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Title:	A Single Arm Phase 2 Study of Adjuvant Nivolumab after salvage resection in head and neck squamous cell carcinoma patients previously treated with definitive therapy
IND Number:	135562
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STUDY SYNOPSIS

Protocol Title: A Single Arm Phase 2 Study of Adjuvant Nivolumab after salvage resection in head and neck squamous cell carcinoma patients previously treated with definitive therapy.

Study Phase: II

Study Population: Subjects with head and neck squamous cell carcinoma (HNSCC) must have local recurrent disease after undergoing prior definitive therapy and be amenable to salvage resection.

Objectives:

Primary Objective and Hypothesis:

1. **Objective:** Evaluate the efficacy of an adjuvant treatment with Nivolumab in patients with resected HNSCC using disease-free survival (DFS) at 2-years.
    - **Hypothesis:** Using Nivolumab after salvage resection will increase DFS in patients with resected HNSCC.

Secondary Objectives and Hypotheses:

1. **Objective:** Determine the frequency of Grade 3 and 4 adverse events of Nivolumab when administered in patients after salvage resection of HNSCC.
    - **Hypothesis:** Single agent Nivolumab will be safe, and serious adverse events that occur will be managed without causing any interruption to Nivolumab administration.
2. **Objective:** Determine all grades of adverse events of Nivolumab when administered in patients after salvage resection of HNSCC.
    - **Hypothesis:** Single agent Nivolumab will be safe, and any grade adverse events that occur will be managed without causing any interruption to Nivolumab administration.
3. **Objective:** To estimate the 1-year DFS using Nivolumab in patients with resected HNSCC.
    - **Hypothesis:** Using Nivolumab after salvage resection will increase DFS in patients with resected HNSCC.

Exploratory Objectives:

1. **Objective:** Evaluate resected tumor specimens for CD4, CD8 and T reg ratios. The study will also determine PD-L1 expression on tumor and surrounding infiltrating cells along with KI-67 and granzyme expression in tumor tissue. This analysis will aim to provide a pre-PD1 inhibitor immunophenotype that can be assessed from tumor tissue to identify markers that determine relapse.

2. **Objective:** Study peripheral blood T cell response after anti-PD1 treatment by multi-

color flow cytometry to determine type of immune response on peripheral T cells.

3. **Objective:** Identify an inflammatory gene signature by RNA sequencing in tumor tissue that correlates with those who did not relapse versus those who did.

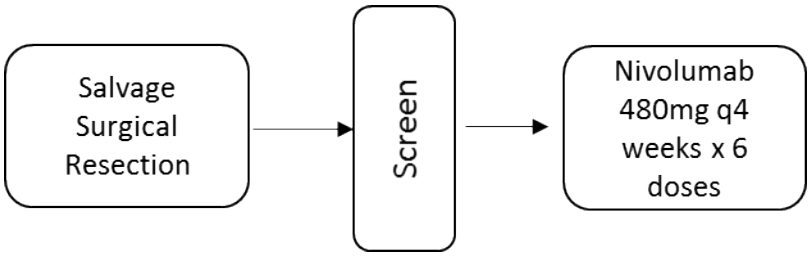
Study Design:

This study will be a 1-arm phase II trial including 39 patients with head and neck squamous cell carcinoma (HNSCC) eligible for salvage resection after definitive radiation +/- chemotherapy. Patients who undergo curative intent salvage resection will be screened and consented to receive Nivolumab following resection. Patients will receive Nivolumab every 4 weeks. Nivolumab will continue for 6 months (6 doses) as shown in schema.

For correlative studies, archived biopsy samples and/or resection tissue will be assessed by H&E and IHC for immune phenotype. Blood samples will also be collected for correlative studies.

Patients will be followed every 4 weeks during treatment, followed by a 30-day safety visit and then every 3 months thereafter for disease and survival status. Patients will be assessed for 1 and 2-year disease free survival (DFS) as well as for toxicity during treatment.

Trial Diagram:



Study Population:

For entry into the study, the following criteria MUST be met:

Key Inclusion Criteria:

- Histologically or cytologically confirmed head and neck squamous cell carcinoma (HNSCC).
- Prior definitive therapy with chemo-radiotherapy or radiation alone.
- Patients must have undergone salvage resection with curative intent.
- Adult subjects ≥ 18 years of age.
- Adequate bone marrow and organ function.
- ECOG Performance status ≤ 2.
- Must be able to understand and sign written informed consent.

Key Exclusion Criteria:

- Patients who did not receive radiotherapy as prior definitive treatment.
- Patients who continue to have gross measurable residual disease after salvage surgery.
- Patients who underwent salvage surgery for palliative purposes i.e. for symptom control.
- Uncontrolled intercurrent illness including, but not limited to, ongoing significant or serious active cardiovascular disease, liver disease, renal disease, infection, psychiatric illness or situations that would limit the patient's ability to participate.
- Patients attempting to conceive, and pregnant or nursing women are excluded from this study.
- Autoimmune disease or other pro-inflammatory conditions other than treated stable asthma or minor allergies (such as seasonal allergies).
- A second malignancy other than HNSCC in the last 3 years. Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin, or curatively treated cervical intraepithelial neoplasia (CIN) are acceptable and are not exclusionary.
- Patients with metastatic disease.
- Any patient requiring systemic corticosteroids or other immune modulatory medications.
- History of symptomatic interstitial lung disease.

Endpoints:

Primary Endpoint

1. Efficacy: measured from the time of treatment allocation to the time of discovery of the first evidence after initiation of investigational treatment of any tumor (local, regional, metastatic, or second primary) or death from any cause. DFS at 2-year will be the primary efficacy endpoint.

Secondary Endpoints

1. Safety: As determined by CTCAE v5.0 and ability to complete a minimum of six months of adjuvant Nivolumab treatment and an expected Grade 3 or 4 adverse event rate similar to Checkmate-141 trial.

2. Safety: As determined by CTCAE v5.0 and ability to complete a minimum of six months of adjuvant Nivolumab treatment and an expected all grade adverse event rate similar to Checkmate-141 trial.

3. Efficacy: DFS at 1-year will be the secondary efficacy endpoint.

Exploratory Endpoints

1. Identifying tumor immunophenotype in those who relapsed versus those who didn't and peripheral blood T cell changes before and after anti-PD1 therapy.

Study Drug:

Nivolumab will be available as an injection at 100mg/10 ml (10 mg/ml) or 40mg/4 ml (10mg/ml) and will be administered at a flat dose of 480 mg every 4 weeks.

