 antibody showed modest tumor growth inhibition alone but when administered in combination with anti-PD1 antibody, resulted in enhanced antitumor activity above that observed for anti-PD1 antibody alone (80% vs. 40% TF mice, respectively).

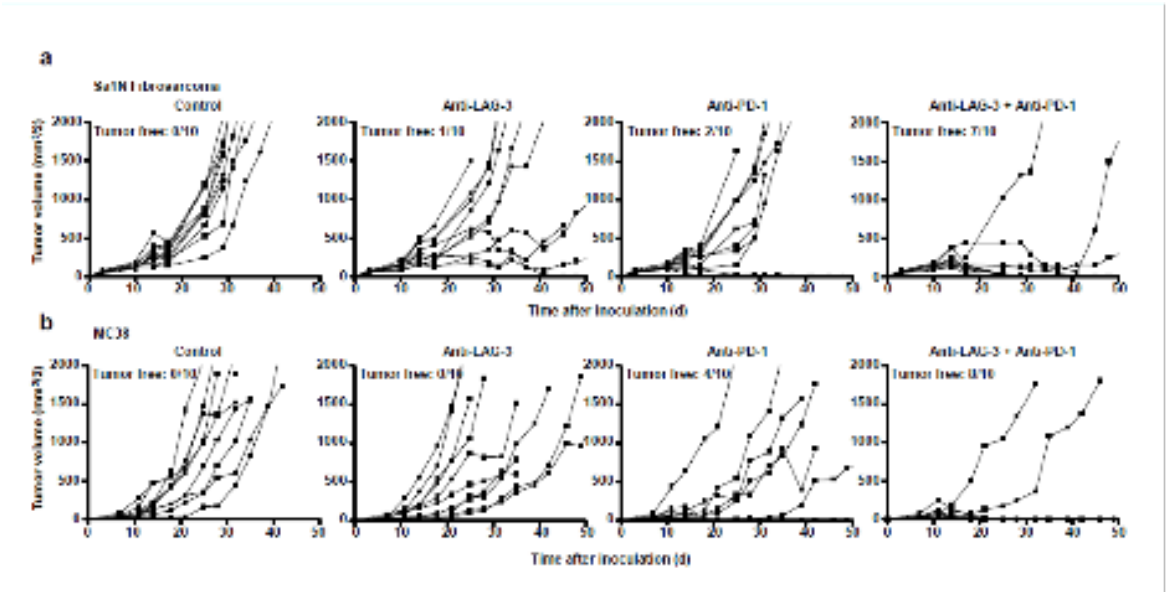


Figure 1: Anti tumor activity of anti-LAG3 and anti-PD1 in murine models.

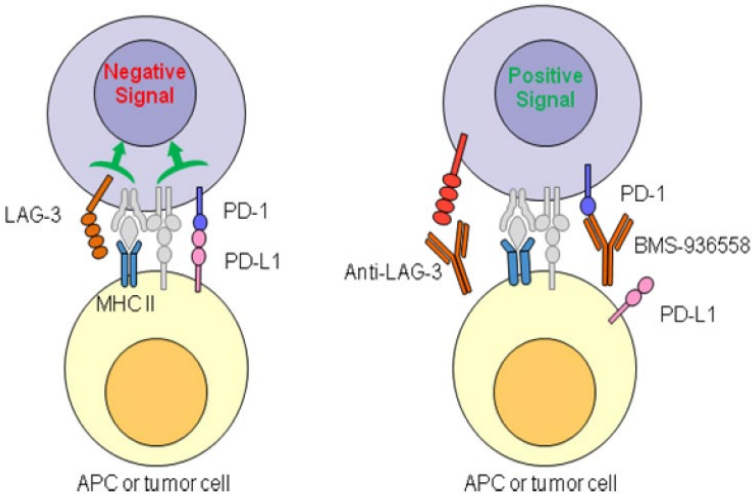
2.2.5 PRECLINICAL STUDIES UTILIZING ANTI-PD1, ANTI-CTLA4 AND ANTI-LAG3 ANTIBODIES

The anti-tumor activity of anti-LAG-3 antibody (C9B7W) as a single agent and in combination with anti-PD-1 antibody (4H2) or anti-CTLA-4 antibody (9D9) was evaluated in 2 independent studies, using MC38 colon carcinoma tumors implanted in C57BL/6 mice (Day 0). The efficacy of combined anti-LAG-3 (C9B7W) and anti-PD-1 (4H2) antibodies was superior to that of the single antibodies alone, as well as the combined anti-LAG-3 (C9B7W) and anti-CTLA-4 (9D9) antibodies. 30% of mice treated with either anti-PD1 monotherapy or anti-CTLA4 and anti-LAG3 were tumor free, however the combination of anti-PD1 and anti-LAG3 rendered 80% of mice tumor free.

2.2.6 RATIONALE FOR COMBINATION THERAPY

Preclinical studies suggest a synergistic effect of anti-PD1 and anti-LAG3. In vitro studies consisting of transgenic antigen-specific T cells co-incubated with APCs, with and without PD-L1 expression, to evaluate the role of LAG3 and PD1 on T-cell function. T cells transduced to express both LAG3 and PD1 incubated with peptide-loaded APCs expressing PD-L1 showed lower levels of IL-2 secretion compared with cells expressing either molecule alone. This shows that PD1 and LAG3 acted synergistically to suppress T-cell stimulation, and that simultaneous blockade of these negative signals can improve T-cell responses in a nonredundant manner (Figure 2).

Figure 2 : Model for augmented T cell activity mediated by inhibition of LAG3 and PD1



Exhausted T cells are characterized by the expression of T cell negative regulatory receptors, predominantly CTLA-4, PD-1, and LAG-3, whose action is to limit the cell's ability to proliferate, produce cytokines, and kill target cells and/or to increase Treg activity. However, the timing and sequence of expression of these molecules in the development and recurrence of tumors have not been fully characterized. It is hypothesized that CTLA-4 acts as the dominant off-switch for tolerance, but it is the strong synergy between the PD-1 and LAG-3 inhibitory pathways that seems to mediate tolerance to both self and tumor antigens(14, 33, 34). Whereas CTLA4 knockout (KO) mice die prematurely from multiorgan inflammation, PD1 and LAG3 single knockout mice present minimal immunopathologic sequelae(34). In contrast, dual knock-out mice (LAG3-/-PD1-/-) abrogates self-tolerance with resultant autoimmune infiltrates in multiple organs and even lethality. These dual knock-out mice also show markedly increased survival from and clearance of multiple transplantable tumors(14).

Conversely, extensive co-expression of PD1 and LAG3 on tumor-infiltrating CD4+ and CD8+ T cells has been shown in distinct transplantable tumors and samples from melanoma, RCC, head and neck, NSCLC and ovarian cancer patients(35-37). Blockade of PD1/PD-L1 interactions has been successfully used to restore antitumor immunity in preclinical and clinical studies. But the simultaneous blockade of PD1 and LAG3 pathways on T cells may exert an even more robust antitumoral immunity in naive as well as in recurrent tumors due to the possibility of reversing LAG3–mediated T cell exhaustion. In two syngeneic mice models, for example, dual anti– LAG3/anti–PD1 antibody therapy is able to cure most mice of established tumors that are largely resistant to single antibody treatment(14). Furthermore, recurrent tumors from a melanoma mouse model with increased Treg cell numbers and increased expression of checkpoint inhibitors PD1, LAG3, TIGIT, and TIM3, can be controlled by depletion of Tregs (via FoxP3-DTR) plus the administration of anti–PD-L1 antibody. But more importantly, tumor regression of these recurrent tumors can also be accomplished with the combination of anti-PD-L1 plus anti-LAG-3 antibodies (C9B7W mAb) which also increases T cell activity.

2.3 NIVOLUMAB

2.3.1 MECHANISM OF ACTION

Nivolumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 146 kDa. Binding of the PD1 ligands, PD-L1 and PD-L2, to the PD1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD1 ligands occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

2.3.2 HUMAN PHARMACOKINETICS

The pharmacokinetics (PK) of nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Based on a population PK analysis using data from 909 patients, the geometric mean (% coefficient of variation [CV%]) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) is 8.0 L (30.4%), and geometric mean

elimination half-life (t1/2) is 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.

2.3.3 CLINICAL PHARMACODYNAMICS

The pharmacodynamics of nivolumab have been examined by measuring PD1 receptor occupancy on circulating CD3 with flow cytometric analysis. In the phase 1 study of nivolumab in melanoma, PD1 occupancy appeared to be dose-independent in some patients, with a mean peak occupancy of 85% (range, 70% to 97%) and a mean plateau occupancy of 72% (range, 59% to 81%) observed at 4 to 24 hours and 57 days, respectively, after one infusion. These data are consistent with the high affinity of nivolumab for PD1.

2.3.4 CLINICAL STUDIES OF NIVOLUMAB IN CANCER

The efficacy and safety of nivolumab has been examined in a number of tumor types in the phase 1, 2, and 3 settings. Nivolumab is currently approved by the FDA in many solid tumor types including melanoma, non-small cell lung cancer, and head and neck squamous cell carcinoma.

2.3.5 UNRESECTABLE OR METASTATIC MELANOMA

Nivolumab was evaluated in a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either nivolumab administered intravenously at 3 mg/kg every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m2 every 3 weeks. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter (38).

Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received nivolumab in this trial and in whom the minimum duration of follow up was 6 months. The major efficacy outcome measures in this population were confirmed objective response rate (ORR) as measured by blinded independent duration of response.

The ORR was 32% (95% confidence interval: 23- 41), consisting of 4 complete responses and 34 partial responses in nivolumab-treated patients. Of 38 patients with responses, 33 patients (87%) had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer. FDA approval of nivolumab was based on the results of this study.

2.3.6 METASTATIC SQUAMOUS NON-SMALL CELL LUNG CANCER

FDA approval of nivolumab was based on the results of two clinical studies. The first was a randomized (1:1), open-label study enrolling 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen has been completed. Patients received nivolumab (n=135) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=137) administered intravenously at 75 mg/m2 every 3 weeks. This study included patients regardless of their PD-L1 status. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was overall survival (OS) (39).

The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis). Median survival was 9.2 (95% CI: 7.3, 13.3) months and 6.0 (95% CI: 5.1, 7.3) months in nivolumab and docetaxel arm respectively, with p-value of 0.00025 (39).

In a separate analysis of the biomarker data from this study, the effect of expression of PD-L1 on the tumor was examined in relation to response rate. In this analysis, the tumor samples were collected and tested for PD-L1 expression. Positive samples were defined as those with ≥ 5% of tumor cells expressing PD-L1. Objective responses were seen in patients with both PD-L1 positive (PD-L1^{+}) and negative (PD-L1^{-}) tumors. However there was a statistically significant increase in overall response rate for subjects with PD-L1^{+} and PD-L1^{-} patients (31% vs 10%), indicating that degree of PD-L1 expression may be a useful biomarker in identifying subjects who may benefit from therapy (40).

The second NSCLC trial was a single-arm, multinational, multicenter trial in patients with metastatic squamous NSCLC. All patients had progressed after receiving a platinum-based therapy and at least one additional systemic treatment regimen. This study included patients regardless of their PD-L1 status. Patients received 3 mg/kg of nivolumab administered intravenously over 60 minutes every 2 weeks. The first tumor assessments were conducted 8 weeks after the start of treatment and continued every 6 weeks thereafter. A total of 117 patients received treatment with nivolumab (41).

The major efficacy outcome measure was confirmed objective response rate (ORR) as measured by independent review committee using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Additional outcome measures included duration of response (DoR).

Based on independent review committee review and with a minimum follow-up of at least 10 months on all patients, confirmed ORR was 15% (17/117) (95% CI: 9, 22), of which all were partial responses. The median time to onset of response was 3.3 months (range: 1.7 to 8.8 months) after the start of nivolumab treatment. Thirteen of the 17 patients (76%) with a confirmed response had ongoing responses with duration ranging from 1.9+ to 11.5+ months; 10 of these 17 (59%) patients had durable responses of 6 months or longer.

2.3.7 HEAD AND NECK SQUAMOUS CELL CARCINOMA

The recent approval of nivolumab for platinum refractory recurrent/metastatic head and neck squamous cell carcinoma resulted from the Checkmate 141 trial. This phase 3 trial assessed 361 patients randomized to receive nivolumab 3 mg/kg every 2 weeks or standard single agent systemic therapy (docetaxel, cetuximab or methotrexate). Randomization was based on prior cetuximab therapy. Patients were enrolled regardless of tumor PDL1 or HPV status. Baseline characteristics were generally balanced between the two groups. 90% had Stage IV disease, 66% had two or more lesions, 45%, 34% and 20% received 1, 2, or 3 or more prior lines of systemic therapy, respectively, and 25% were HPV-16 status positive. The overall response rate with Nivolumab by RECIST 1.1 criteria was 13.3%, with 2.5 % of patients had a complete response and 22.9 % had stable disease. Treatment with Nivolumab significantly improved overall survival compared to the standard of care group (Median OS 7.1 months vs. 5.1 months (95% CI, 4.0 to 6.0) in the standard therapy group (hazard ratio for death, 0.70; 97.73% CI, 0.51 to 0.96; P = 0.01)) (1). This trial led to the FDA approval of Nivolumab in 2016 for Recurrent/Metastatic HNSCC patients that have progressed on or after platinum based chemotherapy

Quantifiable PDL1 expression, measured using the PDL1 IHC 28-8 pharmDx assay, was measured in 67% of patients in the nivolumab treated group. Patients with PDL1 expression ≥1%, ≥5%, ≥10% had a statistically significant improvement in overall survival [HR .53 (95% CI .37-.77), HR .51 (95%CI .32-.8), HR .57(.34-.95) respectively]. Patients with <1% PDL1 expression had improvement in overall survival which did not reach statistical significance [HR .83 (95% CI .54-1.29)]. In an exploratory post-hoc analysis using a non-validated assay, tumor cell and tumor associated immune cell (TAIC) PDL1 expression. TAIC PDL1 were qualitatively assessed. This analysis showed that not only tumor cell PDL1, but TAIC PDL1 appeared to be associated with benefit from nivolumab compared to investigator's choice. Patients with abundant TAIC PDL1 and either PDL1≥1% or PDL1<1% had improved overall response rate compared to the standard therapy arm [19.7%(95%CI 10.6-31.8) and 18.6% (95%CI 8.4-33.4), respectively]. Patients with tumor PDL1 expression by all predefined expression levels in the nivolumab group demonstrated greater overall survival.

Clinically significant adverse reactions were evaluated in a total of 11,551 patients treated with nivolumab monotherapy in clinical trials. The following are the identified common adverse reactions:

- Immune-mediated pneumonitis
- Immune-mediated colitis and gastritis
- Immune-mediated hepatitis
- Immune-mediated nephritis and renal dysfunction
- Immune-mediated hypothyroidism and hyperthyroidism
- Immune-mediated hyperglycemia
- Diarrhea
- Nausea/vomiting

- Arthralgia/myalgia
- Dry mouth
- Fatigue
- Fever/chills
- Peripheral edema
- Infusion related reactions
- Headache
- Maculopapular rash

While the rates of treatment-related adverse events of any grade were similar between Nivolumab and standard chemotherapy in HNSCC patients treated on Checkmate 141, there were fewer events of grade 3 or 4 in the nivolumab group compared to the standard chemotherapy arm (occurring in 13.1% vs. 35.1% of patients). In the nivolumab group, the most frequent adverse events of any grade were fatigue, nausea, rash, decreased appetite, and pruritus. Among the select adverse events, gastrointestinal events were less common with nivolumab than with standard therapy (occurring in 6.8% vs. 14.4% of the patients; primarily diarrhea), whereas adverse events of the skin were more common with nivolumab (in 15.7% vs. 12.6%; primarily rash and pruritus), as were adverse events of the endocrine system (in 7.6% vs. 0.9%; primarily hypothyroidism). Pneumonitis was observed in 2.1% of the patients treated with nivolumab. Two treatment-related deaths were reported in the nivolumab group (pneumonitis and hypercalcemia in one patient each), and one patient in the standard-therapy group died from a treatment-related lung infection (1).

The FDA approved dosage of Nivolumab as a single agent in R/M HNSCC is 240mg IV every 2 weeks or 480mg IV every 4 weeks.

2.4 IPILIMUMAB

2.4.1 MECHANISM OF ACTION

Ipilimumab (MDX-010, MDX-CTLA4, BMS-734016) was developed by CTEP as an anticancer agent in collaboration with Bristol-Myers-Squibb (BMS). On March 25, 2011, the FDA approved ipilimumab injection (YERVOY, BMS) for the treatment of unresectable or metastatic melanoma. Ipilimumab is a human $IgG_{1\kappa}$ mAb specific for human cytotoxic T lymphocyte-associated antigen-4 (CTLA4, CD152) expressed on activated T cells.

By blocking CTLA4, ipilimumab increases the percentage of peripheral activated T cells and central memory T cells. These changes are evidenced by Week 4 and generally remain sustained through Week 12.

2.4.2 HUMAN PHARMACOKINETICS

The PK of ipilimumab has been extensively studied in subjects with melanoma, at the ~3- and 10-mg/kg doses administered as a 1.5-hour IV infusion. The PK of ipilimumab was characterized by population pharmacokinetic (PPK) analysis and determined to be linear and time invariant in the dose range of 0.3 to 10 mg/kg. The mean CL (+/-SD) value after IV administration of 10 mg/kg was 18.3 ± 5.88 mL/h, and the mean steady-state volume of distribution (Vss) [+/- SD] value was 5.75+/- 1.69 L. The CL and Vss from Studies CA184007 and CA184008 were similar to those reported from Study MDX010-15.

The PPK of ipilimumab was studied in 785 subjects (3,200 serum concentrations) with advanced melanoma in four Phase 2 studies (CA184004, CA184007, CA184008, and CA184022), 1 Phase 3 study (CA184024), and one Phase 1 study (CA184078). The PPK analysis demonstrated that the PK of ipilimumab is linear, the exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time-invariant, similar to that determined by noncompartmental analyses.

Upon repeated dosing of ipilimumab, administered q3w, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less, and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab CL of 16.8 mL/h from PPK analysis is consistent with that determined by noncompartmental PK analysis. The terminal T-HALF and Vss of ipilimumab calculated from the model were 15.4days and 7.47 L, respectively, which are consistent with that determined by noncompartmental analysis. Volume of central compartment (Vc) and peripheral compartment were reported to be 4.35 and 3.28 L, respectively, suggesting that

ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in BW. However, there was no significant increase in exposure with increase in BW when dosed on a milligram/kilogram basis, supporting dosing of ipilimumab based on a weight normalized regimen. The PK of ipilimumab is not affected by age, gender, race, and immunogenicity (ADA status); concomitant use of chemotherapy; prior therapy; BW; performance status; or tumor type. Other covariates had effects that were either not statistically significant or of minimal clinical relevance.

2.4.3 CLINICAL STUDIES OF IPILIMUMAB IN CANCER

Ipilimumab has been studied in various solid tumors both as a single agent and in combination with nivolumab. Ipilimumab as a single agent is currently approved in melanoma. Ipilimumab in combination with Nivolumab is currently approved in melanoma, renal cell carcinoma, and MSI-H/dMMR Metastatic Colorectal Cancer. Ipilimumab is currently being used in trials with HNSCC patients. This includes NCT02823574 Ipilimumab Versus Nivolumab in Combination With Ipilimumab Placebo in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (CheckMate 714) and NCT02741570 An Open Label, Randomized, Two Arm Phase III Study of Nivolumab in Combination With Ipilimumab Versus Extreme Study Regimen (Cetuximab + Cisplatin/Carboplatin + Fluorouracil) as First Line Therapy in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (HNSCC). Preliminary efficacy or toxicity data is not currently available from these trials.

Ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity, likely to be related to its mechanism of action. These Immune-related adverse events (irAEs) are defined as AEs that are 1) related to ipilimumab per investigator and 2) consistent with an inflammatory process. The most common treatment-related AEs associated with the use of ipilimumab were immune related (named immune-related AEs or irAEs), reflecting ipilimumab's mechanism of action. The irAEs primarily involved the GI tract (e.g., diarrhea and colitis); skin (e.g., pruritus and rash); and, less frequently, the liver (e.g., transaminase elevations), endocrine glands (including the thyroid, pituitary and adrenal glands, manifested by hypothyroidism, hypophysitis with hypopituitarism, or adrenal insufficiency, respectively), and nervous system (e.g., motor neuropathy with or without sensory neuropathy). Immune-related AEs were generally manageable using symptomatic or immuno-suppressive therapy as recommended through detailed diagnosis and management guidelines. In the sections below efficacy and toxicity of single agent ipilimumab as well as combination Ipilimumab and Nivolumab is discussed.

2.4.4 ADVANCED AND METASTATIC MELANOMA

Study CA184169

Study CA184169 was a randomized, multicenter, double-blind Phase 3 study in subjects with previously treated or untreated unresectable Stage III or Stage IV melanoma who had not received a B-Raf inhibitor or prior immune checkpoint modulatory therapy. Subjects were randomized in a 1:1 ratio to be treated with ipilimumab at a dose of either 3 mg/kg or 10 mg/kg by IV infusion q3w for 4 doses. Randomization was stratified by M substage, prior treatment for metastatic melanoma, and ECOG Performance Status. The primary endpoint was OS. Consistent with what has been previously reported, treatment with 3 mg/kg ipilimumab resulted in an improvement in median OS of 11.53 months (95% CI: 9.86, 13.27). Additional benefit was reported with 10 mg/kg ipilimumab with a median OS of 15.70 months (95% CI: 11.63, 17.84; HR of 0.84 and P-value = 0.0400 compared to 3 mg/kg ipilimumab). The survival rate at 1 year was 47.62% (95% CI: 42.35, 52.70) in the ipilimumab 3 mg/kg group and 54.28% (95% CI: 49.01, 59.25) in the ipilimumab 10 mg/kg group. The secondary endpoint of PFS showed no statistically significant difference between the 2 groups. Due to the pre-specified hierarchical testing procedure, the non-significant P-value for PFS meant that statistical significance for overall response rate (ORR) and disease control rate (DCR) was not formally tested.

Study CA184029

Study CA184029 was a randomized, double-blind, parallel-group, 2-arm, multicenter, Phase 3 study in high-risk subjects with completely resected Stage IIIA (> 1 mm metastasis), IIIB, and IIIC (no in-transit metastases) melanoma. A total of 951 subjects were randomized, stratified by disease stage (according to American Joint Committee on Cancer [AJCC] 2002 classification) and region. Subjects received blinded study drug (ipilimumab 10 mg/kg or placebo) q3w for a total of 4 doses, followed by blinded study drug every 12 weeks (q12w) for up to 3 years or until disease recurrence or unacceptable toxicity. The primary endpoint was to determine whether postoperative adjuvant therapy with ipilimumab improves recurrence-free survival (RFS) as compared to placebo.

Baseline demographic and disease characteristics were generally balanced between the ipilimumab and placebo groups. The median RFS interval was longer for the ipilimumab group (26.1 months) than for the placebo group (17.1 months), and treatment with ipilimumab resulted in a 25% reduction in the risk of recurrence relative to treatment with placebo (HR = 0.75; 95% CI: 0.64, 0.90). Adjuvant immunotherapy with 10 mg/kg ipilimumab monotherapy after complete resection of high-risk Stage III melanoma was associated with statistically and clinically superior OS and distant metastases-free survival (DMFS) compared with placebo.

2.4.5 IPILIMUMAB IN OTHER SOLID TUMORS

Study CA184043

Study CA184043 was a double-blind, randomized, parallel-group, 2-arm, multicenter, Phase 3 study in subjects with mCRPC who had received at least 1 line of treatment with docetaxel for their disease. A total of 789 subjects (393 ipilimumab; 396 placebo) received study treatment (RT, blinded study drug, or both) and constituted the safety population. The mean number of total doses of ipilimumab and placebo was 3.6 and 3.7, respectively (mean cumulative dose of ipilimumab of 2888.7 mg). The percentage of subjects treated in the maintenance phase was 23.8% (n = 95) for the ipilimumab group and 15.5% (n = 62) for the placebo group. In a subset of subjects (n = 207) who participated in the ECG substudy, treatment with 10 mg/kg ipilimumab had no meaningful effect on ECG internals and, in particular, did not cause prolongation of the QTc interval. The overall safety profile for ipilimumab in this study was generally consistent with the previous Phase 2 and 3 studies of ipilimumab monotherapy (at a dose of 10 mg/kg). SAEs and AEs leading to drug discontinuation were more frequently reported in the ipilimumab group than in the placebo group. A total of 65.4% of subjects in the ipilimumab group experienced an on-study SAE of any grade compared with 41.7% of subjects in the placebo group. The overall incidence of AEs (any grade) leading to discontinuation was higher for the ipilimumab group (34.9%) than for the placebo group (15.7%). Severe (Grade 3 or 4) AEs leading to discontinuation were also more common in the ipilimumab group than in the placebo group (25.2% versus 8.3%, respectively. Progressive disease was the most frequent cause of death over the entire study period in the ipilimumab and placebo groups (51.9% [204/393] and 61.4% [243/396] subjects, respectively). Across the entire study period, study drug toxicity was the reason for death for 4 subjects (1.0%) in the ipilimumab group according to the investigator's assessment; one of these deaths occurred more than 70 days after the last dose of study drug. In addition, 2 related, on-study SAEs had a fatal outcome (cause of death reported as 'Other'): cholangitis in the ipilimumab group and multi-organ failure in the placebo group. No subject in the placebo group died as a result of study drug toxicity. One additional subject in the ipilimumab group had related SAEs with a fatal outcome (peritonitis and perforation) that occurred > 70 days after the last dose of ipilimumab.

Study CA184095

Study CA184095 was a double-blind, randomized, 2-arm, multicenter, Phase 3 study in subjects with asymptomatic or minimally symptomatic, chemotherapy-naïve mCRPC who had progressed despite receiving hormonal therapies and who had no known visceral metastases. A total of 598 subjects (399 ipilimumab, 199 placebo) received study treatment and constituted the safety population. The mean number of total doses of ipilimumab and placebo was 4.3 and 4.9, respectively (mean cumulative dose of ipilimumab of 3745.3 mg). The percentage of subjects treated in the maintenance phase was 38.9% for the ipilimumab group and 35.5% for the placebo group. The overall safety profile for ipilimumab in this study was generally consistent with the previous Phase 2 and 3 studies of ipilimumab monotherapy (at a dose of 10 mg/kg). Nine deaths (2.3%) in the ipilimumab group occurred due to study drug toxicities, including 2 deaths due to post study events (i.e., onset after 70 days from last dose) of pneumonia and hepatotoxicity. One death occurred due to intestinal perforation, 2 deaths occurred due to cardiac arrest, 1 death occurred due to renal failure, 1 death occurred due to hepatitis, 1 death occurred due to pneumonitis, and 1 death occurred due to multi-organic lymphatic infiltration that resulted in cardiac arrest. There were no deaths due to drug-related AEs in the placebo arm.

2.4.6. COMBINATION IPILIMUMAB AND NIVOLUMAB

The combination of Nivolumab and Ipilimumab is currently approved for advanced melanoma, RCC, and MSI-H/dMMR Metastatic Colorectal Cancer.

The approval in RCC is based on CheckMate 214, a randomized open-label trial. Patients with previously untreated advanced RCC received nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every 3 weeks for 4 doses

followed by nivolumab monotherapy (3 mg/kg) every 2 weeks, or sunitinib (Sutent) at 50 mg daily for 4 weeks followed by 2 weeks off every cycle. Efficacy was evaluated in intermediate- or poor-risk patients (n = 847). The trial demonstrated statistically significant improvements in overall survival and objective response rate for patients receiving the combination (n = 425) compared with those receiving sunitinib (n = 422). Estimated median overall survival was not estimable in the combination arm compared with 25.9 months in the sunitinib arm (hazard ratio = 0.63, 95% confidence interval [CI] = 0.44–0.89; *P* < .0001). The objective response rate was 41.6% (95% CI = 36.9%–46.5%) for the combination vs 26.5% (95% CI = 22.4%–31%) in the sunitinib arm (*P* < .0001). The efficacy of the combination in patients with previously untreated RCC with favorable-risk disease was not established. The most common adverse reactions (reported in at least 20% of patients treated with the combination) were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, and decreased appetite. Treatment-related adverse events of any grade occurred in 93% of patients treated with nivolumab plus ipilimumab and 97% treated with sunitinib. Grade 3 or 4 events occurred in 46% of patients treated with Ipilimumab and Nivolumab and 63% of patients treated with sunitinib. Treatment-related adverse events leading to discontinuation occurred in 22% and 12% of patients treated with Ipi/Nivo and sunitinib respectively. There were 8 treatment related deaths in the Ipilimumab plus nivolumab patients and 4 in the patients treated with sutent (42).

In Checkmate 067, 945 previously untreated patient with unresectable stage III or IV melanoma were randomized in a 1:1:1 ratio to nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone. Progression-free survival and overall survival were coprimary end points. The median progression-free survival was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001), and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (hazard ratio for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001). In patients with tumors positive for the PD-1 ligand (PD-L1), the median progression-free survival was 14.0 months in the nivolumab-plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1–negative tumors, progression-free survival was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] vs. 5.3 months [95% CI, 2.8 to 7.1]). Treatment-related adverse events of grade 3 or 4 occurred in 16.3% of the patients in the nivolumab group, 55.0% of those in the nivolumab-plus-ipilimumab group, and 27.3% of those in the ipilimumab group. Treatment-related adverse events of any grade occurred in 82.1% of the patients in the nivolumab group, 95.5% of those in the nivolumab plus ipilimumab group, and 86.2% of those in the ipilimumab group. The most common adverse events in the nivolumab plus ipilimumab group were diarrhea (in 44.1% of patients), fatigue (in 35.1%), and pruritus (in 33.2%). Treatment-related adverse events of any grade that led to discontinuation of the study drug occurred in 7.7% of the patients in the nivolumab group, 36.4% of those in the nivolumab plus ipilimumab group, and 14.8% of those in the ipilimumab group, with the most common events being diarrhea (in 1.9%, 8.3%, and 4.5%, respectively) and colitis (in 0.6%, 8.3%, and 7.7%, respectively). One death due to toxic effects of the study drug was reported in the nivolumab group (neutropenia) and one in the ipilimumab group (cardiac arrest), but none were reported in the nivolumab plus ipilimumab group. The most frequent treatment-related events determined to be potentially immune related of grade 3 or 4 were diarrhea (in 2.2% of patients in the nivolumab group, 9.3% of those in the nivolumab-plus-ipilimumab group, and 6.1% of those in the ipilimumab group), colitis (in 0.6%, 7.7%, and 8.7%, respectively), and increased alanine aminotransferase level (in 1.3%, 8.3%, and 1.6%, respectively) (43).

2.4.7 JUSTIFICATION FOR DOSAGE OF IPILIMUMAB IN COMBINATION WITH NIVOLUMAB USED IN THIS TRIAL:

Ipilimumab appears to have dose dependent toxicity in combination with nivolumab across different studies. The combination with the higher dose ipilimumab showed higher Grade 3 - 5 drug-related AEs. The nivolumab 240mg Q2weeks plus ipilimumab 1 mg/kg Q6 weeks X 4 doses followed by Nivolumab 480mg IV Q4 weeks offers a better safety profile and similar efficacy in Melanoma and NSCLC (see investigator brochure). This dosage is being used in an ongoing trial with HNSCC (NCT02741570) and will be used in this protocol.

2.5 RELATLIMAB

2.5.1 MECHANISM OF ACTION

Relatlimab is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human Ig genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation

(S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. Relatlimab binds to a defined epitope on LAG-3 with high affinity (dissociation constant [Kd], 0.25-0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its known ligands, MHC Class II (half maximal inhibitory concentration [IC50], 0.7 nM) and FGL-1. The antibody exhibits potent in vitro functional activity in reversing LAG-3-mediated inhibition of an antigen-specific murine T cell hybridoma overexpressing human LAG-3 (IC50, 1 nM). In addition, relatlimab enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab. Refer to Relatlimab IB Section 4.1 and Section 4.2.8.

2.5.2 HUMAN PHARMACOKINETICS

An interim determination of relatlimab multiple dose PK was carried out using all available serum concentration data from Studies CA224020 and CA224022. Noncompartmental analysis was performed using concentration-time data after the first dose (Cycle 1) and ninth dose (Cycle 3). In general, the maximum observed concentration (Cmax) and area under the concentration versus time curve over the dosing interval (AUC[TAU]) values over the first dosing interval increased approximately proportional to the increment in the relatlimab dose. Relatlimab accumulation from the first to ninth doses of a Q2W regimen was around 2- to 3-fold for AUC(TAU) and 1.2- to 1.8-fold for Cmax. Relatlimab effective half-life was estimated to be approximately 20 days. The PK of relatlimab or nivolumab were not altered when given in combination.

Relatlimab population PK was best described by a 2 compartment model with parallel linear and non-linear CL. The linear portion represents the non-specific clearance (CL), and non-linear component represents target-mediated CL. The linear CL was 0.18 L/day, and the volume of distribution in the central compartment was 4.5 L. The maximum rate of non-linear elimination (Vmax) was 2.5 mg/day, and the concentration that achieved 50% of Vmax (Km) was 5.7 μg/mL.

Currently available data suggest that relatlimab monotherapy exhibits a low level of immunogenicity, with 6 out of 42 subjects having at least 1 post-baseline positive ADA samples. There are limited data available in combination cohort to make inference on immunogenicity rate.

2.5.3 CLINICAL PHARMACODYNAMICS

Receptor occupancy (RO) of LAG-3 on CD8 T cells in the blood was measured at trough levels (14 days after dosing) during dose escalation of monotherapy relatlimab in Study CA224022. Preliminary analysis of the data showed that RO had incrementally similar increases, with an average of 74%, 83%, and 93% RO after flat doses of 20, 80, and 240 mg, respectively. At the highest dose level tested of 800-mg, RO was 98.7%, representing a smaller incremental increase of 6% from the lower 240-mg dose level.

2.5.4 CLINICAL STUDIES OF RELATLIMAB IN CANCER

Study CA224020

Response Evaluation Criteria in Solid Tumors (RECIST v1.1) criteria were used in Study CA224020 to evaluate response to treatment. As of the efficacy cutoff date of 15-Jun-2017 for Part A, no responses were observed in subjects with advanced solid tumors treated with relatlimab monotherapy. In Part A1, 1 partial response was seen in an NSCLC subject, who had previously progressed on single agent nivolumab, treated with 800 mg relatlimab monotherapy Q2W. Although the response was confirmed, it was transient due to progression of non-target lesions. As of the efficacy cutoff date of 29-Mar-2018 for Part B, One subject with melanoma who was previously treated with nivolumab experienced a partial response lasting 12months with combined treatment with 20 mg relatlimab/80 mg nivolumab Q2W. A second subject with cervical cancer achieved a partial response after 3 doses of combination therapy with 20 mg relatlimab/240 mg nivolumab Q2W. The response was ongoing at 12 months even though the subject received no further therapy. A third subject with NSCLC, naive to anti-PD-1 therapy, achieved a partial response that was ongoing at 19 months while receiving 20 mg relatlimab/240 mg nivolumab Q2W. A fourth subject with SCCHN achieved a partial response that was ongoing at 13 months while receiving 240 mg relatlimab/240 mg nivolumab Q2W. A fifth subject with melanoma, naive to anti-PD-1 therapy, achieved a partial response that was ongoing at 12 months while receiving 240mg relatlimab/240 mg nivolumab Q2W. Preliminary proof-of-concept efficacy has been revealed in Part C of Study CA224020 in the combination treatment expansion cohort of advanced melanoma with prior treatment with anti-PD-1/PD-L1. The treatment group had the following characteristics: 1) Most subjects had M1C disease (68%), 2) the cohort was heavily pretreated (77% with 2 or more prior therapies and 57% with prior anti-CTLA-4 therapy), 3) all subjects had

progressed while receiving anti-PD-1/PD-L1, and 4) progressive disease was the best response to prior anti-PD-1/PD-L1 in 46% of subjects. All subjects were treated with 80 mg relatlimab/240 mg nivolumab Q2W. The overall objective response rate (ORR) was 11.5% (7/61, response evaluable) with a disease control rate of 49%. Biomarker analyses suggested that subjects whose TIL expressed more LAG-3 had a higher response rate, with a greater than 3-fold increase in ORR observed in subjects with evidence of LAG-3 expression in at least 1% of nucleated cells within the tumor margin, compared to less than 1% LAG-3 expression (18.2% [6/33] and 5.0% [1/20], respectively). PD-L1 expression did not appear to enrich for response. Sixty-five HNSCC patients have been treated in part C however at this time preliminary efficacy data is not available.

Study CA224047

Primary results from CA224-047 evaluating the fixed-dose combination of relatlimab and nivolumab vs nivolumab monotherapy in patients with previously untreated metastatic or unresectable melanoma met its primary endpoint of progression-free survival (PFS). Follow up for overall survival, a secondary endpoint, is ongoing. The fixed-dose combination was well-tolerated and there were no new safety signals reported in either arm of this trial."

2.5.5 SAFETY INFORMATION FOR RELATLIMAB

As of the clinical data cutoff dates of 15-Jul-2020 for CA224020, CA224022, CA224034, and CA224087, and 27-Jul-2020 for CA224048, 1623 subjects have been treated with relatlimab or relatlimab in combination with nivolumab in 5 ongoing studies (Studies CA224020, CA224022, CA224034, CA224048, and CA224087) assessing PK, clinical efficacy, and safety. The current clinical program is evaluating advanced solid tumors (special focus in advanced melanoma that has previously progressed on prior anti-PD1 therapy) in Study CA224020, relapsed-refractory hematological malignancies (Hodgkin lymphoma) in CA224022, advanced solid tumors (special focus in a Japanese population) in Study CA224034, and in study CA224048, the focus is on advanced solid tumors including melanoma, non-small cell lung cancer (NSCLC), and squamous cell cancer of head and neck (SCCHN). Study CA224087 is designed to assess the efficacy and safety of subcutaneous (SC) administration of relatlimab (480 or 720 mg) using recombinant human hyaluronidase PH20 (rHuPH20) with nivolumab 480 mg, followed by 480 mg SC relatlimab and 480 mg nivolumab Q4W

In CA224020, **single-agent** relatlimab has had an acceptable safety profile at all tested doses: 20-, 80-, 240- and 800-mg flat doses. The maximum tolerated dose (MTD) was not reached up to 800-mg relatlimab Q2W. The safety profile of relatlimab monotherapy appears manageable. No MTD was identified for monotherapy, up to the highest tested dose level of 800 mg Q2W. Of the 25 subjects treated with relatlimab monotherapy in study CA224020, 24 (96.0%) subjects experienced at least 1 event. The most commonly reported AEs (≥20% of subjects) were malignant neoplasm progression (52.0%); fatigue (40.0%); decreased appetite and nausea (36.0% each); back pain (28.0%); dizziness and pyrexia (24.0% each); and anemia, cough, and vomiting (20.0% each). Drug-related AEs were reported in 15 (60.0%) subjects, with the most commonly reported (≥5% of subjects) being fatigue (24.0%); decreased appetite (12.0%); and arthralgia, cough, dry mouth, headache, lipase increased, maculo-papular rash, myalgia, nausea, pneumonitis, pruritus, and rash (8.0% each). Most drug-related AEs were Grade 1 or 2. Grade 3 drug-related AEs were lipase increased (8.0%), maculo-papular rash, pneumonitis, and allergic reaction (4.0% each). The MTD for monotherapy was not reached at the tested doses up to a flat dose of 800 mg relatlimab Q2W. At least 1 SAE, regardless of causality, has been reported in 20 of 25 (80.0%) subjects treated with relatlimab monotherapy. The most commonly reported SAEs (≥5% of subjects) were malignant neoplasm progression (13 [52.0%] subjects); and diarrhea, pneumonitis, and spinal cord compression (2 [8.0%] subjects each). There were 2 reported drug-related SAEs in monotherapy: Grade 2 pneumonitis and Grade 3 allergic reaction; both were reported in Part A1 monotherapy at a dose of 800 mg relatlimab Q2W. In addition, 1 subject in Part A1 monotherapy experienced a Grade 3 pneumonitis after crossover to combination therapy. All events resolved.