Study Assessments:

The primary objective is to assess efficacy of Nivolumab in these patients who have been subjected to multiple modalities of treatment using DFS at 2-years. Each subject will be assessed to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Sample Size Justification:

We expect that the use of the Nivolumab-based adjuvant therapy will improve 2 year disease-free survival (DFS) by 20%. The optimal single-arm two-stage design with time-to-event endpoints will be used to test the null hypothesis that DFS at 2 years ≤ 33%, which is based on historic data, versus the alternative that DFS at 2 years ≥ 53%, by a one-sided, one-sample log-rank test with the power of 80% at a 5% significance level. After 17 patients are entered in the first stage, the trial will be temporarily suspended to new enrollment to allow for an interim statistical analysis. The trial will be terminated if the test statistic at stage 1 > 0.76.

If the trial goes on to the second stage, a total of 35 patients will be studied. We reject the null hypothesis if the test statistic at stage 2 > -1.62. Considering a drop-out rate of 10%, a total of 39 patients are expected to be required for this study.

Efficacy Analyses:

All patients who received ≥1 dose of Nivolumab will be assessed for efficacy and the primary and secondary endpoints for efficacy will be disease-free survival (DFS) at 2- and 1-year, respectively. DFS is defined as the duration from the time of treatment allocation to the time of discovery of the first evidence after initiation of investigational treatment of any tumor (local, regional, metastatic, or second primary) or death from any cause. The distribution of DFS will be summarized by Kaplan-Meier curve, and the median DFS and its associated 95% confidence interval (CI) will be calculated. The DFS at 1- and 2-years will also be summarized with its associated 95% CIs. In addition, patients will be censored at the end of the study (end of two years of follow-up of last patient enrolled), and both disease free survival (or DFS defined as no recurrence by the time of censoring) and overall survival (OS, defined as being alive by the time of censoring) will be assessed using Kaplan-Meier curves.

Safety Analyses:

The All-Patients-as-Treated (APaT) population will be employed for safety analyses. The secondary safety endpoints are the Grade 3 and 4 adverse events and the all adverse event graded from 1 to 5. Both safety secondary endpoints are dichotomous and will be summarized using frequency (in %). In addition, the 95% CI's will be calculated using the exact method, i.e. the binomial distribution method. We expect to reach 13% of Grade 3 and 4 adverse events and 58.9% of all Graded Adverse events, similar to those reported in the Checkmate 141 study.

Biomarker Assessments:

All biomarker measures will be summarized with descriptive statistics, i.e., percentages for categorical outcomes and means/medians for continuous outcomes, with corresponding standard errors and 95% confidence intervals. Responses will be tabulated by determined response and toxicities will be tabulated by type and grade. For IHC, the percentage of positive cells per area will be multiplied by the staining intensity for each tumor to determine quantitative expression pre- and post-treatment; a 25% change in expression will be considered a positive response. Patient level exploratory endpoints will be summarized using frequency (in %) if they are dichotomous or categorical and mean (std) if they are numerical respectively. Endpoints will be assessed of relations or associations using regression models, ANOVA models and logistical models respectively to accommodate numerical and categorical types of dependent and independent variables (i.e. endpoints).

Accrual Rate:

At the University of Cincinnati, we see approximately 300-350 new cases of HNSCC per year. Of those, approximately 100-150 stage III/IV HNSCC are treated with radiation +/- chemotherapy. Our institution conducted a retrospective analysis and identified twenty-eight patients over a 1-year period that were initially treated with definitive concurrent CRT or RT alone who subsequently developed local recurrence and required salvage resection. Based on this, we expect to accrue approximately 1-2 patients per month at UC. From the similar consideration to UC, we expect that the accrual rates would be 2 patients per month at Karmanos Cancer Institute. That will yield a combined 2-institution effective accrual rate of 3-4 patients per month. Thus we expect enrollment for this phase II study to be completed within 10-13 months based on 39 patients.

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1.0 BACKGROUND & RATIONALE

1.1 PRODUCT DEVELOPMENT BACKGROUND

1.1.1 MECHANISM OF ACTION AND RATIONALE FOR USE OF DRUG

Immunotherapeutic approaches for cancer treatment have existed for several decades. Recent advances in immunotherapeutics have recognized key regulatory pathways that are involved in the anti-tumor response. Multiple immune checkpoint molecules are up regulated during the immune response in an attempt to prevent autoimmune damage to normal tissue by maintenance of tolerance to self-antigens. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) as well as programmed death-1 (PD-1) and its ligands are key inhibitors of the anti-tumor response. CTLA-4 acts a dampener in lymph nodes preventing early activation of T cells whereas PD-1 is induced on T cells after activation by immune stimulation either by infection or tumor progression. Interestingly, the negative immune cell regulator, PD1 ligand-1 (PD-L1), has been found to be up regulated on many tumors including HNSCC.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

PD-1 (or CD279), a 55-kilodalton Type 1 transmembrane protein is a member of the CD28 family of T-cell co-stimulatory receptors that include immunoglobulin super family members CD28, CTLA-4, ICOS, and BTLA. PD-1 is highly expressed on activated T cells and B cells. PD-1 expression can also be detected on memory T-cell subsets with variable levels of expression. Two ligands specific for PD-1 have been identified: PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems. The interaction of PD-1 with its ligands, PD-L1 and PD-L2, which are expressed on antigen-presenting cells (APCs) and DCs, transmits negative regulatory stimuli to down-modulate the activated T-cell immune response. The absence or inhibition of PD-1 in murine models has resulted in the development of various autoimmune phenotypes and autoimmune diseases. Taken together, these results suggest that inhibition of PD-1 binding to its ligands has the potential to activate T-cell responses. Since these responses are variable and dependent upon various host genetic factors, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Tumors can express tumor-specific antigens as a result of mutational burden, and ongoing immune surveillance is believed to control the development of many tumors. Tumor progression may depend on the acquisition of mechanisms that permit them to evade an effective immune response.

One such mechanism of evasion may be the expression of ligands, which engage inhibitory receptor(s) on anti-tumor T-cells of many tumors. PD-L1 expression has been found on a number of tumors and may be a mechanism by which tumors can directly engage PD-1 to evade an effective anti-tumor immune response. Expression of IFN-γ by activated T cells is known to induce PD-L1 expression in tumors. PD-1 engagement on T-cells by PD-L1-positive APC or PD-L1-positive tumor cells in the tumor microenvironment may limit effective immune responses. Conversely, PD-L1 expression may be a positive prognostic factor as it may indicate infiltration of tumor-specific T cells that secrete IFN-gamma, which up regulates PD-L1 expression. Consistent with this hypothesis is the co-localization of lymphoid cell infiltrates and PD-L1 staining observed in human melanoma lesions.