Overall, the safety profile of relatlimab in combination with nivolumab is manageable in the 5 ongoing studies, with no MTD reached at the tested doses up to 960 mg relatlimab/480 mg nivolumab (Q4W). There was no dose relationship between the incidence, severity, or causality of AEs and combination therapy (see Section 5.5.1, Section 5.5.2, and Section 5.5.3). In Study CA224020, most drug-related AEs were CTCAE Grade 1 or Grade 2. A total of 890 (66.8%) subjects out of the 1332 subjects receiving combination therapy reported drug related AEs. Two (0.1%) subjects reported infusion-related reactions during infusion of study drug and were manageable using

the updated protocol guidelines; only 2 subjects required treatment discontinuation (in each case due to recurrent Grade 2 infusion related reactions). A total of 804 deaths occurred in subjects treated with combination therapy in Studies CA224020, CA224022, and CA224034. In Studies CA224022 (18 deaths), and CA224034 (9 deaths), all deaths were due to complications of disease progression and were considered by the investigator to be not related to study drug. In Study CA224087, a total of 6 deaths occured in subjects; 2 deaths in the 480 mg relatlimab/480 mg nivolumab group, and 4 deaths in the 720 mg relatlimab/480 mg nivolumab group; all deaths were considered not related to study drug. In Study CA224048, a total of 24 deaths (7 deaths in the BMS-986205 group; 17 deaths in the ipilimumab group) occured. The majority of the deaths (18 deaths) were due to complications of disease progression and were considered by the investigator to be not related to study drug; the other 6 deaths occured due to study drug toxicity. Although an MTD has not been reached for the combination of relatlimab and nivolumab, the 2 dose-limiting toxicities (DLTs) (Grade 5 myocarditis and Grade 3 aseptic meningitis) in 5 evaluable patients at the 240 mg relatlimab/240 mg nivolumab dose level has led to further testing at the intermediate dose level of 160 mg relatlimab for ongoing studies. This intermediate level of 160mg of Relatlimab is being recommended for combination with either 240mg Nivolumab given q 2 weeks or with 480mg of Nivolumab given q 4 weeks. In this study the later dosing (Relatlimab 160mg and Nivolumab 480mg IV q 4 weeks) will be used.

The all-combination group of study CA224020 includes 1332 subjects treated with relatlimab and nivolumab. Based on an analysis of adverse events in the all-combination group, 1295 (97.2%) subjects experienced at least 1 event. The most frequently reported AEs (≥ 10%) were malignant neoplasm progression (30.9%), fatigue (29.4%), nausea (22.7%), diarrhea (21.5%), anaemia (17.4%), decreased appetite (16.7%), headache (11.7%), asthenia (16.1%), constipation (15.8%), pyrexia (15.7%), arthralgia (14.2%), pruritus (15.7%), rash (10.2%), vomiting (13.1%), cough (13.4%), dysponea (12.2%), back pain (11.4%) and abdominal pain (11.0%). Drug related AEs were reported in 890 (66.8%) subjects, with the most commonly reported (≥ 5% of subjects) being fatigue (15.5%), pruritus (7.4%), diarrhea (8.6%), asthenia (7.4%), rash (7.1%), arthralgia (7.5%), hypothyroidism (7.2%) and increased lipase (6.5%). Most drug-related AEs were Grade 1-2. Grade 3-4 drug-related AEs were reported in 199 (14.9%) subjects, and 2 (0.2%) subjects reported Grade 5 events (dyspnoea and pulmonary fibrosis).

2.6 OMNISEQ IMMUNE REPORT CARD

2.6.1 OVERVIEW OF THE IMMUNE REPORT CARD^{SM} ASSAY

Immune Report Card^{SM} is a comprehensive immune profiling assay that provides the simultaneous measurement of known, clinically relevant immune biomarkers (proteins, RNA, DNA, cells) in formalin-fixed paraffin embedded (FFPE) solid tumor tissue specimens. For clinical research purposes, IRC provides a comprehensive profile of multiple novel immune markers to support correlative studies, drug development and combination immunotherapy approaches.

2.6.2 IMMUNE MARKERS

The Immune Report Card test was designed to provide concurrent testing of multiple immune biomarkers and multiple measures of the same marker using different technologies to improve the predictive value of single marker measurement. Specifically, IRC uses five (5) test modes:

1) **RNA-seq** to semi-quantitatively measure transcript levels of 384 immune related genes, for which 43 genes related to T-cell receptor signaling or other components of the immune cycle and 11 genes related to tumor infiltrating lymphocytes have been validated. (Appendix 1)
2) **DNA-seq** to estimate tumor mutational burden (TMB).
3) **MSI-NGS** to assess microsatellite instability.
4) **Fluorescent in situ hybridization (FISH)** to detect copy number gain of PD-L1 and PD-L2.
5) **Immunohistochemistry (IHC)** to measure protein expression of PD-L1 in the context of an FDA-approved assay and also to provide the pattern of expression for this marker as well as CD3 and CD8.

Table 1. Sample requirements, technical specifications and performance characteristics

Test Component (# Unstained Slides or nucleic acid needed)	Technical Specifications	Performance
IHC (4)	• FDA approved **PD-L1 expression including pharmaDx 22C3 (Dako)**, reported as Tumor Proportion Score (TPS) in lung and non-melanoma, or as Complete Positive Score (CPS) in gastric cancer; **pharmaDx 28-8 (Dako)** reported as percent staining in melanoma, or **SP142 Ventana**, reported as % immune cell staining for urothelial carcinoma.	Sensitivity and specificity >90%
	• **TILs expression pattern** (CD3/CD8) reported as strongly infiltrating or non-infiltrating.	Sensitivity and specificity >90%
MSI-NGS (20ng DNA)	• **Microsatellite instability (MSI)** by NGS analyzes 29 homopolymer loci within 28 amplicons, including BAT-25 and BAT-26, by sequencing tumor only DNA. • Results are reported as MSI or MSS	Sensitivity and specificity >95%
FISH (1)	• Measures **PD-L1 (CD274) and PD-L2 (PDCD1LG2) copy number amplification** • Reported using ASCO-CAP HER2 Test Guideline Recommendations for determining copy number as amplified, equivocal, or not amplified.	Sensitivity and specificity >95%
DNA-Seq (20ng DNA)	• 1.75 Mb capture of 409 oncogenes with 6,602 exons (full exon coverage) covering 1,165,294 base pairs of unique exon DNA to measure **tumor mutational burden (TMB).**	Sensitivity and specificity >90% at 50% tumor nuclei
RNA-Seq (10ng RNA)	• Validated to quantitatively measure transcript levels of 43 genes related to **T-cell receptor signaling (TCRS) including PD-L1,** and 11 genes associated with **tumor infiltrating lymphocytes (TILS), including CD8.** • Reported as normalized relative rank of 1-100 compared to reference population.	Limits of detection: 20 reads

Table 2: Validated Immune Response Marker List

Immune Cycle Step	Immune Markers	Action
Neoantigen release and presentation	Microsatellite Instability (MSI) Mutational Burden (MUB)	Tumor genomic instability and immunogenicity
T-cell priming	**CD137, CD27,** CD28, **CD40,** CD40LG, CD80, CD86, **GITR,** GZMB, **ICOS,** ICOSLG, IFNG, **OX40,** OX40L, TBX21	Direct interaction of stimulatory receptors and ligands required to prime T Cells to infiltrate the tumor
T-cell trafficking	CXCL10, CXCR6, DDX58, GATA3, **IL10,** IL1B, MX1, STAT1, **TGFB1, TNF**	Pro and anti inflammatory cytokines and chemokines released in the stroma and vessels that drive the movement of T-cells to the tumors
T-cell infiltration	Tumor Infiltrating Lymphocytes (**TILs**) CD2, CD3, CD4, CD8, FOXP3, KLDR1	Expression of immune activation within the tumor microenvironment
T-cell recognition	BTLA, **CTLA4, LAG3, PD-1, PD-L1,** PD-L2, **TIM3,** TNFRSF14, **VISTA**	Interaction of checkpoint receptors and ligands inhibit T Cells to initiate cancer cell death
Killing cancer cells	**ADORA2A,** CCL2, **CCR2, CD163, CD38,** CD39, CD68, **CSF1R, IDO1**	Inhibit activated T-cells from killing cancer cells

2.6.3 ANALYTICAL VALIDITY

Immune Report Card is approved for clinical use by New York State Clinical Laboratory Evaluation Program (NYS CLEP). The performance characteristics of Immune Report Card were analytically validated by OmniSeq Laboratories under the requirements of the Clinical Laboratory Improvement Amendments (CLIA) of 1988. OmniSeq, Inc. is licensed by CLIA, CAP and the New York State Clinical Laboratory Evaluation Program (NYS CLEP) to perform high-complexity molecular diagnostic testing. Omniseq laboratory is CLIA certified for all components of the Immune report card including 43 genes by RNA seq quantification (see table 3), which includes CTLA4 and LAG3. Expression of each gene is compared to a reference population, normalized to a value between 1 and 100, and referred to as the relative rank score. The baseline reference population for Immune Report Card consisted of RNA-seq results derived from 167 unique tumors. Based on tested samples, the median/range in 46 HNSCC patients (clinical data not available) analyzed by immune gene expression for LAG3 is 57/4-98 and for CTLA4 is 58/4-95. Thirty seven percent of these patients had a minimum difference in relative rank score of 15.2 between CTLA4 and LAG3.

Table 3. Validated Genes Reported in the Immune Report Card

Immune Phenotype	Markers Tested	Action
Checkpoint Blockade (PD-1/CTLA4)	PD-L1, PD-1, CTLA4, PD-L2	T-cell Inhibition
Checkpoint Blockade (Other)	BTLA, LAG3, TIM3, VISTA (B7-H5), TNFRSF14 (HVEM; CD270)	T-cell Inhibition
T-cell Primed	CD137 (TNFRSF9), CD27, CD28, CD40, CD40LG, GITR, ICOS, ICOSLG, OX40, OX40LG, GZMB, INFG, TBX21 (T-bet)	T-cell activation
Myeloid Suppression	CCL2, CCR2, CD163, CD68, CSF1R	Promote M2 TAMs
Metabolic Immune Escape	ADORA2A, CD39, IDO1	Self-amplifying T-reg loop
Pro-Inflammatory Response	IL1B, STAT1, TNF, DDX58, MX1, CXCL10, CXCR6	Promote NK T-cell functions
Anti-inflammatory Response	IL10, TGFB1	Promote MDSCs

The predictive value of an algorithmic OmniSeq response score (RS) based on mutational burden, CD8 T cell infiltration pattern and transcriptomic data, was evaluated in melanoma patients treated with single agent anti-PD-1 or anti-CTLA-4 mAb therapy. Patients with a RS of $\geq$ 50 (range of score 0-100) had significantly improved OS as well as ORR, with a response rate of 82.9% with RS score $\geq$ 50 vs. 23.8% if <50 (p=0.0012), with a positive predictive value of 78.6%, and negative predictive value of 82.9% for response (10).

2.6.4 REPORT

The Immune Report Card report is generated as a PDF and provides relevant patient and sample information, immune marker results, therapeutic associations and key references. Additionally, each report has a summary interpretation provided by a board-certified pathologist. The report is generated in approximately 5 days of receipt of tissue by OmniSeq.

3.0 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

Estimate the probability of objective response to treatment determined by gene expression of LAG3 and CTLA4 per Omniseq Immune Report card in R/M HNSCC patients who have progressed on prior immunotherapy.

3.2 SECONDARY OBJECTIVES

1. Estimate the disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety of treatment determined by gene expression of LAG3 and CTLA4 per Omniseq Immune Report card for R/M HNSCC patients who have progressed on prior immunotherapy;
2. Estimate the probability of objective response, DCR, PFS, OS and safety of treatment that is randomly assigned instead of determined by gene expression. This will be compared in an exploratory fashion to the objective response of those patients with treatment determined by gene expression.
3. Estimate the probability of objective response, Disease control rate (DCR)PFS, OS and safety of treatment determined by gene expression of LAG3 and CTLA4 per Omniseq Immune Report card for R/M HNSCC patients who have progressed on trial treatment and undergo a second biopsy and second treatment determined by a second gene expression analysis of LAG3 and CTLA4.;

3.3 Exploratory Biomarker studies:

A. Evaluate immune gene expression, immune co-signaling molecule expression by IHC, and immune cell populations over time via paired samples after exposure to combination immunotherapy;
B. Evaluate co-signaling molecule expression by IHC and correlate with gene expression by RNAseq as well as the predictive value of co-signaling molecule expression by IHC and the efficacy of the combination selected;
C. Evaluate immune cell populations and other biomarkers (as per section 14.0) in the peripheral blood at baseline and over time;
D. Evaluate saliva and stool microbiome to determine if any correlation with efficacy of the combination selected.

4.0 INVESTIGATIONAL PLAN

4.1 SUMMARY

Each patient's tumor biopsy sample will be analyzed for gene expression for CTLA4 and LAG3 using the OmniSeq Immune Report Card. The drug to be added to Nivolumab will be based on which relevant gene has the highest relative rank expression score (CTLA4 or LAG3) assuming that the difference between the relative rank score of the two genes are atleast 15.2 (as per the treatment assignment rule (section 15.0). For example, if analysis shows that LAG-3 is at least 15.2 higher than CTLA-4 then the patient will receive Nivolumab plus Relatlimab. If the difference between CTLA4 and LAG3 is less than 15.2 than the patient will be randomly assigned 1:1 to either Ipilimumab plus Nivolumab or Relatlimab plus Nivolumab. Because the relative efficacy of the two combinations has not been established in anti-PD-1/PD-L1 failure HNSCC patients, there is equipoise for randomizing if the minimum difference in relative rank score is not met. The patient will then receive the

prescribed therapy continuously for up to 24 cycles (1 cycle = 4 weeks of treatment), with repeat imaging prior to every 3rd cycle. RECIST 1.1 with modifications, to allow for continued therapy until progressive disease is confirmed if the patient is clinically stable, will be used in the trial. If the patient has confirmed progression and meets eligibility criteria to obtain a second biopsy (section 7.4), the patient will continue on trial and undergo a repeat biopsy for gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card to select another agent to add to Nivolumab (see section 7.6 below). The patient will then be treated with this new combination continuously, with repeat imaging prior to every 3rd cycle as per initial treatment, until progression of disease (see Schema A).

5.0 INCLUSION/EXCLUSION CRITERIA

5.1 INCLUSION CRITERIA

1. Recurrent and/or Metastatic squamous cell carcinoma of the head and neck that is not amenable to therapy with curative intent. Patients who refuse salvage surgery or radiation for recurrence are eligible.

2. Failure of prior immunotherapy as defined as:
   a. Progression of disease on anti-PD-1 mAb or anti-PD-L1 mAb treatment in the R/M setting.
   b. Both patients that have received platinum based chemotherapy prior or have not yet received platinum based chemotherapy are eligible.

3. Patients cannot have received more than 3 total lines of prior systemic therapy in the recurrent/metastatic setting

4. ECOG performance status of 0-1

5. Have at least one measurable area of disease (Target Lesion) based on RECIST 1.1.

6. Provide adequate tissue (core or incisional/excisional biopsy) prior to starting study for analysis for gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card. FNA is not adequate. Archival tissue can only be used if it was obtained in the recurrent/metastatic setting and there has been no subsequent cancer treatment after that tissue was obtained.

7. Life expectancy of at least 12 weeks based on investigator estimate.

8. Age $\geq$ 18 years old

9. LVEF assessment with documented LVEF $\geq$50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration

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

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤ institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN
– creatinine	≤ institutional ULN

OR

– glomerular filtration rate ≥40 mL/min/1.73 m^2 for patients with creatinine levels (GFR) above institutional normal.

10. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy testing will be repeated on C1D1 prior to the first does of study medication.

11. Female subjects of childbearing potential should be willing to use 1 method of birth control or abstain from heterosexual activity for the course of the study through 24 weeks after the last dose of study medication. Women of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

12. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 7 months after the last dose of study therapy.

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

5.2 EXCLUSION CRITERIA

1. SCC of salivary gland origin or cutaneous SCC of the head and neck. HNSCC of unknown origin ARE eligible.

2. Patients who received Ipilimumab or Relatlimab in the recurrent/metastatic setting will be excluded.

3. Is currently participating in or has participated in a study of an investigational agent or used an investigational device within 2 weeks of the first dose of treatment.

4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (equivalent of $\geq$10 mg of prednisone) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

5. Has had a prior monoclonal antibody, chemotherapy, or targeted small molecule therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier (alopecia is an exception). Note: Subjects with ≤ Grade 2 neuropathy, ototoxicity, hypothyroidism or hyperthyroidism, are an exception to this criterion and qualify for the study.

6. History of other malignancy within 3 years with the exception of prior HNSCC, adequately treated basal cell or squamous cell skin cancer, or carcinoma of the cervix.

7. Has an active autoimmune disease requiring systemic immunosuppressive treatment within the past 3 months. Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic therapy or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

8. Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
   a. Myocardial infarction (MI) or stroke/transient ischemic attack (TIA) within the 6 months prior to consent;
   b. Uncontrolled angina within the 3 months prior to consent;
   c. Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, or poorly controlled atrial fibrillation);
   d. QTc prolongation > 480 msec;
   e. History of other clinically significant cardiovascular disease (i.e., cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, poorly controlled deep venous thrombosis, etc.);
   f. Cardiovascular disease-related requirement for daily supplemental oxygen
   g. History of two or more MIs OR two or more coronary revascularization procedures
   h. Subjects with history of myocarditis, regardless of etiology.

9. A confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent

10. Subjects with history of life-threatening toxicity related to prior immune therapy (eg. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after endocrinopathy).

11. Troponin T (TnT) or I (TnI) > 2 × institutional ULN. Subjects with TnT or TnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤1 x ULN. If TnT or TnI levels are >1 to 2 × ULN within 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment based on the discretion of the PI. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT or TnI repeat levels beyond 24 hours are < 2 x ULN, the subject may undergo a cardiac evaluation and be considered for treatment, based on the discretion of the PI.

12. Has a history of non-infectious pneumonitis that required steroids, evidence of interstitial lung disease, or currently active non-infectious pneumonitis.

13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

15. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 24 weeks after the last dose of trial treatment.

16. Has a history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

17. Has active Hepatitis B or Hepatitis C

18. Has a history of a solid organ transplant.

Inclusion of Women and Minorities
Women and members of minority groups and their subpopulations will be included in this study.

6.0 CLINICAL TRIAL PROCESSES AND PROCEDURES

The schedule of study visits, procedures, and assessments are in Section 7.0. Individual trial procedures are described in detail below.

6.1 STUDY SITE

Patients will be evaluated and treated at the University of Pittsburgh Medical Center (UPMC) and the Outpatient Services of the UPMC Hillman Cancer Center. Patients will be registered and data management will be performed by Clinical Research Services of the UPMC Hillman Cancer Center.

6.2 PROCEDURE FOR REGISTRATION AND RANDOMIZATION (IF APPLICABLE) OF SUBJECTS

Patients must not start protocol treatment prior to registration. Subjects can be enrolled after eligibility criteria are met. Registration will require the following information: 1) protocol name and number; 2) date treatment begins; 3) subject name; 4) date of birth; 5) primary study physician; 6) confirmation of eligibility; 7) copies of the informed consent signature page; 98) verification that the informed consent was signed. If a patient will be randomized to treatment (when the difference between OmniSeq LAG3 and CTLA4 scores are less than 15.2), they will be randomized 1:1 to anti-LAG3 or anti-CTLA4. Treatment will be block-randomized, with blocks of size 4.

Randomization will be performed via the UPMC Hillman Cancer Center Biostatistics Facility randomization system (https://randomize.upci.pitt.edu/randomizer/home.seam). A standard operating procedure will describe the use of the system.

6.3 INFORMED CONSENT

The study team must obtain documented consent from each potential subject prior to participating in a clinical trial. Consent must be documented by the subject's dated signature. A copy of the signed,dated and timed consent form should be given to the subject before participation in the trial. The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the Institutional Review Board's (IRB's) approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature.

6.4 CONCOMITANT MEDICATIONS (allowed and prohibited)

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

6.4.1 ACCEPTABLE CONCOMITANT MEDICATIONS

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

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs.

6.4.2. PROHIBITED CONCOMITANT MEDICATIONS

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

1. Anti-cancer systemic chemotherapy or biological therapy
2. Immunotherapy not specified in this protocol
3. Glucocorticoids at a dosage of ≥ 10mg of prednisone or equivalent for any purpose other than the treatment or prophylaxis of any adverse event(intermittent use of bronchodilators or local steroid injections is allowed),

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

6.4.3 DIET

Subjects should maintain a normal diet unless modifications are required to manage an AEs such as diarrhea, nausea or vomiting, mucositis, or dysphagia. Consultation with nutrition during radiation therapy is strongly recommended.

6.4.4 PREGNANCY TEST AND CONTRACEPTION:

6.4.4.1 CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 24 weeks after the end of study treatment.*

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • Lactation amenorrhea method (LAM)

*** Local laws and regulations may require use of alternative and/or additional contraception methods.**

6.4.4.2 CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 33 weeks after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 33 weeks after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

6.5 USE IN PREGNANCY

If a subject inadvertently becomes pregnant while on study treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor and to BMS as per section 9.3 The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the information to the sponsor and to BMS. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately, and the pregnancy must be reported to the sponsor and to BMS, and followed as described above.

6.6 USE IN NURSING WOMEN

It is unknown whether nivolumab, relatlimab or ipilimumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

6.7 SUBJECT WITHDRAWAL/DISCONTINUATION CRITERIA

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the

investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

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

- The subject withdraws consent.
- Confirmed radiographic disease progression. See Section 13.0
- Unacceptable adverse events as described in Section 12.0
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

6.8 SUBJECT REPLACEMENT STRATEGY

A subject who withdraws from the trial for reasons other than toxicity, progression of disease or death and withdraws before the initial efficacy evaluation can be replaced. These cases will be recorded and accounted for in the report of the trial.

6.9 Tumor Tissue Acquisition.

A Patient must provide adequate tumor tissue (minimum of 2 cores or a surgical/incisional/excisional biopsy) prior to starting study for analysis for gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card. FNA is not adequate. Archival tissue can only be used if it was obtained in the recurrent/metastatic setting and no subsequent treatment was received after biopsy. If this is not available a new biopsy is needed. If a patient undergoes a second biopsy on trial for potential retreatment (see section 7.4) a new biopsy of adequate tumor tissue (as defined above) will need to be obtained. Biopsy will be obtained including but not limited to: radiology guided, surgical procedure, during direct laryngoscopy. The investigator to should obtain adequate tumor tissue in the least invasive way possible to minimize risks to the patient as much as possible.

7.0 TRIAL TREATMENTS

7.1 STUDY CALENDAR (SCREENING)

Eligibility Assessments	Screening Day -28 to -1
Informed consent	X
Inclusion/Exclusion Criteria	X
Medical History	X
Medication History	X
Physical Examination	X
Vital Signs and Weight [1]	X
ECOG PS	X
12 Lead EKG	X
Pregnancy Test-urine or serum B-HCG [2]	X
PT/INR and aPTT	X
CBC w/ differential [3]	X
Comprehensive Metabolic Panel[4]	X
TSH, FT4, T3	X
Hepatitis C Ab [5]	X
Hep B sAg, Hep B sAb	X
HIV 1/2 antibodies	X
Troponin [6]	X
2D echo/MUGA [7]	X
Tumor Tissue [8]	X
Tumor Imaging [9]	X

1. Vital signs to include temperature, pulse, respiratory rate, blood pressure. Height will be recorded at screening visit only.
2. For women of reproductive potential, a urine pregnancy test will be performed during screening. If a urine pregnancy result cannot be confirmed as negative, then a serum pregnancy test will be required. Pregnancy testing may be repeated if pregnancy is suspected. Repeat pregnancy testing must occur within 1 day prior to first dosage of study drugs.
3. CBC to include white blood cells, hgb/hct, platelets and differential.
4. Chemistry tests to include sodium, Potassium, Chloride, CO2, Glucose, BUN, Creatinine, Calcium, total Protein, Albumin, AST, ALT, Alkaline Phosphatase, Total Bilirubin, Magnesium, and Phosphorus
5. If Hep C Ab is positive a Hep C virus RNA PCR can be checked. If the Hep C virus RNA PCR is negative then the patient does not have active Hep C and therefore would still qualify for the trial.
6. Troponin T (TnT) or I (TnI) will be checked. If > 2 × institutional ULN patients will be excluded. Subjects with TnT or TnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤1 x ULN. If TnT or TnI levels are >1 to 2 × ULN within 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment based on the discretion of the PI. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT or TnI repeat levels beyond 24 hours are < 2 x ULN, the subject may undergo a cardiac evaluation and be considered for treatment, based on the discretion of the PI.
7. Transthoracic 2D echo is required during screening to evaluate ejection fraction. TTE or MUGA (TTE preferred test) has to have been done within 6 months from first study drug administration.
8. Patient must provide adequate tumor tissue (core or surgical/incisional/excisional biopsy) prior to starting study for analysis for gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card. FNA is not adequate. Archival tissue can only be used if it was obtained in the recurrent/metastatic setting and no subsequent treatment was received after biopsy. If this is not available a new biopsy is needed. If a patient undergoes a second biopsy on trial for potential retreatment a new biopsy of adequate tumor tissue (as defined above) will need to be obtained.
9. Tumor imaging is required at baseline and then every 8 weeks (+/- 7 days) during study treatment. Unless there is a dose delay, imaging should be done within 7 days prior to odd cycles. If a patient completes 24 cycles without progression repeat imaging will be done every 3 months (+/- 7 days) from last receipt of study therapy as per section 7.7. Tumor imaging should be at minimum with a CT neck with IV contrast, CT chest with IV contrast, and CT abdomen/pelvis with IV contrast. If MRI is determined to be a better modality to follow the patients malignancy an MRI can be used. If a patient has an allergy to CT contrast dye that precludes usage than MRI can be used for disease in the head and neck and CT non-contrast can be used for the chest, abdomen and pelvis if the investigator has determined that tumor measurements can be made without the usage of CT IV contrast.

7.2 STUDY CALENDAR FOR PATIENTS TREATED WITH NIVOLUMAB AND RELATLIMAB (CYCLE = 28 DAY)

Assessments	C1D1	C1D14 (±3d)	C2D1 (± 3d)	C2D14 (±3d)	C3D1 and D1 of all subsequent cycles (± 3d)	Safety Follow up [B]	Survival Follow up [C]
Administer Nivolumab[A]	X		X		X		
Administer Relatlimab[A]	X		X		X		
Medical History	X		X		X	X	X
Medication History	X		X		X	X	
Physical examination	X	X	X	X	X	X	
Vital Signs and Weight [1]	X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	
12 Lead EKG [2]	X	X	X	X	X		
Review adverse events	X	X	X	X	X	X	
Pregnancy Test[3]	X						
CBC w/ differential[4,5]	X	X	X	X	X	X	
Comprehensive Metabolic Panel[5]	X	X	X	X	X	X	
TSH, FT4, T3[6]					X		
Troponin [2,7]	X	X	X	X	X		
Tumor Tissue [8]							
Biomarker Studies/ Microbiome[9]	X				X *(Cycle 3 only)*		
Tumor Imaging [10]					X		

1. Vital signs to include temperature, pulse, respiratory rate, blood pressure. Height will be recorded at screening visit only.
2. For patients receiving Relatlimab, troponin and 12 lead EKG will be done every 2 weeks for the first 2 months. Subsequently they will be done at the discretion of the treating investigator. Troponin can be drawn within 48 hours of D1 of each cycle
3. For women of reproductive potential, a urine pregnancy test will be performed within 1 day prior to first dosage of study drugs. If a urine pregnancy result can't be confirmed as negative, then a serum pregnancy test will be required. Pregnancy testing may be repeated if pregnancy is suspected.
4. CBC to include white blood cells, hgb/hct, platelets and differential.
5. CBC and CMP will be done at scheduled visits every 2 weeks for the first 2 cycles and then prior each cycle of study drug therapy. These labs can be obtained up to 72 hours prior to study therapy. Chemistry tests to include sodium, Potassium, Chloride, CO2, Glucose, BUN, Creatinine, Calcium, total Protein, Albumin, AST, ALT, Alkaline Phosphatase, Total Bilirubin, Magnesium, and Phosphorus
6. Thyroid function tests (TSH, Free T4, Total T3) will be done prior to every 3rd cycle or more frequently at the discretion of the treating physician
7. Troponin T (TnT) or I (TnI) will be checked. If > 2 × institutional ULN patients will be excluded. Subjects with TnT or TnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤1 x ULN. If TnT or TnI levels are >1 to 2 × ULN within 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment based on the discretion of the PI. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT or TnI repeat levels beyond 24 hours are < 2 x ULN, the subject may undergo a cardiac evaluation and be considered for treatment, based on the discretion of the PI.
8. If a patient undergoes a second biopsy on trial for potential retreatment a new biopsy (core or surgical/incisional/excisional) will need to be obtained. See section 7.6
9. Blood will be drawn for correlative studies. Instructions on tubes needed for biomarkers study blood draws are in section 14.0. They will be drawn prior to first dosage of study drug combination C1D1, and C3D1 prior to infusion, and at next study visit after progression is confirmed. Microbiome studies as per section 14.0 will also be obtained at these same timepoints.
10. Tumor imaging is required at baseline and then every 8 weeks (+/- 7 days) during study treatment. Unless there is a dose delay, imaging should be done within 7 days prior to odd cycles If a patient completes 24 cycles without progression repeat imaging will be done every 3 months (+/- 7 days) from last receipt of study therapy as per section 7.7 Tumor imaging should be at minimum with a CT neck with IV contrast, CT chest with IV contrast, and CT abdomen/pelvis with IV contrast. If MRI is determined to be a better modality to follow the patients malignancy an MRI can be used. If a patient has an allergy to CT contrast dye that precludes usage than MRI can be used for disease in the head and neck and CT non-contrast can be used for the chest, abdomen and pelvis if the investigator has determined that tumor measurements can be made without the usage of CT IV contrast.

A See section 7.4 for details of treatment with Relatlimab plus Nivolumab

B For patients with progressive disease who don't qualify for a second treatment on study per section 7.6, or who are withdrawn from the study for any reason including toxicity, safety follow up will occur for patients that discontinue trial treatment for any reason 30 days (+/- 7 days) after the last dosage of study drug combination

C For patients with progressive disease who don't qualify for a second treatment on study per section 7.6, or who are withdrawn from the study for any reason including toxicity, survival follow up will occur starting 3 months after the last dosage of study drug. A call will be placed to the patient for survival status and if alive whether subsequent anti-neoplastic therapy was received. Patient will receive calls every 3 months for the first year and then every 6 months for the second year, then yearly thereafter.

7.3 STUDY CALENDAR FOR PATIENTS TREATED WITH NIVOLUMAB AND IPILIMUMAB (CYCLE=28 DAYS)

	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		C6 – C24	Safety F/U [B]	Survival F/U [C]
Assessments	**D1**	**D14 (±3d)**	**D1 (±3d)**	**D14 (±3d)**	**D1 (±3d)**	**D14 (±3d)**	**D1 (±3d)**	**D14 (±3d)**	**D1 (±3d)**	**D14 (±3d)**	**Day 1 All subsequent cycles (± 3d)**		
Administer Nivolumab[A]	X	X	X	X	X	X	X	X	X	X	X		
Administer Ipilimumab[A]	X			X			X			X			
Medical History	X		X		X		X		X		X	X	X
Medication History	X		X		X		X		X		X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight [1]	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	
Review adverse events	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[2]													
CBC w/ differential [3, 4]	X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Metabolic Panel[4]	X	X	X	X	X	X	X	X	X	X	X	X	
TSH, FT4, T3[5]	X						X[5]				X[5]		
Tumor Tissue[6]													
Biomarker Studies/ Microbiome[7]	X				X								
Tumor Imaging [8]					X						X[8]		

1. Vital signs to include temperature, pulse, respiratory rate, blood pressure. Height will be recorded at screening visit only.
2. For women of reproductive potential, a urine pregnancy test will be performed within 1 day prior to first dosage of study drugs. If a urine pregnancy result can't be confirmed as negative, then a serum pregnancy test will be required. Pregnancy testing may be repeated if pregnancy is suspected.
3. CBC to include white blood cells, hgb/hct, platelets and differential.
4. CBC and CMP will be done at scheduled visits every 2 weeks for the first 5 cycles and then prior each cycle of study drug therapy. These labs can be obtained up to 72 hours prior to study therapy. Chemistry tests to include sodium, Potassium, Chloride, CO2, Glucose, BUN, Creatinine, Calcium, total Protein, Albumin, AST, ALT, Alkaline Phosphatase, Total Bilirubin, Magnesium, and Phosphorus
5. Thyroid function tests (TSH, Free T4, Total T3) will be done prior to every 3rd cycle or more frequently at the discretion of the treating physician
6. If a patient undergoes a second biopsy on trial for potential retreatment a new biopsy (core or surgical/incisional/excisional) will need to be obtained. See section 7.6
7. Blood will be drawn for correlative studies. Instructions on tubes needed for biomarkers study blood draws are in section 14.0. They will be drawn prior to first dosage of study drug combination C1D1, and C3D1 prior to infusion, and at next study visit after progression is confirmed. Microbiome studies as per section 14.0 will also be obtained at these same timepoints.
8. Tumor imaging is required at baseline and then every 8 weeks (+/- 7 days) during study treatment. Unless there is a dose delay, imaging should be done within 7 days prior to odd cycles. . If a patient completes 24 cycles without progression repeat imaging will be done every 3 months (+/- 7 days) from last receipt of study therapy as per section 7.7. Tumor imaging should be at minimum with a CT neck with IV contrast, CT chest with IV contrast, and CT abdomen/pelvis with IV contrast. If MRI is determined to be a better modality to follow the patients malignancy an MRI can be used. If a patient has an allergy to CT contrast dye that precludes usage than MRI can be used for disease in the head and neck and CT non-contrast can be used for the chest, abdomen and pelvis if the investigator has determined that tumor measurements can be made without the usage of CT IV contrast.

A See section 7.5 for details of treatment with Ipilimumab plus Nivolumab

B For patients with progressive disease who don't qualify for a second treatment on study per section 7.6 or who are withdrawn from the study for any reason including toxicity a safety follow up will occur 30 days (+/- 7 days) after the last dosage of study drug combination

C For patients with progressive disease who don't qualify for a second treatment on study per section 7.6, or who are withdrawn from the study for any reason including toxicity, survival follow up will occur starting 3 months after the last dosage of study drug. A call will be placed to the patient for survival status and if alive whether subsequent anti-neoplastic therapy was received. Patient will receive calls every 3 months for the first year and then every 6 months for the second year, then yearly thereafter.

7.4 TREATMENT WITH RELATLIMAB PLUS NIVOLUMAB

Nivolumab will be dosed 480mg IV q 28 days and Relatlimab 160mg IV q 28 days, as per section 8.0. Therapy will be given every 28 days (+/- 3 days) and one cycle is defined as 28 days. During treatment the patient will be seen at least every 2 weeks by the treating physician in addition to the day of the cycle during the first 2 cycles than at least monthly on the day of the cycle, starting after the 3rd cycle. Patients will be treated with up to 24 cycles or until progression or discontinuation of study therapy for adverse events or any other reason, whichever occurs first. Repeat imaging will be done prior to (within 7 days) every 3rd cycle of therapy. If a patient completes 24 cycles without progression repeat imaging will be done every 3 months (+/- 7 days) from last receipt of study therapy as per section 7.7. Anytime during the course of treatment or after completion of 24 cycles if the patient is found to have progression the patient may be eligible for a second biopsy and second treatment if they meet eligibility criteria as detailed in section 7.6.

7.5 TREATMENT WITH IPILIMUMAB PLUS NIVOLUMAB

A cycle of therapy will be defined as 28 days of treatment. Nivolumab will be dosed at 3mg/kg IV q 14 days (+/- 3 days) and Ipilimumab 1mg/kg IV q 42 days (+/- 3 days). Patients will receive four doses of Ipilimumab and the last dosage of Nivolumab 3mg/kg IV q 14 days will be given at the time of the 4th dose of Ipilimumab (C5D14), followed 2 weeks later by Nivolumab 480 mg IV q 28 days which will be C6D1. Nivolumab 480mg IV q 28 days (+/- 3 days) will be given for the remainder 19 cycles for total of 24 cycles. The patient will be seen every 2 weeks during the first 6 cycles and then every 4 weeks after the 6th cycle is received. There is a +/- 3 day window for each dosage of Nivolumab and Ipilimumab. Patients will be treated with up to 24 cycles or until progression or discontinuation of study therapy for adverse events or any other reason, whichever occurs first. Repeat imaging will be done prior to (within 7 days) every 3rd cycle of therapy. If a patient completes 24 cycles without progression repeat imaging will be done every 3 months as per section 7.7. Anytime during the course of treatment or after completion of 24 cycles if the patient is found to have progression the patient may be eligible for a second biopsy and second treatment if they meet eligibility criteria as detailed in section 7.6.

7.6 CRITERIA FOR A SECOND BIOPSY AND SECOND TREATMENT ON TRIAL

If a patient progresses anytime during the course of treatment or after completion of 24 cycles they may be potentially eligible for a second biopsy and second treatment based on gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card on trial if the following criteria are met:

1. Has not been treated for recurrence/disease progression with other anti-cancer treatment.
2. Still meets all inclusion/exclusion criteria with the exception of exclusion criteria #2.

If patient meets the above criteria they can undergo a repeat biopsy and analysis by OmniSeq immune report card for immune gene expression. If a patient progresses during study therapy and has received Ipilimumab and Nivolumab initially (either via selection based on gene expression or randomization) then expression of LAG3 must be greater (criteria as per treatment assignment rule) than CTLA4 for a patient to stay on trial and receive Relatlimab and Nivolumab. If a patient has received Relatlimab and Nivolumab initially (either via selection based on gene expression or randomization) then gene expression of CTLA4 must be greater than LAG3 (criteria as per treatment assignment rule) for a patient to stay on trial and receive Ipilimumab and Nivolumab. If a patient undergoes a second biopsy and he/she does not meet the minimum required difference in relative rank score between CTLA4 and LAG3 as per the treatment assignment rule, than the patient will be taken of of study (will not be randomized to treatment). If a patient completes all 24 cycles of therapy without progression but then recurs within 3 months discontinuation of therapy than the ability to receive retreatment is the same (as described above) as for patients that progressed on study therapy. If the patient progresses after 3 months after completion of all 24 cycles than retreatment can be with the same combination received prior of that gene expression marker is highest on repeat biopsy. Patients that meet criteria for retreatment can be treated for up to 24 additional cycles with this second treatment with dosing and schedule the same as per section 7.2 and 7.3 above.

These patients will undergo trial screening procedures as per Section 7.1, with the following exceptions:

- Patients will not have to sign another informed consent document.