Nivolumab (anti-PD-1 mAb) is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the programmed death-1 (PD-1) cell surface membrane receptor; a negative regulatory molecule expressed by activated T and B-lymphocytes. It has been approved in the metastatic setting for lung cancer, renal cell cancer, melanoma, and most recently in metastatic HNSCC. This is based on the Checkmate-141 phase III clinical trial, in which 361 patients with platinum-refractory, recurrent or metastatic squamous cell carcinoma of the head and neck were randomly assigned to either Nivolumab (3 mg/kg every two weeks) or a single-agent investigator's choice of therapy (methotrexate, docetaxel, or cetuximab). [1] Overall survival (OS) was significantly improved in Nivolumab arm (7.5 vs. 5.1 months) and it was noted that OS increased with immunotherapy in patients with programed death ligand 1 (PD-L1) expression ≥1%. [1] Several studies are now ongoing to study PD-1 inhibitors in the upfront and adjuvant setting. However, no study yet exists to study the inhibitor in HNSCC patients who have undergone salvage resection.

1.2 ADJUVANT TREATMENT IN HEAD AND NECK CANCER

Head and neck squamous cell cancer (HNSCC) is the sixth most common cancer type worldwide and accounts for approximately 350,000 deaths per year.[2, 3] Approximately 30 to 40% of patients with HNSCC present with stage I or II (early stage) disease.[4] In general, these patients are treated with either primary surgery or definitive radiation therapy (RT). [4] However, patients who present with advanced stage disease (Stage III or IV) not only pose a treatment challenge but also have a higher risk of both local recurrence and distant metastasis. Combined modality approaches (surgery, RT, and/or chemotherapy) are generally required to optimize the chance for long-term disease control for patients with advanced stage disease. These combined modality approaches include primary surgery followed by postoperative RT or concurrent chemoradiotherapy (CRT), induction chemotherapy (the addition of chemotherapy prior to surgery and/or RT), concurrent CRT without surgery, or sequential therapy (induction chemotherapy followed by concurrent CRT) without surgery.

Despite advances in the treatment of localized HNSCC, 15 to 50% of patients will develop recurrent disease [5], which is further, complicated by lack of reliable salvage treatment options. Tissues of the head and neck such as skin, nerves, blood vessels, and spinal cord normally receive maximally tolerated radiation doses during the initial course of radiation therapy (RT), therefore, re-irradiation exposes these tissues to more toxicities and complications. This often leaves surgical salvage as the only potential curative intent treatment for recurrent head and neck cancer which confers local control rates of 33-50% and a long term overall survival of 20-40% suggesting that novel treatments are necessary in order to improve outcomes in these high risk patients. [6, 7]

In the primary adjuvant setting, two pivotal studies published in 2004 (Bernier et al., and Cooper et al.) demonstrated increased progression free and overall survival (Bernier et al) in patients with high-risk features who received adjuvant concurrent cisplatin and radiation albeit with higher toxicity over radiation alone. [8,9] However, in the salvage setting, there is no standard of care for patients who have high risk (extra capsular extension of lymph nodes and/or positive margins) or intermediate risk (perineural invasion, lymphovascular invasion, close margins and multiple lymph node involvement) features after resection. In addition patients have often already received maximum radiation dose and chemotherapy alone has not shown any benefit in these patients. Therefore, there is currently little evidence to recommend further adjuvant therapy even in setting of high or intermediate pathological features despite the fact that these patients are at high risk of metastasis.[7]

2.0 RATIONALE

2.1 RATIONALE FOR THE TRIAL AND SELECTED SUBJECT POPULATION

University of Cincinnati sees 300-350 new head and neck cancer patients each year. Our institution conducted a retrospective analysis and identified twenty-eight patients over a 1-year period that were initially treated with definitive concurrent CRT or RT alone who subsequently developed local recurrence and required salvage resection. Amongst the twenty-eight patients identified, seven patients developed a recurrence within 12 months and twelve patients died over the course of 2 year follow up which necessitates the need for additional active therapy. However, because these patients have already undergone multiple treatment modalities, it is important to study the efficacy and safety of this approach.

The known side effects of PD-1 inhibitors are unique from chemotherapy and radiation effects, and therefore we hypothesize that the addition of adjuvant Nivolumab to those patients who have undergone salvage resection is feasible and safe and will not result in excessive toxicity.

2.2 EFFICACY ENDPOINTS

Relapses are the most common cause of death in these patients. Therefore, our primary and secondary efficacy endpoints will be disease-free survival (DFS) at 2 and 1 years, respectively, which will reflect late and early relapse. DFS is defined as the duration from the time of treatment allocation to the time of discovery of the first evidence after treatment of any tumor (local, regional, metastatic, or second primary) or death from any cause.

2.3 SAFETY ENDPOINTS

Clinically, the addition of Nivolumab after salvage resection has not been explored. Nivolumab has already been approved in lung cancer, renal cell cancer and now head and neck cancer. Based on the current safety profile of Nivolumab alone we do not expect to observe any additional adverse effects and that this will therefore be a safe combination. Checkmate-141 reported a 13% Grade 3 and 4 adverse event rate [1] and we anticipate similar results from our trial.

2.4 BIOMARKER RESEARCH/ENDPOINTS RATIONALE

Multiple trials have demonstrated that PD-L1 expression on tumor can correlate with response but this does not appear to be a consistently predictive biomarker. The goal of this collateral study is to identify possible patterns in responders and non-responders. This will be done by (1) characterizing the type of tumor infiltrating lymphocytes (TIL) that are present at baseline (pre-drug) which include

CD4, CD8 and T reg cells as well as ratios (2) identifying an inflammatory gene signature from tumor tissue in patients that did not relapse versus those who did and (3) unique alterations of T cell phenotype and function pre-drug and after therapy.

3.0 ETHICAL CONSIDERATIONS

3.1 GOOD CLINICAL PRACTICE

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and the United States Code of Federal Regulations, Title 21, Part 50 (21 CFR 50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

3.2 INSTITUTIONAL REVIEW BOARD

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator should provide the IRB with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 INFORMED CONSENT

Investigators or properly delegated study personnel must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects, their legally acceptable representatives must be clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject will participate.

4.0 METHODOLOGY/INVESTIGATIONAL PLAN

4.1 DIAGNOSIS/CONDITION FOR ENTRY INTO THE TRIAL

Histologically or cytologically confirmed locally recurrent HNSCC including the oral cavity, larynx or pharynx (except nasopharynx).

4.2 SUBJECT INCLUSION CRITERIA

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.

3. Patients must have had prior definitive therapy with radiation (with or without prior surgical resection and/or chemotherapy) who have underwent salvage resection and have no other curable options.
4. Patients must undergo salvage resection with curative intent.
5. Pre-operative scans including neck imaging preferably PET/CT and CT neck w/contrast. Chest imaging (which would be included in PET/CT) must also be completed but can be performed pre- or post-operatively as long as before trial treatment. CT chest and CT neck w/contrast or MRI neck and chest would also be acceptable.
6. Be able to provide archived biopsy or resected tissue.
7. Have a performance status of ≤ 2 on the ECOG Performance Scale.
8. Demonstrate adequate organ function as defined in Table 1.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1, 000 /mcL
Platelets	≥75, 000 / mcL
Hemoglobin	≥8 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of clinical assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	Within upper limit of normal (ULN) **OR** ≥30 mL/min for subject with creatinine levels > institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[a]Creatinine clearance should be calculated per institutional standard.

9. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours 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.
10. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 5 months after the last dose of study. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
11. Male subjects who are sexually active with women of childbearing potential 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.

4.3 SUBJECT EXCLUSION CRITERIA

The subject must be excluded from participating in the trial if the subject:

1. Did not receive at least radiotherapy as prior definitive treatment.
2. Has gross measurable residual disease after surgery or underwent surgery for palliative purposes i.e. for symptom control.
3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Short bursts of steroids of 5-7 days (for COPD exacerbation or other similar indication) are allowed.
4. Has nasopharyngeal or sinonasal carcinoma.
5. Has confirmed distant metastatic disease. Metastatic disease in neck lymph nodes is considered local disease.
6. Has a known history of active TB (Bacillus Tuberculosis).
7. Hypersensitivity to Nivolumab or any of its excipients.
8. Has a known additional malignancy that was diagnosed within the last three years that is either progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
10. Has known history of, or any evidence of active, non-infectious pneumonitis.

11. Has an active serious infection requiring systemic (IV) therapy.
12. 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.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
16. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
17. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
18. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

4.4 WOMEN OF CHILDBEARING POTENTIAL

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over the age of 45 years in the absence of other biological or physiological causes.

4.4.1 HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence. *
  *Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

4.4.2 LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom. A male and female condom must not be used together.

WOCBP must not be pregnant or breastfeeding while they are receiving study treatment and up to 5 months from the last dose of Nivolumab. MOCBP must not impregnate a female while they are receiving the study treatment and up to 7 months after the last dose of Nivolumab.

4.5 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. 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.

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.9 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 100 days after the end of treatment). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up or the end of the study whichever occurs first. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.6 SUBJECT REPLACEMENT STRATEGY

Subjects will not be replaced. The power calculation allows for early study withdraw.

5.0 STUDY DRUG

5.1 INVESTIGATIONAL PRODUCT

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by BMS for all sites. Nivolumab will be available as an injection at 100 mg/10 ml (10 mg/ml) and will be given at a flat dose of 480 mg.

5.2 PACKAGING AND LABELING INFORMATION

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

5.3 CLINICAL SUPPLIES DISCLOSURE

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor Investigator and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

5.4 STORAGE AND HANDLING REQUIREMENTS

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

An authorized person at the trial site must record receipt and dispensing of trial medication.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

5.5 RETURNS AND RECONCILIATION

The investigator is responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. The sponsor will provide BMS with a copy of the drug destruction certificate at the end of the study.

5.6 TREATMENT OUTLINE

The treatment to be used in this trial is outlined below in Table 2

Table 2. Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Nivolumab	480 mg	Q4W	IV infusion	Day 1 of each 4 week cycle starting 4-11 weeks after surgery for 6 doses	Experimental

Treatment will be administered on an outpatient basis. Protocol treatment (pre-surgical Nivolumab dose) must begin only after eligibility criteria are confirmed by the UC PI (registration), see study flow for more specific timeframes.

5.6.1 NIVOLUMAB INJECTION GUIDELINES

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 0.22-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of Nivolumab injection may be provided in the clinical protocol or latest IB. Care must be

taken to assure sterility of the prepared solution, as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles. The latest IB contains specific instructions for the preparation of the Nivolumab infusion fluid and administration of infusion solution. Specific questions regarding preparation and administration may be referred to the sponsor for expertise on the topic.

5.6.2 COMPLIANCE CRITERIA

5.6.3 TIMING OF DOSE ADMINISTRATION

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Study Drug may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

5.6.4 CONCOMITANT MEDICATIONS/VACCINATIONS (ALLOWED & PROHIBITED)

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

5.6.4.1 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 the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of 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 and non-serious adverse events as defined in Section 8.

5.6.4.2 PROHIBITED CONCOMITANT MEDICATIONS

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

- Biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy
- Investigational agents other than Nivolumab

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids should be avoided if possible. Steroids are allowed as short bursts of 5-7 days if required for clinical indication (i.e. COPD) or to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The chronic use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

5.6.5 NIVOLUMAB DOSE MODIFICATION

Adverse events (both non-serious and serious) associated with Nivolumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Nivolumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Appendix 2 below.

Nivolumab administration should be delayed for the following:

- Any Grade $\geq$ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade $\geq$ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade $\geq$ 3 toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness, which, in the judgment of the investigator, warrants delaying the dose of study medication

5.6.5.1 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

Immuno-Oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events:

- Gastrointestinal
- Renal

- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological.

The algorithms recommended for utilization in this protocol are found in the Investigator Brochure and are included in Appendix 2 of this protocol.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in Appendix 2.

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

5.6.5.2 DOSE MODIFICATIONS FOR NIVOLUMAB

Dose reductions or dose escalations are not permitted.

5.6.5.3 CRITERIA TO RESUME NIVOLUMAB

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

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

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time-point per protocol. However, if the treatment is delayed past the next scheduled time-point per protocol, the next scheduled time-point will be delayed until dosing resumes. For example, if a dose is missed for 5 weeks, a subject can re-start immediately but if dosing is delayed 3 weeks, a subject will need to wait until the next scheduled dose at 4 weeks.

Treatment may be delayed for up to a maximum of 8 weeks from the last dose; if treatment is delayed > 8 weeks, the subject must be permanently discontinued from study therapy, except as

specified in Section 5.6.7.5. Please see also Appendix 2 (Management Algorithms) for guidance on appropriate management and follow-up of adverse events.

5.6.5.4 DOSE DISCONTINUATION OF NIVOLUMAB

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
            - AST or ALT > 8 x ULN
            - Total bilirubin > 5 x ULN
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Any dosing delay lasting > 8 weeks with the following exceptions:
    - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 8 weeks, the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
    - Dosing delays > 8 weeks that occur for non-drug-related reasons may be allowed if approved by the PI. Prior to re-initiating treatment in a subject with a dosing delay lasting > 8 weeks, the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness, which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued Nivolumab dosing.

5.6.6 MANAGEMENT OF INFUSION REACTIONS:

Since Nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to University of Cincinnati PI (coordinating center), as well as to the local PI and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 5.0) guidelines.

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 325 to 1000 mg at least 30 minutes before additional Nivolumab administrations.

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

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

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [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]). Grade 4: (life threatening; presser or ventilator support indicated).

Immediately discontinue infusion of Nivolumab. Begin an IV infusion of normal saline, and treat the

subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (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).

5.7 USE IN PREGNANCY

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the University of Cincinnati PI and BMS of this event and complete and forward a Pregnancy Surveillance Form to BMS within 24 hours and in accordance with SAE reporting procedures described in Section 8.