- Tumor imaging will need to be repeated if last imaging was greater than 28 days ago
- Patient will not need to undergo repeat testing for HIV and Hepatitis B and C
- Patients will undergo serum collection for correlative studies before initiation of second treatment.

7.7 FOLLOW UP SCHEDULE FOR PATIENTS THAT COMPLETE 24 CYCLES OF THERAPY WITHOUT PROGRESSION OF DISEASE

If a patient completes all 24 cycles of therapy without progression the patient will be seen as per safety follow up visit at 30 days (+/- 7 days) and then every 3 months (+/- 7 days) from the last receipt of study therapy. Patient will undergo repeat imaging every 3 months and may be eligible for retreatment as per section 7.4 if the patient progresses.

8.0 STUDY THERAPY SUPPLY AND ADMINISTRATION

8.1 DRUG INVENTORY RECORDS

In general, the product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact BMS immediately.

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site. All study drug, both used and unused, will be destroyed at the site using standard practice at UPMC Hillman. No study drug will be returned to BMS.
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form. BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements. At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

8.2 NIVOLUMAB

8.2.1 Supplier/How supplied

Nivolumab comes as a 100 mg/10 mL (10 mg/mL) solution in a single-dose vial. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, 24-hour sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 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. Nivolumab will be obtained via research supply for this study.

8.2.2 Storage Requirement/stability

After preparation, store the infusion at room temperature for no more than 8 hours from time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the

infusion. Nivolumab can be refrigerated at 2 degrees Celsius to 8 degrees Celsius for no more than 24 hours from the time of infusion preparation.

8.2.3. Preparation and Administration

Withdraw required volume of Nivolumab and dilute with either 0.9% sodium chloride injection, USP or 5% dextrose injection USP to prepare an infusion with a final concentration of 1 to 10 mg/ml. Mix diluted solution by gentle inversion and do not shake. The total volume of infusion must not exceed 160 mL. Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not co administer other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

8.3 IPILIMUMAB

8.3.1 Supplier/How supplied

The ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles. The ipilimumab injection, 200 mg/40 mL, is supplied in 10-cc or 50-cc Type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0. Ipilimumab will be obtained via research supply for this study.

8.3.2 Storage Requirement/stability

Ipilimumab injection, 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

8.3.3 Preparation and administration

Ipilimumab injection (5 mg/mL) can be used for intravenous (IV) administration without dilution after transferring to a polyvinyl chloride (PVC), non-PVC/non-di-(2-ethylhexyl)phthalate (DEHP), or glass container and is stable for 24 hours at 2°C to 8°C or room temperature/room light. Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP to concentrations between 1 and 4 mg/mL and stored in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 to 1.2 μm). Ipilimumab injection must not be administered as an IV push or bolus injection.

For patients that are receiving Nivolumab plus Ipilimumab, when administered on the same day, Nivolumab will be infused first followed by ipilimumab. Use separate infusion bags and filters for each infusion.

Administration Instructions

- Do not mix with, or administer as an infusion with, other medicinal products.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

8.4 RELATLIMAB

8.4.1 Supplier/How supplied

Relatlimab injection, 80mg/vial (10mg/mL) 8mL, is a clear to opalescent, colorless to pale, yellow liquid, with light (few) particulates that may be present. There are two drug formulations that are available. The same

excipients are used for both formulations, except for pentetic acid: Relatlimab, L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injection, and pH 5.0 to 6.0. It is supplied in 10-cc type I flint glass. Relatlimab will be obtained via research supply in this study

8.4.2 Storage Requirement/stability

The drug products should be stored at 2°C to 8°C (36°F to 46°F) with protection from light. Do not freeze the drug product.

The administration of relatlimab infusions and the co-administration of relatlimab and nivolumab 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 24 hours and a maximum of 4 hours of the total 24 hours can be at room temperature (20°C to 25°C; 68°F to 77°F) and exposed to room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

8.4.3 Preparation and administration

Relatlimab injections (10 mg/mL) can be co-administered with nivolumab injection (also referred to as BMS-936558 injection) as an IV infusion through a compatible low-protein-binding in-line filter at the protocol-specified doses. Total infusion volume not to exceed 160 mL for flat dose. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. Relatlimab injections (10 mg/mL) may be mixed with nivolumab injection (10 mg/mL) as follows:

- Relatlimab injections (10 mg/mL) may be mixed with nivolumab injection (10 mg/mL) at a ratio of 1:3 and the resultant drug product solution may be diluted with either NS or D5W to a total protein concentration no lower than 0.8 mg/mL (0.2 mg/mL of relatlimab and 0.6 mg/mL of nivolumab). No incompatibilities have been observed between the combined drug product solutions and EVA, PO, or PVC IV containers, DEHP-plasticized PVC IV sets, DEHP-free IV sets and in-line filters with 0.2 µm or 1.2 µm PES, 0.2 µm nylon, or 0.2 µm PVDF membranes.

Care must be taken to assure sterility of the prepared solution, as the products do not contain any anti-microbial preservative or bacteriostatic agent.

Nivolumab and relatlimab are to be co-administered as a 60 minute IV infusion, using a volumetric pump with a 0.2 micron to 1.2 micron pore size, low protein binding (polyethersulfone membrane) in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. . At the end of the infusion, flush the line with a sufficient quantity of normal saline (approximately 15-20 mL).

8.5 Potential Side Effects of the Study Drug Treatments (please refer to the current investigator brochures for a complete list of all potential side effects)

NIVOLUMAB COMBINED WITH IPILIMUMAB

Very common side effects (may affect more than 10% of people)

- ALT increased: lab test result associated with abnormal liver function
- AST increased: lab test result associated with abnormal liver function
- Diarrhea
- Fatigue
- Itching
- Fever
- Nausea
- Rash

Common side effects (may affect 5 to 10% of people)

- Abdominal pain
- Adrenal gland function decreased
- Alkaline phosphatase increased: lab test result associated with liver or bone abnormalities

- Amylase increased: lab test result associated with pancreas inflammation
- Appetite decreased
- Bilirubin (liver function test) increased
- Chills
- Constipation
- Cough
- Creatinine increased: lab test result associated with decreased kidney function
- Dehydration
- Dizziness
- Dry mouth
- Dry skin
- Hair loss
- Headache
- Inflammation of the colon
- Inflammation of the mouth
- Inflammation of the pituitary gland
- Infusion related reaction
- Joint pain or stiffness
- Lipase increased: lab test result associated with pancreas inflammation
- Liver inflammation
- Loss of color (pigment) from areas of skin
- Low blood pressure
- Lung inflammation (pneumonitis)
- Musculoskeletal pain
- Renal (kidney) failure or damage to your kidneys
- Shortness of breath
- Sodium levels in blood low
- Swelling, including face, arms, and legs
- Thyroid gland function decreased
- Thyroid gland function increased
- Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet
- Vision blurred
- Vomiting
- Increased blood sugar
- Inflammation of the pancreas
- Inflammation of the thyroid gland
- Redness of skin

Uncommon side effects (may affect up 2 to 5% of people):

- Allergic reaction/hypersensitivity
- Bronchitis
- Cranial nerve disorder
- Diabetes
- Diabetes complications resulting in excess blood acids and diabetic coma
- Disease caused by the body’s immune system attacking healthy organs
- Double vision
- Drug-induced liver injury
- Dry eye
- Guillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
- Heart rate increased
- Heart rhythm abnormal
- High blood pressure

- Hives
- Inflammation of the brain (potentially life threatening or fatal)
- Inflammation of the eye
- Inflammation of the heart
- Inflammation of the kidney
- Inflammation of the small intestine and colon
- Inflammation of the stomach
- Lung infiltrates, associated with infection or inflammation
- Muscle inflammation
- Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles.
- Pituitary gland function decreased
- Psoriasis: characterized by patches of abnormal, scaly skin
- Rhabdomyolysis: muscle fiber released into the blood stream which could damage your kidneys
- Respiratory failure or distress
- Rupture of the intestine / hole in the intestine
- Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes
- Upper respiratory infection
- Vertigo

Rare side effects (may affect less than 2% of people):

- Syndrome associated with fever, white blood cell activation and abnormal function (including destruction of other blood cells by certain white blood cells), low blood cell counts, rash, and enlargement of the spleen
- Anaphylactic reaction (severe allergic reaction)
- Damage to protective covering of the nerves in the brain and spinal cord
- Erythema multiforme: skin inflammatory reaction
- Inflammation of the lining of the brain and spinal cord
- Inflammation of blood vessels
- Stevens Johnson syndrome: inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin
- Toxic epidermal necrolysis: a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn
- Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis: disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains.
- Vogt Koyanagi Harada syndrome: a disease that affects the pigmented tissue; this may affect the eye leading to swelling, pain, and/or blurred vision; the ear leading to hearing loss, ringing in the ears, and/or the skin leading to loss of skin color.
- Polymyalgia rheumatica (inflammatory disorder that causes muscle pain and stiffness, especially in the shoulders)
- Disease caused by the body's immune system attacking healthy organs

NIVOLUMAB COMBINED WITH RELATLIMAB

Approximately322 subjects have been treated with relatlimab in combination with nivolumab (322 patients). Among these subjects, two life-threatening cardiac (effecting the heart) events have occurred, one of which contributed to a subject's death. One subject experienced an episode of ventricular fibrillation (a life-threatening heart rhythm abnormality). This event was not associated with known side effects of either drug but it was considered as possibly caused by either Relatlimab or the combination therapy with Nivolumab. At present time, there is not enough information to determine whether ventricular fibrillation might occur in subjects treated in this protocol with Relatlimab alone or in combination with Nivolumab. The second subject developed severe inflammation of the

heart muscle (myocarditis) which led to dysfunction of the heart's electrical impulses and also severely decreased the heart muscle's ability to pump blood. Biopsy of the heart muscle showed that the combination of Relatlimab and Nivolumab resulted in the immune system attacking the heart muscle. Therapies to inhibit the immune system were used to treat the inflammation and partial heart function was restored but the subject subsequently suffered from sudden death a few months later. Because of this event an increased number of blood tests and electrocardiograms are performed to try and identify any early signs of heart muscle inflammation.

The side effects observed with Relatlimab (BMS-986016) in combination with Nivolumab are:

Very common side effects (may affect more than 10% of people):

- Fatigue
- Fever
- Nausea
- Diarrhea
- Dizziness
- Weight loss
- Constipation
- Cough
- Decreased appetite
- Joint pain
- Decrease in red or white blood cell counts
- Shortness of breath
- Difficulty breathing

Common side effects (may affect 5 to 10% of people):

- Infusion related reaction (e.g., rash & chills)
- Rash
- Abdominal pain and discomfort
- Anemia (Decrease in red or white blood cell counts)
- ALT increased: lab test result associated with abnormal liver function
- AST increased: lab test result associated with abnormal liver function
- Itching
- Lipase increased: lab test result associated with pancreas inflammation
- Muscle pain or weakness
- Headache
- Back pain
- Vomiting
- Infection
- Decrease in thyroid function
- Swelling in the arms or legs
- Dry mouth

In addition, there are other side effects that are important to know about that have affected patients treated with Relatlimab in combination with Nivolumab. These include: inflammation of the pancreas (leading to pancreatitis or diabetes), inflammation of the protective covering of the nerves in the brain and spinal cord (aseptic meningitis), inflammation of the thyroid leading to abnormal thyroid function and thyroid lab abnormalities (hypothyroidism or hyperthyroidism), inflammation of the lining surrounding the heart (pericarditis), and inflammation of the lungs (pneumonitis). Lastly, some patients have experienced colitis or proctitis (inflammation of the colon or rectum) that typically presents with diarrhea, which can become life-threatening if not treated promptly, and may also present with abdominal pain.

Potential Immune related adverse events. .

- **Uveitis:** inflammation of the eyes that may cause eye redness, eye pain, sensitivity to light, blurred vision, decreased vision, and floating spots in your vision
- **Hypophysitis:** inflammation of the pituitary gland that may cause low blood sugar, dehydration, weakness, dizziness, and other symptoms
- **Hyperthyroidism:** overactive thyroid gland activity that may lead to fatigue, weakness, muscle aches, anxiety, weight loss, intolerance to heat, in addition to other symptoms
- **Hepatitis:** inflammation of the liver that may result in nausea, fatigue, abdominal pain, impart a yellowish hue to your skin or eyes, or darkness of your urine
- **Pancreatitis:** inflammation of the pancreas that may lead to high levels of lipase and that may be accompanied by nausea, vomiting, and abdominal pain
- **Colitis:** inflammation of the lining of the colon, usually resulting in diarrhea and possibly abdominal pain.
- **Arthritis:** painful swelling, inflammation and stiffness of the fingers, wrists, arms and legs
- **Myocarditis:** life-threatening inflammation of the heart muscle which could result in chest pain, swelling of the legs, weakness, difficulty breathing, and or altered hear rate or rhythm.
- **Aseptic Meningitis**: inflammation of the lining of the brain and/or the spinal cord, which could result in symptoms such as headache, fever, increased sensitivity to noise and light, visual changes or altered level of consciousness.
- **Nephritis**: inflammation of the kidney which could result in symptoms such as pain in the kidney area or abdomen, changes in frequency or appearance of the urine, swelling of the body (most commonly the legs and feet), and pain with urination.

9.0 ASSESSING, RECORDING, AND REPORTING ADVERSE EVENTS

9.1 DEFINITIONS

The following definitions of terms apply to this section:

Adverse event: **Any untoward medical occurrence or worsening of a preexisting medical condition associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.**

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

Serious adverse event **or** ***serious suspected adverse reaction:*** **An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.**

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and new 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).

Suspected adverse reaction: **Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.**

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected adverse event or *unexpected suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation

9.2 POTENTIAL DRUG INDUCED LIVER INJURY IS DEFINED AS:

1) An (ALT or AST) elevation > 3 times upper limit of normal (ULN)
AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.3 PREGNANCY

- If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).
- The investigator must immediately notify appropriate individuals/agencies as per section 11.3
- Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.
- Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, or approved site SAE form.
- Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.
- See section 9.8.2 for reporting requirements for pregnancy.

9.4 OVERDOSE

- An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

9.5 THE FOLLOWING HOSPILIZATIONS ARE NOT CONSIDERED SAEs:

- 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 (applies to oncology protocols)

9.6 ABNORMAL TEST FINDINGS

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.

Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.

- The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.
- The test finding is considered an AE by the Sponsor-Investigator of the IND application.

9.7 ELICITING AE INFORMATION

Research subjects will be routinely questioned about AEs at all study visits. AEs will be categorized and severity will be graded according to the NCI-CTCAE version 5.0.

9.8 RECORDING REQUIREMENTS

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

AEs or abnormal test findings felt to be associated with the investigational drug or study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

9.8.2 REPORTING OF SERIOUS ADVERSE EVENTS

All events meeting the definition of a serious adverse event (per section 9.1-9.4) including pregnancy should be reported according to the departmental SAE checklist and SAE form. Serious adverse events are collected from the date of the subject's first dose of treatment until 100 days after the final dose. The initial SAE form should be sent to the following within 24 hours/1 business days of the Sponsor-Investigator becoming aware:

1. Dan Zandberg, MD
2. crssafetysubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met.
4. Email to Worldwide.Safety@BMS.com or by fax +1 609-818-3804

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on the internal departmental SAE form.

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 \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections B and C of the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up reports:

All SAEs should be followed to resolution or stabilization. Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form. All follow-up forms must include the date the form is revised.

9.8.3 REPORTING OF NON-SERIOUS ADVERSE EVENTS

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

10.0 REVIEW OF SAFETY INFORMATION: SPONSOR RESPONSIBILITIES

The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

Note: The requirements of the Sponsor for the reporting of suspected adverse drug reactions to the FDA differ from the requirements of the Investigator (see below and Investigator Responsibilities on the O3IS website) for the reporting of adverse events to the Sponsor. Sponsor-investigators of IND applications are subject to compliance with both the adverse reaction reporting requirements of the Sponsor and the adverse event reporting requirements of the Investigator.

10.1 IND SAFETY REPORTS

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under sections below. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction,

and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information..

10.2 SERIOUS AND UNEXPECTED ADVERSE EVENTS

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

10.3 FINDINGS FROM OTHER STUDIES

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

10.4 FINDINGS FROM ANIMAL OR IN VITRO TESTING

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

10.5 INCREASED RATE OF OCCURRENCE OF SERIOUS SUSPECTED ADVERSE REACTIONS

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

10.6 SUBMISSION OF IND SAFETY REPORTS

The sponsor must submit each IND safety report in a narrative format or on Form FDA 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a Form FDA 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

10.7 UNEXPECTED FATAL OR LIFE-THREATENING SUSPECTED ADVERSE REACTION REPORTS

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

10.8 REPORTING FORMAT OR FREQUENCY

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

10.9 INVESTIGATIONS OF MARKETED DRUGS

A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements.

10.10 REPORTING STUDY ENDPOINTS

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under Section 10.11 third bullet of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under *Serious and unexpected suspected adverse reaction* as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

10.11 FOLLOW-UP

- The sponsor must promptly investigate all safety information it receives.
- Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under section IND safety reports of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

10.12 DISCLAIMER

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

The Sponsor-Investigator must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible.

10.13 ADDITIONAL SITE AND SPONSOR-INVESTIGATOR RESPONSIBILITIES TO BRISTOL-MYERS SQUIBB (BMS)

The Sponsor-investigator will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com) (BMS GPV&E). 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 In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously

described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report

UPMC Hillman Cancer Center acknowledges and agrees that the Study Drug Relatlimab is a BMS early asset and the safety and efficacy of the Study drug is not as well-known as a marketed drug or drug in late-development. Notwithstanding that BMS is not the regulatory sponsor of the Study, in order to protect the safety and well-being of Study subjects, UPMC Hillman agrees to collaborate with BMS on safety issues arising from the Study Drug

UPMC Hillman Cancer Center shall disclose de-identified, patient level Study Data to BMS upon request, and in the format reasonably requested by BMS under this Agreement. BMS shall have unlimited rights to access, use, or disclose this Study Data for internal research and development purposes or to support an application to the FDA and other regulatory authorities without further obligation to UPMC Hillman Cancer Center or the sponsor-investigator.

11.0 DATA SAFETY MONITORING PLAN

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

Minutes from the disease center DSMB meetings are available to those who are unable to attend in person.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria Version 5.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB and FDA. Any modifications necessary to ensure subject safety and decisions to continue or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed bi-annually.

Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these

meetings.. If the DSMB recommends any study changes related to safety, the sponsor-investigator will also notify BMS and FDA.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

12.0 MANAGEMENT OF ADVERSE EVENTS

12.1 IMMUNE RELATED ADVERSE EVENTS

For the purposes of this study, an immune-related adverse reaction is defined as an adverse reaction of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an event an irAEs. Serologic, immunologic, and histologic (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Suspected immune-related adverse reactions must be documented on an AE or SAE form.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune-mediated adverse reactions (e.g., systemic lupus erythematosus-like diseases) or organ-specific immune-mediated adverse reaction (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an immune-mediated adverse reaction is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

Recommended guidelines for specific immune-mediated adverse reactions are included in Appendix II. These recommendations should be utilized as clinically appropriate for the treatment of individual patients. Please contact the PI for any questions

12.2 DOSE DELAY CRITERIA:

Toxicity from Ipilimumab plus Nivolumab and Relatlimab plus Nivolumab will be graded by CTCAE v5.0. No dose reductions will occur for drug related adverse events but rather drug therapy will be held and next cycle delayed.

Subjects who experience the following must have all study drugs held:

Select drug-related AEs and drug-related laboratory abnormalities:

- ≥Grade 2 pneumonitis
- > Grade 2 elevation of liver tests (AST or ALT and/or total bilirubin)
- ≥Grade 2 increased creatinine
- ≥Grade 2 diarrhea or colitis
- ≥Grade 2 neurological AE
- > Grade 3 skin AE
- Myocarditis (any grade)
- All troponin elevations require a dose delay to allow for prompt cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discretion of the PI.
- Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestations.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects that have drug-related toxicities that meet the criteria for dose delay, should have both drugs delayed until retreatment criteria are met. When retreatment criteria are met, subsequent dosing visits will follow every 2 weeks (or 4 weeks as applicable) after the delayed dose.

12.3 ADVERSE EVENT TREATMENT DISCONTINUATION CRITERIA

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

2. Any Grade ≥ 3 non-skin, drug-related AE lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:

    a. Grade ≥3 drug-related myocarditis, diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation:-- Grade ≥3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

    b. Grade >3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        i. Grade >3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

    c. Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
        i. Grade >3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
        ii. Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Sponsor

3. Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
    -Grade 4 neutropenia ≤ 7 days
    -Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
    -Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    -Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Sponsor.

4. Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:

    -Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. A drug related adverse event where steroids are not indicated but the management of the adverse event causes a dose delay lasting >6 weeks may be allowed if approved by the Sponsor.

    -Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor.

5. Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued study drug combination dosing.

6. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the sponsor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study

visits to assess safety and laboratory studies should also continue if clinically indicated during such dosing delays.

7. Subjects who meet criteria for permanent discontinuation should receive no further study therapy. The following exceptions apply:

    - If the toxicity resolves to < Grade 1 or baseline > 6 weeks after last dose, but the subject does not otherwise meet the criteria for permanent discontinuation and the Investigator believes that the subject is deriving clinical benefit, then the subject may be eligible to resume the study drug(s) following the approval of the sponsor.
    - Subjects with a grade 4 drug-related amylase and/or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis can be restarted on therapy once the levels have recovered to grade 3 or less, and after consultation with the sponsor.
    - Subjects with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.
    - Subjects who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE Grade or normal, provided the criteria for permanent discontinuation are not met.
    - Subjects may resume treatment in the presence of Grade 2 fatigue.
    - Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

12.4 INFUSION REACTIONS:

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (Mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional study drug administrations.

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

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

For Grade 3 or 4 symptoms (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement;

hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Life-threatening, Grade 4: pressor or ventilatory support indicated).

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous (SC) administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur.
- All study drug(s) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

12.5 CRITERIA TO RESUME TREATMENT

Subjects may resume treatment with combination therapy when the drug-related AE(s) resolve(s) to Grade $\leq$ 1 or baseline and if applicable the patient is no longer on systemic steroids, with the following exceptions:

-Subjects may resume treatment in the presence of Grade 2 fatigue.

−Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

-For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.

-Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Sponsor.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Sponsor.
Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

13.0 ASSESSMENT OF DISEASE

13.1 DEFINITIONS

Measurable Lesions: Lesions that can be accurately measured in at least one dimension with longest diameter at least >10 mm on CT scan (or >20mm by X-ray). Cystic lesions thought to represent cystic metastasis can be considered as measurable lesions.

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be > 15 mm when assessed by CT scan.

Non-measurable Lesions: All other lesions < 10 mm or lymph nodes <15mm by CT scan.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and up to 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 this 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.

13.2 EVALUATION OF DISEASE RESPONSE

Response determination will be defined based on RECIST 1.1. (Table 4,5,6).

Table 4. Definition of Response in Target Lesions.

Response	Definition
Complete Response (CR)	Disappearance of all target lesions
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 compared to baseline sum of target lesions, or any new lesions
Stable Disease (SD)	Neither sufficient decrease to qualify as a PR or sufficient increase to qualify as PD

Per RECIST 1.1, response should be confirmed by a repeat CT scan. The scan for confirmation of response may be performed at the earliest 4 weeks after imaging that showed response (if clinically indicated) or at the next scheduled scan.

Lesions that can be measured clinically on physical exam (skin lesions or palpable lymph nodes) will be measured by the investigator with the longest axis recorded. These measurements can be used to guide clinical decision making, for example prompting an earlier CT scan to evaluate disease. However, only measurements based on radiology will be used to determine response.

Table 5. Assessment of Non-Target Lesions

Response	Definition
Complete Response (CR)	Disappearance of all non-target lesions
Incomplete Response/Stable Disease (SD)	Persistence of one or more non-target lesions
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of “non-target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

13.3 EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence.

Table 6. Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	PR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Given the observed pattern of response with immunotherapy medications where some patients develop evidence of progressive disease by RECIST 1.1, with significant increase in size of target lesions and/or new lesions, followed by regression of disease to SD or PR/CR all imaging showing progressive disease by RECIST 1.1, in the absence of significant clinic deterioration of the patient will be confirmed with a repeat CT scan at least 4 weeks from the initial imaging showing progression. Clinically stable patients will continue treatment in the interim before this scan. If progressive disease is confirmed on subsequent imaging, the patient will be defined as having progressive disease and will be taken off of the study. Progressive disease by RECIST 1.1 with clinical deterioration by the patient will be counted as progressive disease, and study treatment will be discontinued.

Determination of clinical deterioration is at the discretion of the treating physician as defined by progression of disease at critical sites requiring urgent intervention (for example cord compression), or development of signs and symptoms of disease progression and/or significant decline in ECOG performance status.

14.0 TISSUE AND BLOOD COLLECTION AND BIOMARKER STUDIES

The following exploratory biomarker analysis will be conducted:

1. To evaluate changes in immune gene expression, immune co-signaling molecule expression by IHC, and immune cell populations over time via paired samples after exposure to combination immunotherapy

2. To evaluate co-signaling molecule expression by IHC and correlate with gene expression by RNAseq as well as the predictive value of co-signaling molecule expression by IHC and the efficacy of the combination selected.

3. Evaluation of immune cell populations and other potential biomarkers (as detailed in section in the peripheral blood at baseline and over time.

4. To evaluate the predictive value of the oral and stool microbiome on efficacy with treatment.

14.1 TISSUE ANALYSIS.

14.1.1 Omniseq Immune report card

The OmniSeq Immune Report Card will be used for analysis of the tumor specimen for gene expression of LAG3 and CTLA4. As detailed in section 2.0 the immune report card contains IHC, TMB, and other gene expression data in its report. Data from the immune report card including but not limited to Immune Gene expression and TMB will be correlated with analysis done in section 14.1.2 below. Upon receipt of materials the estimated time to generate a report is 5 business days.

Acceptable specimens are limited to:

1) A FFPE block with a minimum tumor surface dimension of 2 mm^2 .

2) A minimum of 10 unstained slides at 4-5 µm are needed, however four to eight previously sectioned unstained slides cut at 10µm sections is preferred

3) Any equivalent combination of slides or blocks

Blocks and or slides with a shipping manifest for OmniSeq Immune report card will be sent to:

Att Blake Burgher
OmniSeq, Inc.
700 Ellicott Street,
Buffalo, New York 14203

14.1.2 CHARACTERIZATION OF THE TUMOR MICROENVIRONMENT

After slides are prepared for shipment to Omniseq as described above additional tissue left over from the fresh biopsy or archival sample will be analyzed in the Ferris Lab. Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin embedded (FFPE) tumor tissue in pre-treatment tumor samples as well as in second paired biopsy samples when available. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2, CTLA4, TIM3 and LAG-3. Hpv status by p16 IHC will be analyzed in patients with oropharyngeal primary site. In cases where fresh tumor is available isolation of TIL from tumor and stromal cells may be performed. Isolated PBMC may be utilized to assess the gene expression (including by RNA seq), phenotype, TCR, and function of immune cells. Additional studies using these specimens may be performed as the field evolves to maximize determination of biomarkers or response.

14.2 TISSUE PROCESSING

Sample Preparation and Shipment Instructions
For the biopsies or archival tissue, after the tissue is prepared for Omniseq immune report card analysis as per section 16.1.1, if additional tissue remains samples may be processed as follows:

FFPE: For head and neck tumors, construction of tissue microarrays (TMAs) and immunohistochemical staining of the patient specimens will be performed at the UPMC/UPCI Head and Neck Tissue Core. These studies will be supervised by our head and neck pathologist, Dr. Raja Seethala, who directs the Tissue Core of the UPCI Head and Neck Cancer SPORE (PI, Ferris). Dr. Seethala is experienced in TMA construction and analysis of protein expression. Paraffin embedded tissue blocks will be sectioned at 5µm and stained with H&E for morphologic characterization and to serve as guide slides for TMA construction.

TIL and Isolated Tumor Cells (if fresh tissue available): Samples should be weighed and added to 9X volume of lysis buffer (100 mg of tissue per 900 µL lysis buffer). The recommended lysis buffer is 60mM Tris-HCL with 2mM EDTA, pH 7.4. Samples should be homogenized immediately following collection; however, if the samples are not homogenized immediately then the samples should be frozen in liquid nitrogen and stored at -80°C. In order to minimize protease activity the following inhibitors should be added: aprotinin, antipain, leupeptin, and pepstatin A (all at 1 µL/mL) and 2mM PMSF (phenylmethylsulfonyl fluoride). Tissues may be homogenized using a Potter-Elvehjem homogenizer (Teflor pestle and glass mortar) attached to a variable-speed drill, a polytron or a tissuemizer. During the homogenization process, the tubes should be submersed in an ice bath to maintain the sample at 2–8°C. Following homogenization, the tissue preparation will be centrifuged for 2 minutes in a microfuge at 13,000xg. Ensure the cell pellet is not disturbed; aspirate the supernatant. A total volume of 350µL is required.

For intracellular flow cytometry, isolated tumor cells will be fixed with 1.5% paraformaldehyde for 10 minutes, then permeabilized with 100% methanol for at least 24 hours. Cell will be washed with fetal calf serum, then stained with primary antisera directed towards TAP1, TAP2, LMP2, or calreticulin, then with a fluorochrome-bound secondary antibody. Both incubations will be for 30 minutes at room temperature. FACS analysis will then be performed immediately after staining using an EPICS XL cytometer (Beckman Coulter). A minimum of 10,000 cells will be analyzed per test. At least 3 independent tests will be performed for each condition, and protein expression reported as a mean ± standard error of the mean.

Shipment Instructions:

1) The formalin-fixed tissue will be delivered to the UPMC/Hillman Head and Neck Tissue Bank as follows:

Raja Seethala, M.D.
University of Pittsburgh
Head and Neck Tissue Core
A-724 Scaife Hall
200 Lothrop Street
Pittsburgh, PA 15213

2) Fresh tumor will be delivered immediately to the laboratory of Robert Ferris, MD, PhD for processing:

Room 2.19 - Ferris lab
Hillman Cancer Center
5117 Centre Ave
Pittsburgh, PA 15213
Phone: 412-623-7738

14.3 BLOOD PROCESSING AND ANALYSIS

Blood for biomarker analysis will be drawn at the following time points

1. Cycle 1 Day 1 of study therapy prior to infusion of the study therapy
2. Cycle 3 Day 1 of study therapy prior to infusion of the study therapy
3. At the next visit after progression of disease is confirmed (if applicable)

Peripheral blood at these time points will be analyzed for immune cell populations including but not limited to CD8 T cells, Tregs, MDSCs and immune cell function, as well as tumor antigen (EGFR, p53, E6, E7) seroreactivity.

Peripheral blood obtained by venipuncture will serve as the source for laboratory testing. Up to 70 mL of blood may be obtained at each draw. One red top tube for serum collection and 5 green top tubes of blood for separation and collection of plasma and mononuclear cells will be collected at each time point. At C1D1, a lavender top tube (EDTA) for DNA will be collected.

Blood Collection Procedures, Green and Red Top:

- Before venipuncture, the phlebotomist prepares five green top (heparin) plastic 10 ml tubes (green top #1, #2, #3, #4, #5) and one red top (no gel) plastic 10 ml blood collection tubes (red top #1) and affixes a label to each blood collection tube. Information to be encoded on the label includes the clinical trial study number, subject's unique identification (ID) number, tube number (1-5), and date. The tubes are placed in a test tube rack, in order of collection (green tops, then red tops).
- The phlebotomist uses standard venipuncture techniques. Following collection of blood, green top tubes will be inverted 5 times to prevent clotting and platelet clumping.
- The phlebotomist uses the blood collection forms to record date and time of phlebotomy and approximate amount of blood collected into each tube.
- Green top tubes may be kept at room temperature and should be shipped by same-day courier (Pittsburgh sites) or overnight (non-Pittsburgh sites) to Dr. Ferris's lab at the address specified below. Enclose the blood collection form with the shipment.
- Red top tube:
  - To allow clot formation, allow red top tube to sit at room temperature (22° to 25° C) for 15 to 30 minutes.
  - If further processing cannot be accomplished immediately after clot retraction, red top tube should be placed at 4° C.
  - Centrifuge red top tube at 2,000 rpm for 10 min to sediment the clot.
  - Aspirate the serum into 1-1.5 mL aliquots and transfer to 1.8 mL freezing tubes (4-8

tubes depending upon volume of serum).
    - Information to be encoded on each freezing tube includes the clinical trial study number, the subject's unique ID number, the tube # (1-8), the contents of the freezer tube (serum), and date.
    - Freeze and store at -80° C.
    - Ship on dry ice to Dr. Ferris's lab at the address specified below (for baseline blood draw, ship with the lavender top tube, detailed below). Enclose the blood collection form with the shipment.

Blood Collection Procedure, Lavender Tube (DNA for SNP Analysis)

- At the baseline blood draw only, one lavender top tube will be collected. It will be collected first, prior to collecting green and red top tubes. An additional (3rd) blood collection form will be used for the lavender top tube.
- Approximate blood volume to be collected is 5 ml.
- Divide the lavender tube contents into four 1-1.5 ml aliquots (in 1.8 ml freezing tubes). Information to be encoded on each freezing vial includes the clinical trial study number, the subject's unique ID number, the tube # (1-4), the contents of the freezer tube (whole blood EDTA), and date.
- Freeze at -80°C.
- Ship on dry ice to Dr. Ferris's lab at the address specified below (ship with the baseline red top tube, detailed above). Enclose the blood collection form with the shipment.

Carly Reeder Room 2.19 - Ferris lab
Hillman Cancer Center
5117 Centre Ave
Pittsburgh, PA 15213
Phone: 412-623-7738

14.4 ORAL RINSE AND STOOL FOR MICROBIOME ANALYSIS

Oral rinse will be collected at the following time points for both arms on the study, to coincide with blood drawing time points:

1. Cycle 1 Day 1 of study therapy prior to infusion of the study therapy
2. Cycle 3 Day 1 of study therapy prior to infusion of the study therapy
3. At the next visit after progression of disease is confirmed (if applicable)

For oral rinse, the patient should pour approximately 10cc of saline into his/her mouth and vigorously swish it against the cheeks for 10 seconds and deliver the solution with a sterile beverage straw into a labeled 15cc polypropylene test tube. Ship the day of collection at ambient temperature overnight.

Coordinator and subject to wear gloves. Saline to be given in a sterile specimen cup and then that cup discarded.

- Have participant ACTIVELY gargle 10ml of sterile saline for 60 seconds.
- Ask participant to swish the saline in the mouth for 5 more seconds and spit oral wash into a new sterile specimen cup.
- Cap the specimen cup and place sample on ice.
- Using moderate pressure, rapidly scrape the tongue 6 times to accumulate a buildup of debris on the sterile, disposable tongue scraper.
- Swirl the tongue scraper in the conical with PBS. Discard tongue scraper.
- Store on ice until transferred to lab for processing.

14.5 FUTURE BIOMEDICAL RESEARCH

With patient consent, the UPMC Hillman Cancer Center will conduct future biomedical research on blood and tumor tissue specimens collected during this clinical trial. This research may include but is not limited to genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the

measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial). The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

15.0 STATISTICAL METHODS

15.1. Assignment to treatment

Participants will be assigned to Nivolumab plus Ipilimumab (aCTLA4) if CTLA4-LAG3>15.2, to Nivolumab+Relatlimab (aLAG3) it CTLA4-LAG3<-15.2, and randomized to aLAG3 or aCTLA4 if |CTLA4-LAG3|<15.2. The value 15.2 was determined from an estimate of 9.2 of the intra-patient standard deviation derived from samples from 16 HNSCC patients, each replicated 6 times (Figure 3).

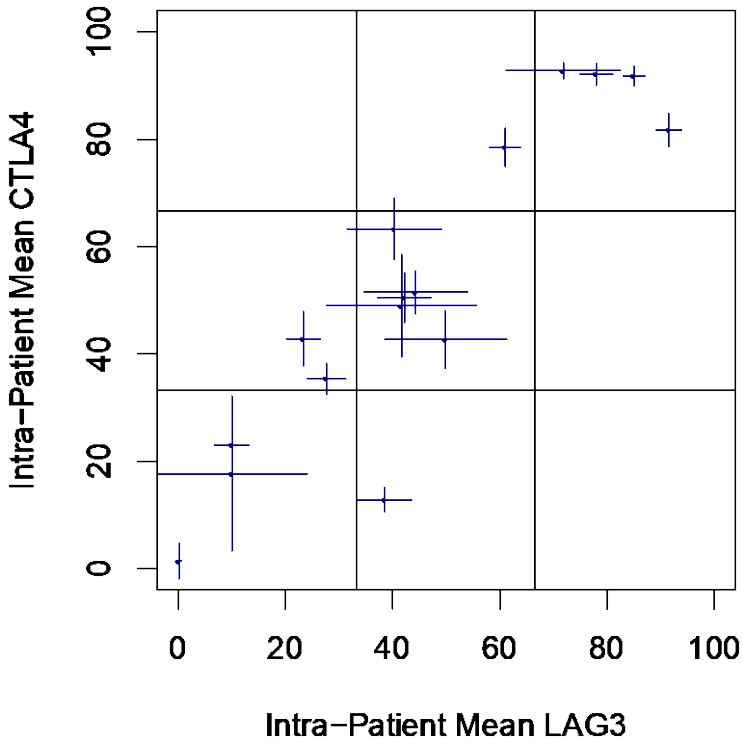


Figure 3. Intra-patient means; lines represent one intra-patient standard deviation (in each direction) from intra-patient mean.

If the values of CTLA4-LAG3 have a Gaussian (normal) distribution and the true value of CTLA4-LAG3 equals 0 for a given sample, then the assayed (observable) values from that sample would have a Gaussian distribution with a mean of 0 and a standard deviation of 9.2, in which case 90% of the assayed values would lie between -1.65×9.2=-15.2 and 1.65×9.2=15.2. If the rule "assume any value of CTLA4-LAG3 between -15.2 and 15.2 (i.e., d=15.2) is truly zero (and hence, the patient should be randomized)" is used, then a 100-90=10% false positive rate (the false negative rate depends on the true value of CTLA4-LAG3). The rule is:

If |CTLA4-LAG3|≤15.2, randomize 1:1 to aLAG3 or aCTLA4.
If CTLA4-LAG3>15.2, assign to aCTLA4.
If CTLA4-LAG3<-15.2, assign to aLAG3

To assess the operating characteristics of this rule, the effect of different probabilities of false positives (5% to 20%) on the assignment to treatment was evaluated for the sixteen patient samples (average value of CTLA4-LAG3 was calculated over all six replicates for each patient)(Table 7).

				Assigned Treatment			
Order_ID	CTLA4	LAG3	CTLA4-LAG3	11.8 (20%)	13.2 (15%)	**15.2 (10%)**	18.0 (5%)
142	81.8	91.5	-9.7	Randomize	Randomize	Randomize	Randomize
359	42.7	49.8	-7.2	Randomize	Randomize	Randomize	Randomize
556	63.3	40.3	23.0	aCTLA4	aCTLA4	aCTLA4	aCTLA4
628	91.8	85.0	6.8	Randomize	Randomize	Randomize	Randomize
649	49.0	41.7	7.3	Randomize	Randomize	Randomize	Randomize
663	23.0	10.0	13.0	aCTLA4	Randomize	Randomize	Randomize
980	51.5	44.3	7.2	Randomize	Randomize	Randomize	Randomize
1149	17.7	10.0	7.7	Randomize	Randomize	Randomize	Randomize
1431	92.8	71.8	21.0	aCTLA4	aCTLA4	aCTLA4	aCTLA4
1685	35.3	27.7	7.7	Randomize	Randomize	Randomize	Randomize
1743	42.8	23.3	19.5	aCTLA4	aCTLA4	aCTLA4	aCTLA4
1851	12.8	38.5	-25.7	aLAG3	aLAG3	aLAG3	aLAG3
1870	50.5	42.2	8.3	Randomize	Randomize	Randomize	Randomize
2065	1.3	0.2	1.2	Randomize	Randomize	Randomize	Randomize
2102	78.5	61.0	17.5	aCTLA4	aCTLA4	aCTLA4	Randomize
2387	92.2	78.0	14.2	aCTLA4	aCTLA4	Randomize	Randomize

Table 7. Treatment assignment as a function of d. Percentages reflect false positive rate

It is seen that the assignment to treatment is robust with respect to changes in the value of d. No patient switched treatment assignment as d varied, although 3 patients moved from treatment assignment to randomization as d increased from 11.8 to 18.0. At d=15.2, 31.2% of patients were directly assigned to treatment. Applying this to samples from 46 different HNSCC patients (data not shown) 37% of patients would have treatment assigned.