In most cases, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS and the University of Cincinnati PI, the pregnant subject may continue study drug, after a thorough discussion of benefits and risk with the subject.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and where applicable, offspring information must be reported on the Pregnancy Surveillance form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS and the University of Cincinnati PI. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

5.7.1 USE IN NURSING WOMEN

It is unknown whether Nivolumab 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

6.0 STUDY FLOW CHART

Trial Period	Screening	Treatment							Post-Treatment/Follow-up[q]
		1	2	3	4	5	6		
Scheduling Window (Days)	-28 to -1	0[(j)]	± 3	± 3	± 3	± 3	± 3	30 Days post-discon +/- 3[(l)]	Every 12 weeks +/- 4 weeks
Adjuvant Treatment (Week)		1	5	9	13	17	21		
Informed Consent	X								
Inclusion/ Exclusion Criteria[(R)]	X								
Demographics and Medical History[(m)]	X								
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	
Nivolumab Administration[(a)]		X	X	X	X	X	X		
Post-study anticancer therapy status								X	
Survival and Disease Status[(k)]									X
Review Adverse Events		X	X	X	X	X	X	X[(i)]	
Full Physical Examination	X							X	
Directed Physical Examination		X	X	X	X	X	X		X[(c)]
Vital Signs and Weight	X[(n)]	X	X	X	X	X	X	X	

Trial Period	Screening	Treatment							Post-Treatment/Follow-up[q]
		1	2	3	4	5	6		
Scheduling Window (Days)	-28 to -1	0[(j)]	± 3	± 3	± 3	± 3	± 3	30 Days post-discon +/- 3[(l)]	Every 12 weeks +/- 4 weeks
Adjuvant Treatment (Week)		1	5	9	13	17	21		
ECOG Performance Status[(b)]	X		X	X	X	X	X		
Pregnancy Test – Urine or Serum -HCG	X[(p)]								
CBC with Differential	X[(o)]	X[(o)]	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel[(d)]	X[(o)]	X[(o)]	X	X	X	X	X	X	
Urinalysis	X[(o)]	X[(o)]			X			X	
T3, FT4 and TSH	X[(o)]	X[(o)]			X			X	X[(h)]
PT/INR, PTT	X[(o)]								
Tumor Imaging[(e)]	X								X[(e)]
Archival Tissue Collection [(f)]	X							X [(f)]	
Correlative Studies Blood Collection [(g)]		X	X					X[(g)]	

a) Nivolumab will start 28-77 days after surgery. Start of cycle on Day 1 +/- 3 days.

b) ECOG to be done prior to treatment administration. For Day 1, must be done within 10 days but does not need to be repeated for Day 1 only.

c) Only required if assessing for disease recurrence.

d) Magnesium, Phosphorous, LDH, uric acid should also be checked as part of CMP labs.

e) PET/CT and CT neck with contrast preferred for screening. CT neck with contrast and CT chest or MRI neck and chest is also acceptable. Neck imaging must be completed pre-operatively but chest imaging may be pre or post-operatively. Follow-up tumor imaging will be at discretion of treating physician but is not required per protocol.

f) Archival Resected tissue will be collected from pathology and sectioned per procedure manual. If biopsy or resection is performed per SOC at recurrence, tissue will also be collected at that time for analysis.

g) On Day 1 and week 5, ensure correlative samples are collected prior to protocol treatment. A 3rd sample should be collected at the end of treatment visit. Correlatives will be placed in four 10ml lavender EDTA tubes.

h) Thyroid function labs can be checked at physician's discretion on post treatment follow up.

i) SAEs should be evaluated out to 100 days after drug discontinuation. All AEs should be followed until ≤ Grade 1 or new therapy has begun. All non-serious AEs must be followed continuously for at least 30 days.

j) Adjuvant treatment must be started 28-77 days after salvage surgery.

k) May be assessed by phone or clinic visit

l) Post discontinuation visit should occur at 30 days +/-3 days as above, or before new therapy begins, whichever occurs first.

m) Medical History from last 10 years should be included

n) Height also required only at screening

o) Labs must be collected within 10 days of first treatment and within 72 hours prior to subsequent treatments. Screening labs can be used for Day 1 as long as within window.

p) Must be collected within 72 hours of Day 1.

q) Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up or the end of the study whichever occurs first. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

r) Protocol treatment must begin only after eligibility criteria are confirmed by the UC PI (registration)

7.0 TRIAL PROCEDURES

7.1 TRIAL PROCEDURES

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

7.2 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.3 PRIOR AND CONCOMITANT MEDICATIONS REVIEW

7.3.1 PRIOR MEDICATIONS

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.3.2 CONCOMITANT MEDICATIONS

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs should be recorded as defined in Section 8.

7.4 DISEASE DETAILS AND TREATMENTS

7.4.1 DISEASE DETAILS

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.4.2 PRIOR TREATMENT DETAILS

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.4.3 SUBSEQUENT ANTI-CANCER THERAPY STATUS

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.4.4 ASSIGNMENT OF SCREENING/STUDY NUMBER

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to eligibility being confirmed. Protocol treatment must begin only after eligibility criteria are confirmed by the UC PI. Sites must provide notification of consent and evidence of eligibility to the UC PI. Each subject will be assigned only one screening

number. Screening numbers must not be re-used for different subjects. The University of Cincinnati will provide any sub-sites with instructions for the methods to be used in assigning screening information to potential subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit. The screening number will be their study number as well once they are allocated to treatment.

7.4.5 TRIAL COMPLIANCE

Interruptions from the protocol specified treatment plan for greater than 8 weeks' delay of Nivolumab doses require consultation between the investigator and the University of Cincinnati PI (if not the same) and written documentation of the collaborative decision on subject management.

The total volume of Nivolumab infused will be compared to the total volume prepared to determine compliance with each dose of Nivolumab administered. The preparing and administering Nivolumab should be completed per the latest IB. Treatment with standard therapies will be prepared and administered as per the approved product label.

7.5 CLINICAL PROCEDURES/ASSESSMENTS

7.5.1 ADVERSE EVENT (AE) MONITORING

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 8 for detailed information regarding the assessment and recording of AEs.

7.5.2 FULL PHYSICAL EXAM

The investigator or qualified designee will perform a full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Full physical exam requires assessment of major organ sites (Constitutional, Head and Neck, Cardiovascular, Pulmonary, Abdominal, Musculoskeletal, Lymph, Neurological, and Skin).

7.5.3 DIRECTED PHYSICAL EXAM

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.5.4 VITAL SIGNS

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.5.5 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCALE

The investigator or qualified designee will assess ECOG status (see Section 11 Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.5.6 TUMOR IMAGING AND ASSESSMENT OF DISEASE

Pre-operative imaging will be performed at each institution and only site investigators (PI or Sub-PIs) may determine the assessment of disease recurrence.

7.5.7 POST-TREATMENT ASSESSMENT IMAGING

Patients will be followed clinically for recurrence every three months. Imaging is not required unless there is suspicion of relapsed disease and is needed for assessment.

7.5.8 ASSESSMENT OF DISEASE

Patients will be assessed for recurrence every 3 months after completion of treatment as above. For patients felt to have a relapse at any time, a thorough ENT exam as well as a repeat biopsy is recommended to confirm relapsed disease. Follow-up imaging in 4-8 weeks is also acceptable if biopsy is not yet felt to be necessary or is non-diagnostic. Patients will be followed clinically every three months and any concern for relapsed disease or progression should trigger either imaging or biopsy for confirmation. Patients will be followed for relapse for a total of 2 years.

7.6 TUMOR TISSUE COLLECTION AND CORRELATIVE STUDIES BLOOD SAMPLING

Any subjects with oropharyngeal cancers must have documented HPV status (either by p16 or in situ hybridization).

Resected tissue, preferably a tissue block (at least 20, but prefer 30, FFPE slides and a tissue scroll if block not feasible) must be submitted and delivered to UCCI for analyses. If patient develops recurrence and undergoes standard of care biopsy or resection, the tissue will also be collected for analysis similar to above. Please see laboratory procedures manual for full details.

Blood samples will be collected at screening after resection and after first adjuvant dose of Nivolumab at week 5. A third collection will be collected at the 30 day post-discontinuation visit.

Detailed processing, shipping and handling will be provided in the laboratory procedures manual.

7.6.1 LABORATORY PROCEDURES/ASSESSMENTS

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.6.2 LABORATORY SAFETY EVALUATIONS (HEMATOLOGY, CHEMISTRY AND URINALYSIS)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 3.

Table 3. Laboratory Test

7.6.3 PHARMACODYNAMIC EVALUATIONS

Please refer to the Laboratory Manual for PBMC Procedures.

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	Total thriiodothyronine (T3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free tyroxine (T4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Prothrombin time PT/INR
Absolute Lymphocyte Count	Uric Acid		Partial Thromboplastin Time (PTT)
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Creatinine		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Blood Urea Nitrogen		
† Done on all women of child-bearing potential			

Immunohistochemistry/Immunofluorescence

Archived resected tissue and if available recurrent biopsy or surgical tissue will be sent to the University of Cincinnati pathology department for processing. FFPE sections will be used to analyze the immune cell phenotype (markers include CD4, CD8, T reg, PD-1, PD-L1, granzyme expression and KI-67).

RNA Sequencing for Inflammatory Gene Signature

FFPE tissue will also undergo RNA and/or whole exome sequencing to identify an inflammatory gene signature and possible genetic alterations in responders versus non-responders.

7.6.4 WITHDRAWAL/DISCONTINUATION

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in Section 8.

7.7 VISIT REQUIREMENTS

Visit requirements are outlined in Section 6.0 - Trial Flow Chart.

7.7.1 SCREENING

Potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in eligibility requirements. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.
Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.
- Any tumor imaging done pre-operatively, does not need to meet the 28 day pre-dose requirement for screening procedures

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria and they have not yet started treatment, however, re-screening tests will not be covered by study. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. Protocol treatment must begin only after eligibility criteria are confirmed by the UC PI.

7.7.2 TREATMENT PERIOD

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.7.3 POST-TREATMENT VISITS/SAFETY FOLLOW-UP VISIT

The mandatory 30 day Safety Follow-Up Visit should be conducted based on one of the following time points. The time point which occurs first must be used to determine the safety follow-up visit timing.

- Approximately 30 days after the last dose of trial treatment or
- Approximately 30 days post-discontinuation if this occurs prior to the planned end of treatment or
- Before the initiation of a new anti-cancer treatment.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 100 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.7.4 FOLLOW-UP VISITS

Patients will move into follow-up after completion of last dose of Nivolumab. They will continue follow-up every 12 weeks +/-4 weeks either by a doctor visit or by phone (if being seen by outside oncologist) for up to 2 years to monitor for relapse, or until time of withdrawal of consent, or death, whichever comes first. If patients develop a relapse, they will be followed for survival. Every effort should be made to confirm relapse if suspected.

7.7.5 SURVIVAL FOLLOW-UP

Once a subject experiences confirmed disease relapse/progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone or seen in clinic every 12 weeks +/- 4 weeks to assess for survival status until death, withdrawal of consent, or at the end of the study, whichever occurs first.

8.0 SAFETY AND REPORTING

8.1 DEFINITIONS OF SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS

8.1.1 ADVERSE EVENT

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. 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.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

8.1.2 SERIOUS ADVERSE EVENTS

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

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

Although pregnancy and potential drug-induced liver injury (DILI), are not always serious by regulatory definition, however, these events must be reported within the SAEs timeline.

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).

NOTE: (PI determines if this information regarding hospitalizations are considered SAEs and should be included in the protocol. This is supplemental information that is included in BMS-sponsored trials)

8.1.3 NON-SERIOUS ADVERSE EVENT

A ***non-serious adverse event*** is an AE not classified as serious.

Non-serious Adverse Events are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.

8.1.4 NON-SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The collection of non-serious AE information should begin upon the signing of informed consent. 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 30 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.

8.2 OVERDOSE

For purposes of this trial 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 as well as a deviation from protocol.

All reports of overdose with and without an adverse event must be reported within 24 hours to the University of Cincinnati PI and to BMS Global Pharmacovigilance (Attn: Worldwide.Safety@bms.com FAX: 609-818-3804)

8.3 PREGNANCY AND LACTATION

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 (e.g., dose tapering if necessary for participant).

The investigator must immediately notify the University of Cincinnati PI and BMS at Worldwide.Safety@bms.com of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

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 Pregnancy Surveillance Form [provided upon request from BMS].

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS and the University of Cincinnati PI. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Such events must be reported within 24 hours to the University of Cincinnati PI and within 24 hours to BMS Global Pharmacovigilance (Attn: Worldwide.Safety@bms.com FAX: 609-818-3804)

8.4 LAB ABNORMALITIES

All laboratory test results captured, as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

8.5 POTENTIAL DRUG INDUCED LIVER INJURY (DILI)

Potential drug induced liver injury is defined as:

1) AT (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.

Wherever possible, timely confirmation of initial liver related- laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

8.6 OTHER SAFETY CONSIDERATIONS

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays-, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

8.7 REPORTING ADVERSE EVENTS

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

If the BMS safety address is not included in the protocol document (e.g., multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the

BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.

A MedWatch or CIOMs SAE form may be used to report SAEs. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator. The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i.

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. The duration of SAE collection should be extended to:

- 100 days for Nivolumab

For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection

The Sponsor will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). 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 the study sponsor all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), 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 an expedited safety report (ESR).

Other important findings which may be reported by BMS as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

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

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

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

MedWatch SAE forms should be sent to the FDA at:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

An SAE report should be completed for any event where doubt exists regarding its seriousness.

For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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

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

8.8 EVALUATING ADVERSE EVENTS

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

8.9 ADVERSE EVENT COLLECTION AND REPORTING

Non-serious AEs and SAEs whether or not related to the BMS product associated to this study, pregnancies, AEs associated with maternal exposure, and pregnancy outcomes ascertained in the study must be reported individually in the time frames noted below. All AEs collected will also be reported in aggregate in the final study report.

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

8.9.1 SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

Following the subject's written consent to participate in the study, all SAEs, whether or not related to the BMS product associated with this study, must be collected, including those thought to be associated with protocol-specified procedures. SAEs must be recorded on the Solicited and Non-interventional Research AE/SAE Form and reported to BMS (or designee) within 24 hours/1 business day to comply with regulatory requirements. A form should be completed for any event where doubt exists regarding its status of seriousness. Although overdose and cancer are not always serious by regulatory definition, these events should be recorded on a form and reported to BMS within 24 hours/1 business day.

Investigators should report to the responsible regulatory authority as appropriate.

All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to Medwatch and BMS. Information for contacting BMS is as follows:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 1-609-818-3804

If only limited information is initially available, follow-up reports may be required.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

If it is discovered a patient is pregnant or may have been pregnant at the time of exposure to the BMS product associated with this study, the pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be recorded on a Pregnancy Surveillance Form and reported to BMS (or designee) within 24 hours/1 business day by confirmed fax or reported via electronic mail to Worldwide.Safety@BMS.com. If only limited information is initially available, follow-up reports may be required. The original BMS forms are to remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

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.

9.0 STATISTICAL ANALYSIS PLAN

9.1 EFFICACY ANALYSIS

All patients who received ≥1 dose of Nivolumab will be assessed of efficacy and the primary and secondary endpoints of efficacy will be disease-free survival (DFS) at 2- and 1-year, respectively. DFS is defined as the duration from the time of treatment allocation to the time of discovery of the first evidence after treatment of any tumor (local, regional, metastatic, or second primary) or death from any cause. The distribution of DFS will be summarized by Kaplan-Meier curve, and the median DFS and its associated 95% confidence interval (CI) will be calculated. The DFS at 1- and 2-years will be also summarized with its associated 95% CIs. In addition, patients will be censored at the end of the study, and both disease free survival (or DFS defined as no recurrence by the time of censoring) and overall survival (OS, defined as being alive by the time of censoring) will be assessed using Kaplan-Meier curves.

9.2 SAFETY ANALYSIS

The All-Patients-as-Treated (APaT) population will be employed for safety analyses. The secondary safety endpoints are the Grade 3 and 4 adverse event and the all adverse events graded from 1 to 5. Both secondary endpoints are dichotomous and will be summarized using frequency (in %). In addition, the 95% confidence intervals (CI's) will be calculated using the exact method, i.e. the binomial distribution method. We expect to reach 13% of Grade 3 and 4 adverse event and 58.9% of all Graded Adverse events, similar to those reported in the Checkmate 141 study.

9.3 SAMPLE SIZE

We expect that the use of the Nivolumab-based adjuvant therapy will improve 2 year disease-free survival (DFS) by 20%. The optimal single-arm two-stage design with time-to-event endpoints(Kwak & Jung, 2014) will be used to test the null hypothesis that DFS at 2 years ≤ 33%, which is based on the historic data, versus the alternative that DFS at 2 years ≥ 53%, by a one-sided, one-sample log-rank test with the power of 80% at a 5% significance level. After 17 patients are entered in the first stage, the trial will be terminated if the test statistic at stage 1 > 0.76. If the trial goes on to the second stage, a total of 39 patients will be studied. We reject the null hypothesis if the test statistic at stage 2 > -1.62. Considering a drop-out rate of 10%, a total of 39 patients are needed for this study.

9.4 ACCRUAL RATE

At the University of Cincinnati, we see approximately 300-350 new cases of HNSCC per year. Of those, approximately 100-150 stage III/IV HNSCC are treated with radiation +/- chemotherapy. Our institution conducted a retrospective analysis and identified twenty-eight patients over a 1-year period that were initially treated with definitive concurrent CRT or RT alone who subsequently developed local recurrence and required salvage resection. Based on this we expect to accrue approximately 1-2

patients per month at UC. From the similar consideration as UC, we expect that the accrual rates would be 2 patients per month at Karmanos Cancer Institute. That will yield a combined 2-institution effective accrual rate of 3-4 patients per month. Thus we expect enrollment for this phase II study to be completed within 10-13 months based on 39 patients.

9.5 STATISTICAL ANALYSIS PLAN FOR ENDPOINTS

9.5.1 EFFICACY ENDPOINTS

Primary and secondary endpoints of efficacy are 2-year and 1-year DFS, respectively. DFS will be defined as the duration from the time of treatment allocation to the time of discovery of the first evidence after treatment of any tumor (local, regional, metastatic, or second primary) or death from any cause.

9.5.2 SAFETY ENDPOINTS

The first secondary safety endpoint of study will be to determine if adjuvant Nivolumab for a minimum of 6 months has similar Grade 3 and 4 adverse event rates as the Checkmate -141 trial.

The second secondary safety endpoint of study will be to determine if adjuvant Nivolumab for a minimum of 6 months has similar all grade adverse event rates as the Checkmate-141 trial.
Both the primary and secondary adverse events will be summarized by frequency in % and its CI's will be calculated using a binomial distribution. The exact test or the binomial test will be used to test the proposed hypotheses specified in 9.3.

9.5.3 EXPLORATORY ENDPOINTS

Patient level exploratory endpoints will be summarized using frequency (in %) if they are dichotomous or categorical and mean (std) if they are numerical respectively. Endpoints will be assessed of relations or associations using regression models, ANOVA models and logistical models respectively to accommodate numerical and categorical types of dependent and independent variables (i.e. endpoints).

9.6 STATISTICAL METHODS

9.6.1 DISEASE FREE SURVIVAL

The distributions of DFS will be summarized using the Kaplan-Meier (KM) curves and the median DFS and its associated 95% CIs will be estimated. The DFSs at 1- and 2-year will be also summarized with its associated 95% CIs. In addition, KM curves will be used to assess DFS and OS of the patients. Median survival time and its associated 95% CI will be estimated from the KM curves.

9.6.2 SAFETY ANALYSIS

Descriptive statistics will be provided for safety endpoints. In particular, the dichotomous primary and secondary endpoints will be summarized using frequency (in %) with a 95% CI calculated using a binomial distribution. The binomial test (or the Exact test) will be used to test the hypothesis proposed in 9.3.