15.2 STATISTICAL ANALYSIS PLAN

15.2.1 PRIMARY OBJECTIVE

Estimate the probability of objective response to therapy determined by gene expression of LAG3 and CTLA4 per OmniSeq Immune Report Card in R/M HNSCC patients who have progressed on prior immunotherapy. The parameter π in the analysis model (probability of response) will be estimated by means of Markov Chain Monte Carlo along with a 95% credible interval, P(π <0.1) and P(π >0.2), as follows:

For binary endpoints, let:

i index trial participant
j index OmniSeq Response Score (*j*=1,2 for unfavorable and favorable, respectively)
k index treatment (*k*=1,2 for anti-LAG3 and anti-CTLA4, respectively)
y_{ijk} be the observed objective response of the participant (y_{ijk}=0,1)

A hierarchical beta-binomial Bayesian model (Valen Johnson, personal communication) for response is employed to borrow information across response score and treatments. The model is defined:

y_{ijk} ~ Bernoulli(π_{jk})
π_{jk} ~ Beta(α_{jk},β_{jk})
$\alpha_{jk} \leftarrow \gamma_{jk} \times \pi$
$\beta_{jk} \leftarrow \gamma_{jk} \times (1-\pi)$
γ_{jk} ~ Gamma(*0.1,0.1*)I(*0.1,*)
π ~ Beta*(y,n-y)*

where I(0.1,) indicates that the γ_{jk} are constrained to be greater than 0.1, n is the current sample size, y is the current total number of observed objective responses over all strata and treatments (or 1, whichever is greater), π_{jk} is the probability of objective response for treatment k in response score category j and π is the overall probability of objective response. This formulation borrows information across the four strata defined by treatment and OmniSeq Response Score. T-cell inflamed phenotype (reported by the OmniSeq Response Score) will be an analysis factor, but not a stratification factor.

15.2.2 SECONDARY OBJECTIVE 1

Estimate the disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety of treatment determined by gene expression of LAG3 and CTLA4 per Omniseq Immune Report card for R/M HNSCC patients who have progressed on prior immunotherapy. The analysis of DCR is similar to that of objective response. PFS and OS will be analyzed by means of proportional hazards (Cox) regression models including treatment and OmniSeq response score as covariates. Safety, represented by serious adverse events at least possibly related to treatment, will be analyzed in a similar fashion to the primary endpoint, where each participant will be scored as experiencing or not experiencing at least one such events. All point estimates will be accompanied by 95% credible or confidence intervals. Adverse events will also be tabulated by type, grade and relatedness to treatment.

15.2.3 SECONDARY OBJECTIVE 2

Estimate the probability of objective response, DCR, PFS, OS and safety of treatment that is randomly assigned instead of determined by gene expression. This will be compared in an exploratory fashion to the objective response of those patients with treatment determined by gene expression. The probability of objective response and DCR will be estimated by logistic regression with treatment, OmniSeq response score and treatment assignment modality (randomized versus OmniSeq) as covariates. PFS and OS will be estimated by proportional hazards (Cox) models. All estimates of odds and hazard ratios will have 95% confidence intervals.

15.2.4 SECONDARY OBJECTIVE 3

Estimate the probability of objective response, DC, PFS, OS and safety of treatment determined by gene expression of LAG3 and CTLA4 per Omniseq Immune Report card for R/M HNSCC patients who have progressed on trial treatment and undergo a second biopsy and second treatment determined by a second gene expression analysis of LAG3 and CTLA4. The analysis is similar to those in the above aims. It is possible the numbers of participants in this category will not support these analyses, in which case descriptive statistics will be presented.

15.2.5 BIOMARKER STUDIES

15.2.5.1 IMMUNE EXPRESSION

Evaluate immune gene expression, immune co-signaling molecule expression by IHC, and immune cell populations over time via paired samples after exposure to combination immunotherapy. Linear mixed models will be used to characterize the changes in LAG3 and CTLA4 over time, in addition to other markers of interest.

15.2.5.2 CO-SIGNALING MOLECULE AND GENE EXPRESSION

Evaluate co-signaling molecule expression by IHC and correlate with gene expression by RNA-Seq as well as the predictive value of co-signaling molecule expression by IHC and the efficacy of the combination selected. The analysis plan is the same as for immune expression.

15.2.5.3 PERIPHERAL BLOOD ANALYSIS

Evaluate immune cell populations and other potential biomarkers (as per section 14.0) in the peripheral blood at baseline and over time. The analysis plan is the same as for immune expression.

15.2.5.4 MICROBIOME ANALYSIS

Evaluate oral and stool microbiome and correlate the baseline distribution and the change over time with efficacy. The analysis plan is the same as for immune expression.

15.3 MONITORING RULES

15.3.1 MONITORING RULE FOR LACK OF EFFICACY

Pausing rule: The parameters in the above model will be estimated by means of Markov Chain Monte Carlo after every ten patients. If, at any of these analyses,

$$Pr(Pr[\pi|\text{Data and Prior}]<0.10)>0.75,$$

Accrual to the trial will be paused and the protocol potentially amended. This is summarized in Table 8.

# Patients	Pause if #OR ≤
10	·
20	1
30	2

Table 8. Pausing Rule in terms of number of objective responses

15.3.2 MONITORING RULE FOR EXCESS TOXICITY

Pausing rule: Adverse events sufficient to warrant discontinuation of treatment (Section 12.3) will be monitored in a similar fashion. If, where π indicates the probability of the specified adverse events, at any of these analyses,

$$Pr(Pr[\pi|\text{Data and Prior}]>0.20)>0.75,$$

Accrual to the trial will be paused and the protocol potentially amended. This is summarized in Table 9.

# Patients	Pause if #Tox≥
10	3
20	5
30	7

Table 9. Pausing Rule in terms of number of patients with adverse events sufficient to warrant discontinuation of their treatment

15.4 JUSTIFICATION OF DESIGN

This trial uses a Bayesian design and fixes the sample size at 40. It is assumed that under standard of care, the probability of objective response in this patient population is ≤0.10. The combination of nivolumab plus the appropriate inhibitor will be of interest if the proportion of patients experiencing objective response increases to 0.20 or more.

To characterize the operating characteristics of the proposed trials, three sets of simulations were run. One hundred trials were simulated in each set, including evaluation of the pausing rule every 10 patients. In all simulations, it was assumed that an average of 43% of patients would exhibit the favorable OmniSeq response score (as in Morrison, et al), but the actual number was allowed to vary per simulated trial. It was also assumed that on average, half of the patients would have increased LAG3 expression, compared to CTLA4. The assumed probabilities of objective response for the four patient categories are displayed in Table 10.

	Unfavorable Response Score		Favorable Response Score		
Simulation	Anti-CTLA4	Anti-LAG3	Anti-CTLA4	Anti-LAG3	All
1	0.10	0.10	0.30	0.30	0.186
2	0.10	0.10	0.10	0.10	0.100
3	0.20	0.20	0.30	0.30	0.243

Table 10. Assumed probabilities of objective response in the simulations.

In the first simulation set, it was assumed that patients have the unfavorable response score would have a probability of objective response of 0.10 and patients in the favorable response score category would have a probability of objective response of 0.30. In the second set of simulations, it was assumed the probability of objective response in both inflammatory categories was unacceptably low, 0.10. The third simulation assumed higher probabilities of objective response.

In Table 10, it is seen that 11% of trials in Simulation 1 and 5% in Simulation 3, where it is desirable the trials all 40 patients, stop early, while 66% of trials in Simulation 2, where early stopping is desirable, stop early.

	Stopped Early at n=			
Simulation	10	20	30	40
1	0	0.1	0.01	0.89
2	0	0.56	0.1	0.34
3	0	0.04	0.01	0.95

Table 11. Proportions of trials stopping at n=10, 20 or 30 or accruing all 40 patients.

The estimates of π in Tables 11 and 12 agree reasonably well with the true overall probability of objective response in Table. Some variation is due to variability in the numbers of patients with a favorable response score, which had an average of 43%, but was allowed to vary from trial to trial.

Simulation	Median estimated P(OR)	Median 95% Credible Interval
1	0.192	(0.090,0.318)
2	0.095	(0.028,0.195)
3	0.244	(0.129,0.379)

Table 12. Observed estimates of π (probability of objective response overall) in trials accruing 40 patients. Note that these will tend to be biased upwards from the true values in Table 7, which is expected.

Simulation	Median estimated P(OR)	Median 95% Credible Interval
1	0.174	(0.077,0.295)
2	0.045	(0.001,0.159)
3	0.224	(0.116,0.355)

Table 13. Observed estimates of π (probability of objective response overall) at end of trial.

The estimates of π_{jk} and 95% in Tables 13 and 14 are biased slightly upwards when the probability of response in the unfavorable response score is 0.10, but overall these estimates are as expected, given that the numbers in some categories can be quite low.

	Unfavorable Response Score		Favorable Response Score	
Simulation	Anti-CTLA4	Anti-LAG3	Anti-CTLA4	Anti-LAG3
1	0.147 (0.021,0.359)	0.148 (0.020,0.362)	0.293 (0.087,0.593)	0.305 (0.091,0.617)
2	0.114 (0.015,0.304)	0.122 (0.015,0.337)	0.154 (0.023,0.402)	0.198 (0.041,0.480)
3	0.226 (0.062,0.478)	0.240 (0.067,0.489)	0.299 (0.078,0.615)	0.318 (0.089,0.618)

Table 14. Median estimates of π_{jk} and 95% credible intervals in trials accruing 40 patients. Note that these will tend to be biased upwards from the true values in Table 2, which is expected.

	Unfavorable Response Score		Favorable Response Score	
Simulation	Anti-CTLA4	Anti-LAG3	Anti-CTLA4	Anti-LAG3
1	0.145 (0.020,0.358)	0.142 (0.020,0.364)	0.276 (0.069,0.586)	0.302 (0.079,0.615)
2	0.106 (0.003,0.346)	0.106 (0.003,0.369)	0.145 (0.004,0.446)	0.143 (0.004,0.448)
3	0.226 (0.062,0.478)	0.240 (0.066,0.489)	0.299 (0.078,0.615)	0.318 (0.088,0.618)

Table 15. Median estimates of π_{jk} and 95% credible intervals at end of trial.

16.0 STUDY MANAGEMENT, AGREEMENT AND ETHICAL CONSIDERATIONS

16.1 STUDY MANAGEMENT

If a protocol amendment requires a change to the Written Informed Consent Form the participating IRB must be notified. The sponsor is responsible for the distribution of these documents to the participating IRB and study staff.

16.2 STUDY AGREEMENT

The Sponsor-Investigator must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. The Sponsor-Investigator reserves the right to conduct interim analyses during the study

16.3 ETHICAL CONSIDERATIONS

16.3.1 ETHICS REVIEW

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB.

The Sponsor-Investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require. The Sponsor- Investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product.

16.3.2 ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice, and applicable regulatory requirements.

17.0 REFERENCES

1. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016;375(19):1856-67.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians. 2011;61(2):69-90.
3. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. The New England journal of medicine. 2010;363(1):24-35.
4. Zandberg DP, Bhargava R, Badin S, Cullen KJ. The role of human papillomavirus in nongenital cancers. CA: a cancer journal for clinicians. 2013;63(1):57-81.
5. Rischin D, Young RJ, Fisher R, Fox SB, Le QT, Peters LJ, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(27):4142-8.
6. Posner MR, Lorch JH, Goloubeva O, Tan M, Schumaker LM, Sarlis NJ, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2011;22(5):1071-7.
7. Ayers M, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, et al. IFN-gamma-related mRNA profile predicts clinical response to PD-1 blockade. J Clin Invest. 2017;127(8):2930-40.
8. Prat A, Navarro A, Pare L, Reguart N, Galvan P, Pascual T, et al. Immune-Related Gene Expression Profiling After PD-1 Blockade in Non-Small Cell Lung Carcinoma, Head and Neck Squamous Cell Carcinoma, and Melanoma. Cancer Res. 2017;77(13):3540-50.
9. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. 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):956-65.
10. Morrison C, Pabla S, Conroy JM, Nesline MK, Glenn ST, Dressman D, et al. Predicting response to checkpoint inhibitors in melanoma beyond PD-L1 and mutational burden. J Immunother Cancer. 2018;6(1):32.
11. Seiwert TY, Haddad R, Bauml J, Weiss J, Pfister D, Gupta S, et al. Biomarkers Predictive of Response to Pembrolizumab in head and neck cancer (HNSCC). Abstract LB-339 Presented at: American Association for Cancer Research Annual Meeting; April 14-18, 2018; Chicago. 2018.
12. Thommen DS, Schreiner J, Muller P, Herzig P, Roller A, Belousov A, et al. Progression of Lung Cancer Is Associated with Increased Dysfunction of T Cells Defined by Coexpression of Multiple Inhibitory Receptors. Cancer Immunol Res. 2015;3(12):1344-55.
13. Koyama S, Akbay EA, Li YY, Herter-Sprie GS, Buczkowski KA, Richards WG, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat Commun. 2016;7:10501.
14. Woo SR, Turnis ME, Goldberg MV, Bankoti J, Selby M, Nirschl CJ, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res. 2012;72(4):917-27.
15. Triebel F, Jitsukawa S, Baixeras E, Roman-Roman S, Genevee C, Viegas-Pequignot E, et al. LAG-3, a novel lymphocyte activation gene closely related to CD4. J Exp Med. 1990;171(5):1393-405.
16. Huard B, Prigent P, Tournier M, Bruniquel D, Triebel F. CD4/major histocompatibility complex class II interaction analyzed with CD4- and lymphocyte activation gene-3 (LAG-3)-Ig fusion proteins. Eur J Immunol. 1995;25(9):2718-21.
17. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell costimulation. Annu Rev Immunol. 1996;14:233-58.
18. Sakaguchi S, Ono M, Setoguchi R, Yagi H, Hori S, Fehervari Z, et al. Foxp3+ CD25+ CD4+ natural regulatory T cells in dominant self-tolerance and autoimmune disease. Immunol Rev. 2006;212:8-27.
19. Simpson TR, Li F, Montalvo-Ortiz W, Sepulveda MA, Bergerhoff K, Arce F, et al. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. J Exp Med. 2013;210(9):1695-710.
20. Selby MJ, Engelhardt JJ, Quigley M, Henning KA, Chen T, Srinivasan M, et al. Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer Immunol Res. 2013;1(1):32-42.
21. Liakou CI, Kamat A, Tang DN, Chen H, Sun J, Troncoso P, et al. CTLA-4 blockade increases IFNgamma-producing CD4+ICOShi cells to shift the ratio of effector to regulatory T cells in cancer patients. Proc Natl Acad Sci U S A. 2008;105(39):14987-92.

22. Romano E, Kusio-Kobialka M, Foukas PG, Baumgaertner P, Meyer C, Ballabeni P, et al. Ipilimumab-dependent cell-mediated cytotoxicity of regulatory T cells ex vivo by nonclassical monocytes in melanoma patients. Proc Natl Acad Sci U S A. 2015;112(19):6140-5.
23. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.
24. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574(1-3):37-41.
25. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol. 2004;173(2):945-54.
26. Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol. 2001;2(3):261-8.
27. Dong H, Chen L. B7-H1 pathway and its role in the evasion of tumor immunity. J Mol Med (Berl). 2003;81(5):281-7.
28. Azuma T, Yao S, Zhu G, Flies AS, Flies SJ, Chen L. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood. 2008;111(7):3635-43.
29. Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. Clin Cancer Res. 2004;10(15):5094-100.
30. Iwai Y, Ishida 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 U S A. 2002;99(19):12293-7.
31. Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. Int Immunol. 2005;17(2):133-44.
32. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002;8(8):793-800.
33. Goding SR, Wilson KA, Xie Y, Harris KM, Baxi A, Akpinarli A, et al. Restoring immune function of tumor-specific CD4+ T cells during recurrence of melanoma. J Immunol. 2013;190(9):4899-909.
34. Okazaki T, Okazaki IM, Wang J, Sugiura D, Nakaki F, Yoshida T, et al. PD-1 and LAG-3 inhibitory co-receptors act synergistically to prevent autoimmunity in mice. J Exp Med. 2011;208(2):395-407.
35. Giraldo NA, Becht E, Pages F, Skliris G, Verkarre V, Vano Y, et al. Orchestration and Prognostic Significance of Immune Checkpoints in the Microenvironment of Primary and Metastatic Renal Cell Cancer. Clin Cancer Res. 2015;21(13):3031-40.
36. Sittig SP, Kollgaard T, Gronbaek K, Idorn M, Hennenlotter J, Stenzl A, et al. Clonal expansion of renal cell carcinoma-infiltrating T lymphocytes. Oncoimmunology. 2013;2(9):e26014.
37. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492-502.
38. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-30.
39. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(2):123-35.
40. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627-39.
41. Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015;16(3):257-65.
42. Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018;378(14):1277-90.
43. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(1):23-34.

18.0 APPENDICES

APPENDIX I: ECOG PERFORMANCE STATUS SCALE

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

APPENDIX II: TREATMENT OF IMMUNE RELATED REACTIONS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology 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.

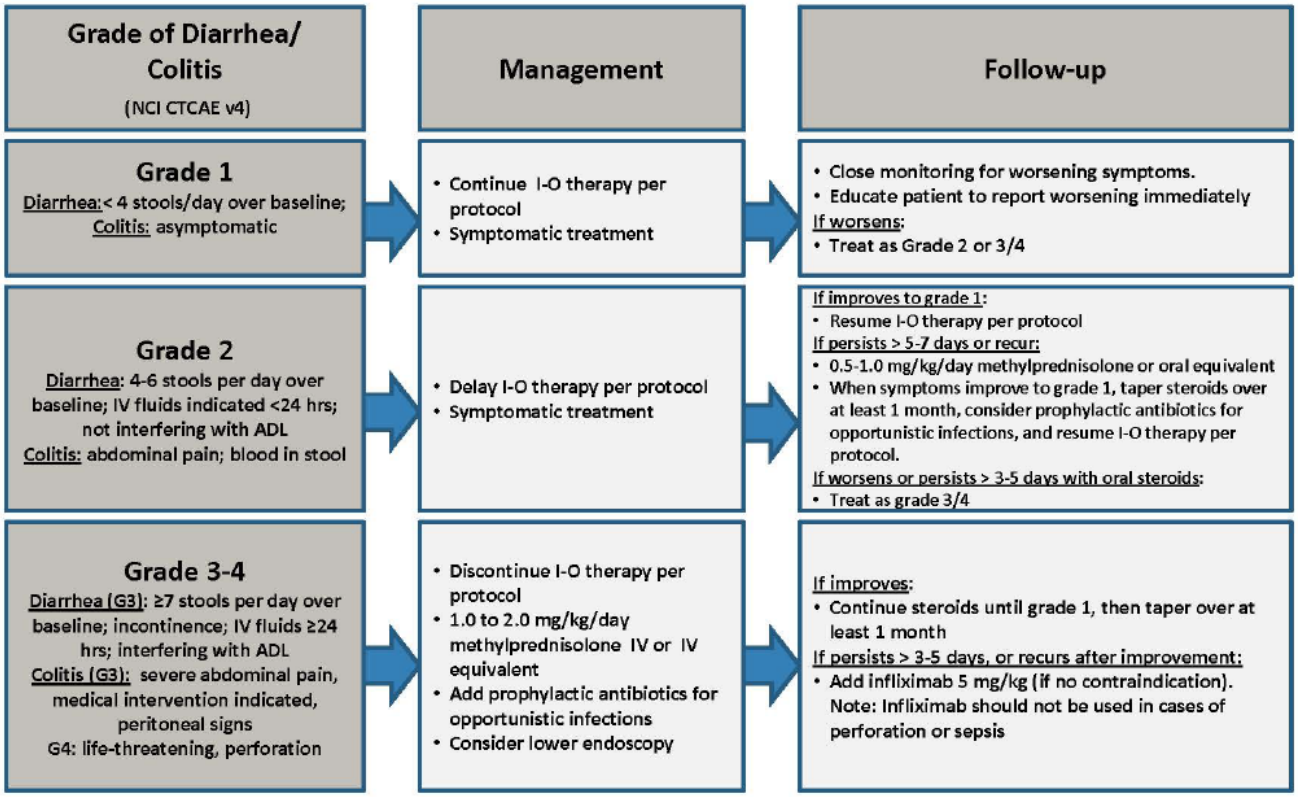
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the 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.