9.6.3 BIOMARKER ASSESSMENTS

All biomarker measures will be summarized with descriptive statistics, i.e., percentages for categorical outcomes and means/medians for continuous outcomes, with corresponding standard errors and 95% confidence intervals. Responses will be tabulated by determined response and toxicities will be tabulated by type and grade. For IHC, the percentage of positive cells per area will be multiplied by the staining intensity for each tumor to determine quantitative expression in pre treatment tissue and post-treatment if available. ; We will use descriptive statistics and graphical displays to evaluate change in plasma markers and flow cytometry markers between pre- and post-treatment.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 CONFIDENTIALITY

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.1 CONFIDENTIALITY OF SUBJECT RECORDS

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.2 CONFIDENTIALITY OF INVESTIGATOR INFORMATION

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. Name, address, telephone number and e-mail address;
2. Hospital or clinic address and telephone number;
3. Curriculum vitae or other summary of qualifications and credentials; and
4. Other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information.

Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.
If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.2 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/sub-investigator's responsibility to comply with any such request.

10.2.1 COMPLIANCE WITH LAW, AUDIT AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

10.2.2 COMPLIANCE WITH TRIAL REGISTRATION AND RESULTS POSTING REQUIREMENT

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.3 QUALITY MANAGEMENT SYSTEM

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.4 DATA MANAGEMENT

10.4.1 DATA STORAGE

Data collection and storage will be managed by the University of Cincinnati Cancer Institute, Clinical Trials Office (UCCI CTO). The UCCI CTO will maintain storage of all clinical data in accordance with federal guidelines and GCP. Data will be entered in a secure, password protected storage database, OnCore as well as RedCap. All hardcopies of data will be securely maintained (in a locked room or cabinet) and will only be accessible to members of the study team.

10.4.2 DATA AND SAFETY MONITORING

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0

Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients. Each patient, once enrolled, will be provided a unique ID for the study. Confidentiality will be maintained during the phases of the trial including any monitoring, and preparation of interim results. Exceptions may be made under circumstances where there are serious adverse events or when it is deemed appropriate for patient safety.

Study progress will be monitored regularly by the UCCI Data Safety Monitoring Board (DSMB). Membership consists of persons independent of, and without any conflicts of interest with, this trial. The DSMB includes experts in the fields of relevant clinical expertise (oncology) and biostatistics.

It is the responsibility of the sponsor-investigator to ensure that the DSMB is apprised of all new safety information relevant to the study IND and the study. Study progress & safety information will be prepared by the DSMB Coordinator with input from the PI as to the current status of the trial. This compiled information presented to the DSMB will include: a narrative summary from the PI as to trial progress and identification of any trends of significance or explanation of any SAEs or other safety related events; the accrual rate with projected completion date for the accrual phase; exclusion rates and reasons; pretreatment characteristics of patients accrued when relevant; and, the frequency and severity of adverse events.

The DSMB will function in an advisory capacity and recommendations/requests from the DSMB will be reviewed by the sponsor-investigator and promptly addressed.

The study data from any participating sub-sites will be reviewed remotely via RedCAP and in person by the Study Monitor as per the Clinical Monitoring Plan (Plan kept on file with UCCI CTO).

11.0APPENDICES

Appendix 1. ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

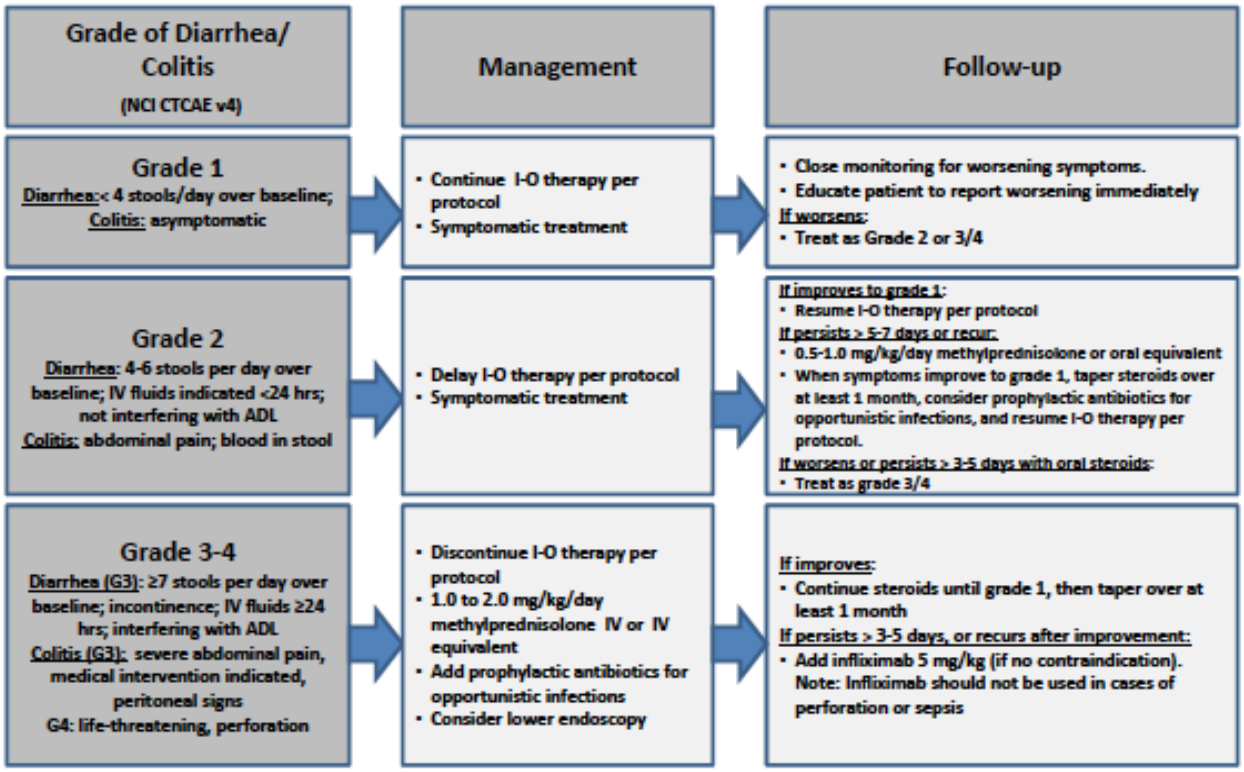
11.1 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0 (CTCAE)

THE DESCRIPTIONS AND GRADING SCALES FOUND IN THE REVISED NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 5.0 WILL BE UTILIZED FOR ADVERSE EVENT REPORTING. (HTTP://CTEP.CANCER.GOV/REPORTING/CTC.HTML)

11.2 APPENDIX 2 IMMUNO-ONCOLOGY ALGORITHMS

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.