GI Adverse Event Management Algorithm

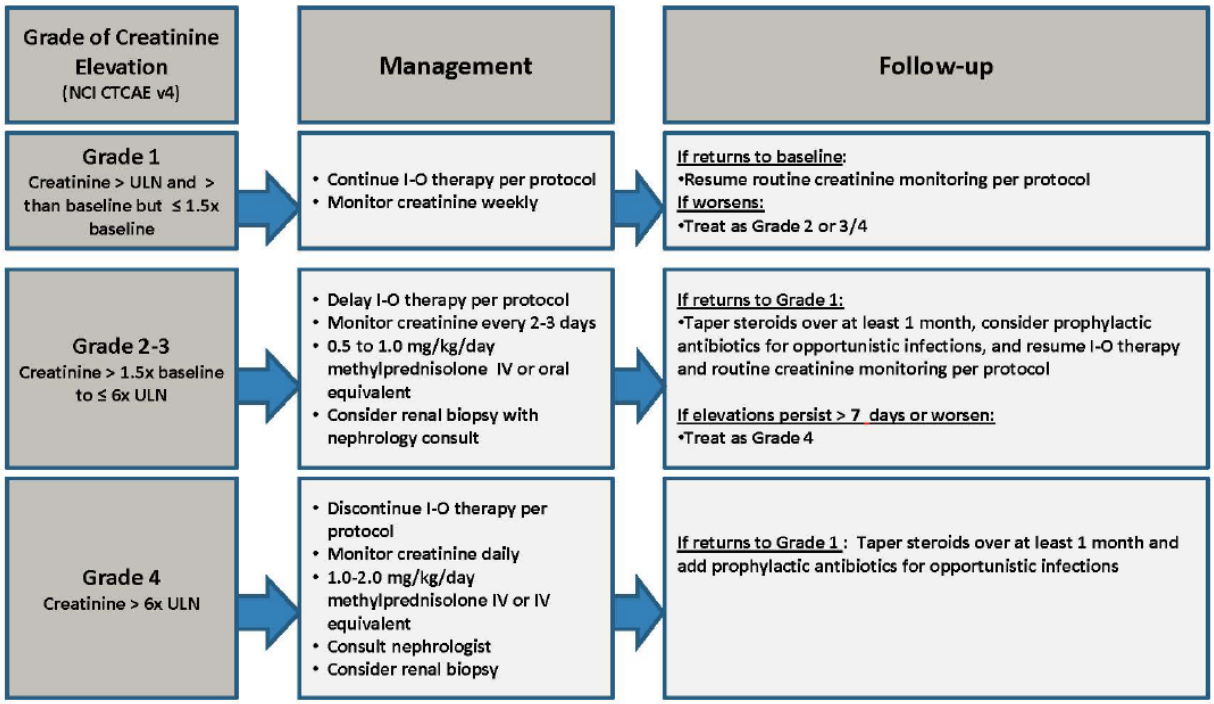
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

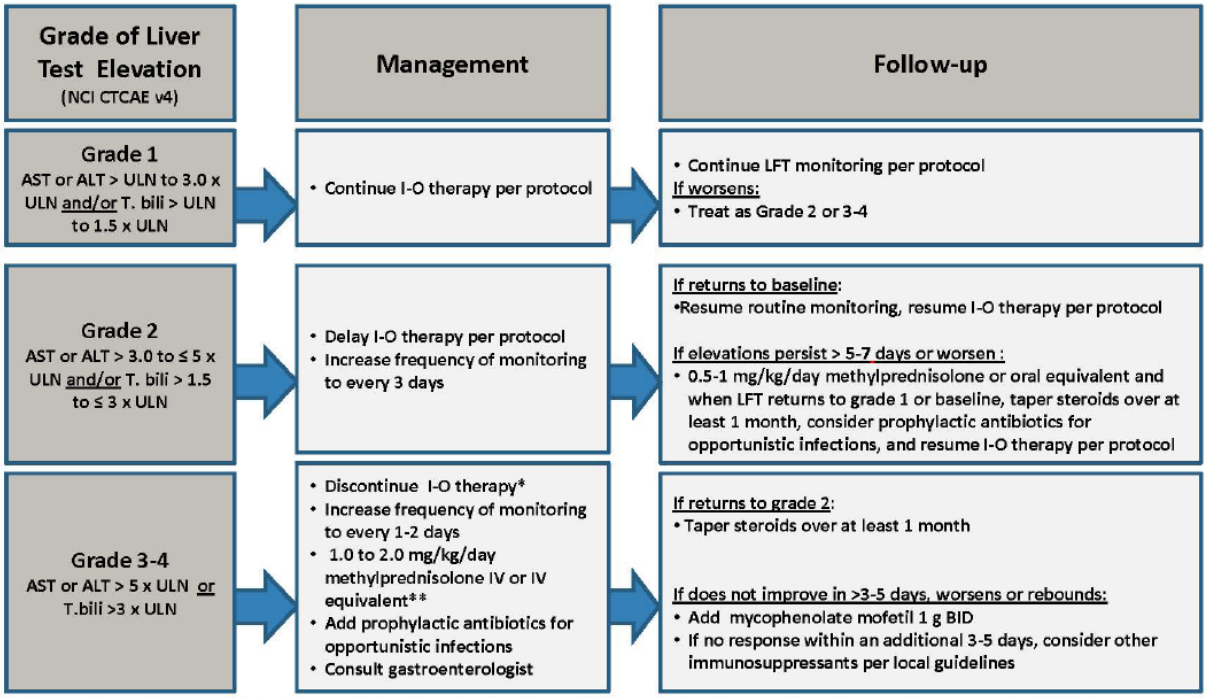
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Hepatic Adverse Event Management Algorithm

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



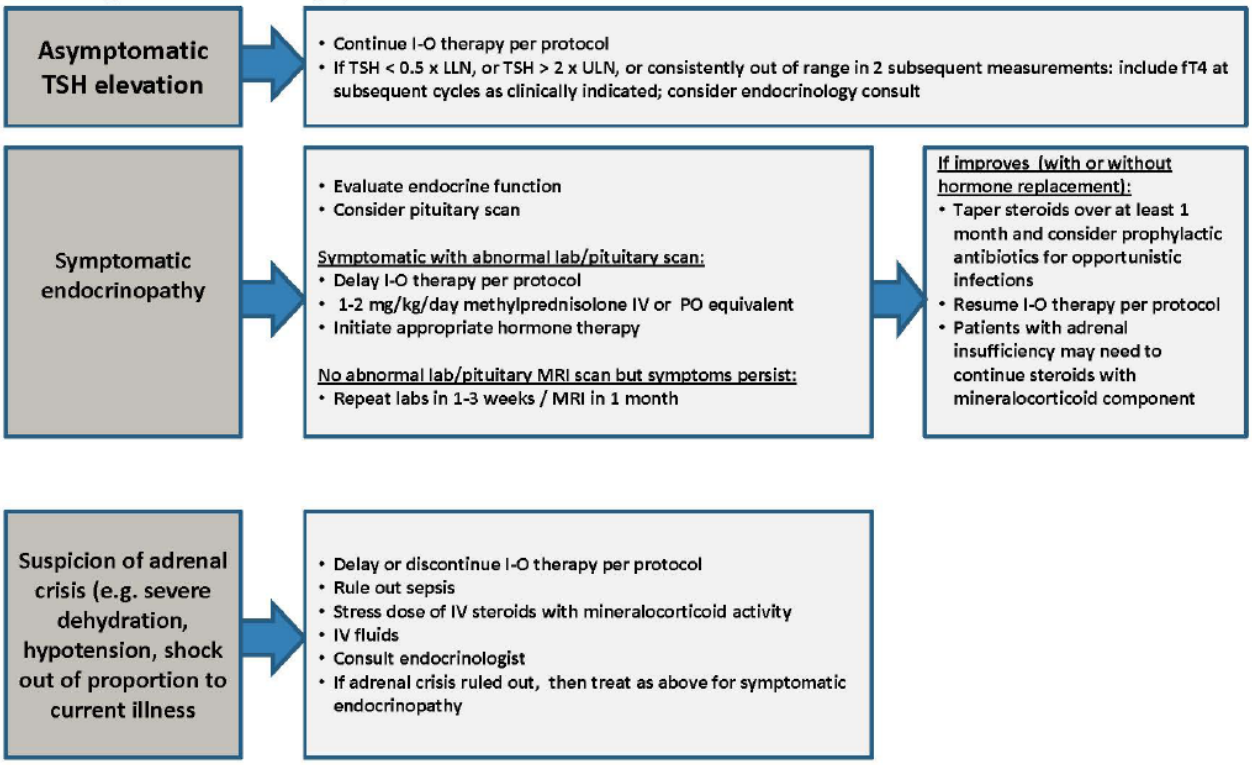
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

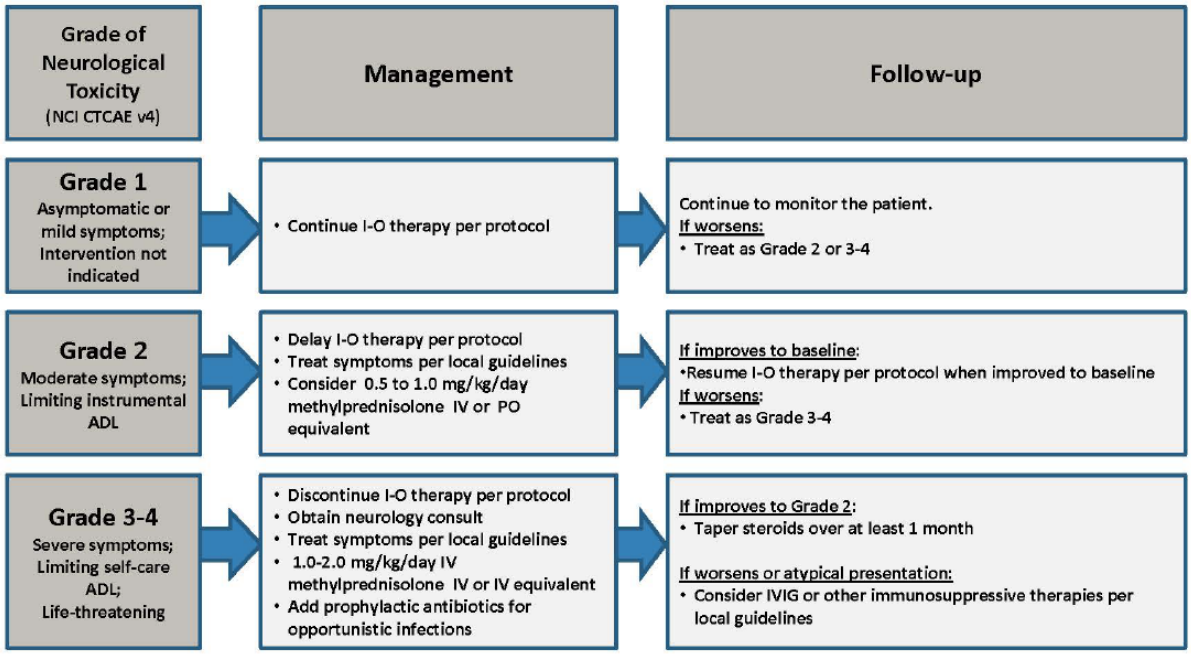
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Neurological Adverse Event Management Algorithm

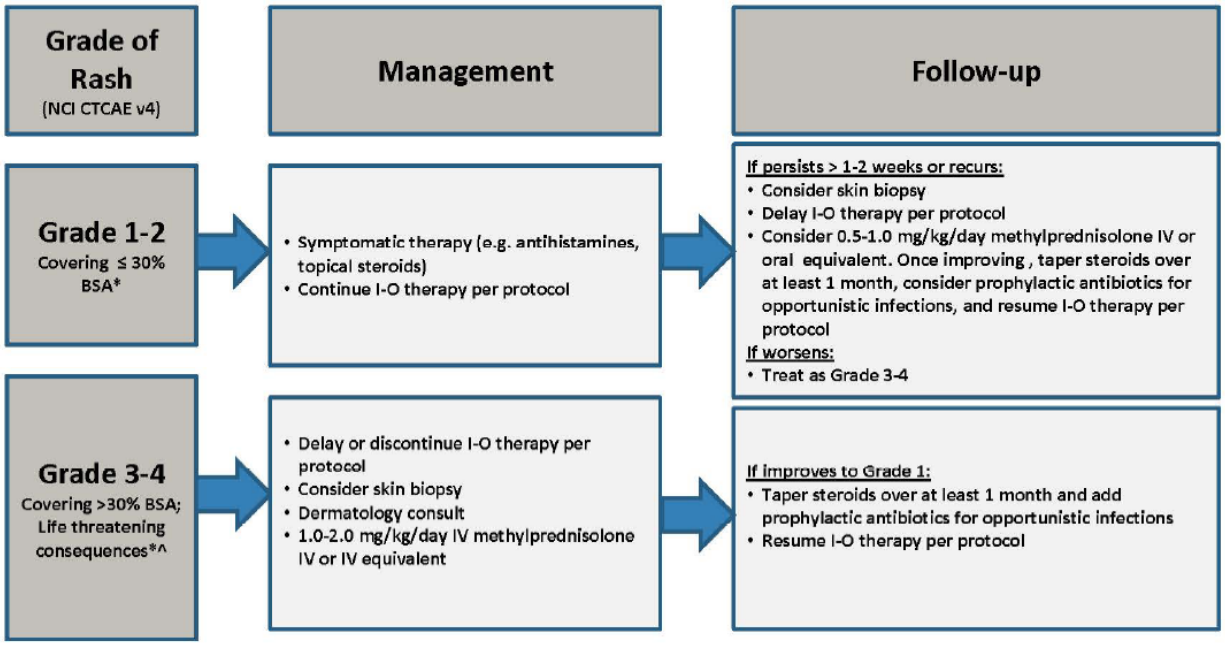
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Skin Adverse Event Management Algorithm

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



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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

MYOCARDITIS ADVERSE EVENT MANAGEMENT ALGORITHM

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

Event	Management	Follow-up
Asymptomatic Troponin Elevation	• Delay I-O therapy • Repeat and monitor troponin • Consider cardiology consultation with diagnostic workup; ECG, echocardiogram, cardiac MRI per recommendation of cardiologist • Consider corticosteroids per treating physician	• Monitor troponin until recovery • Resume I-O therapy upon recovery

Grade 2 Myocarditis
Symptoms with mild to moderate activity or exertion
	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  ○ Troponin and BNP
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

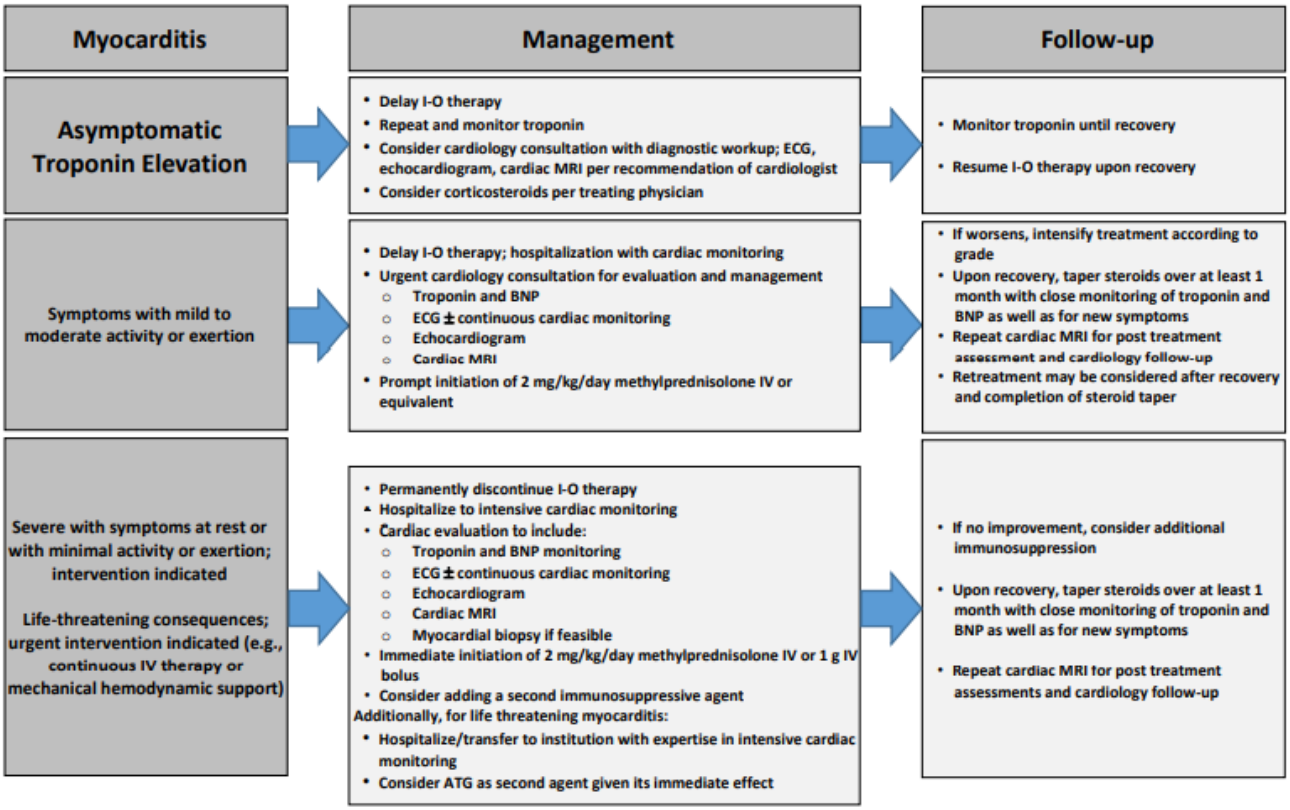
Grade 3-4 Myocarditis
Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac care unit with heart failure therapy as indicated
	• Cardiac evaluation to include:
	  ○ Troponin and BNP monitoring
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	  ○ Myocardial biopsy if feasible
	• Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	Additionally, for Grade 4:
	• Hospitalize/transfer to institution with expertise in cardiac transplant and/or cardiac complications of immunotherapy
	• Consider ATG as second agent given its immediate effect
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessments and cardiology follow-up

For the protocols under CTCAE version 4.0. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; I-O = immuno-oncology; IV = intravenous; MRI = magnetic resonance imaging

RELATLIMAB MYOCARDITIS ADVERSE EVENT MANAGEMENT ALGORITHM



For the protocols under CTCAE version 5.0. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging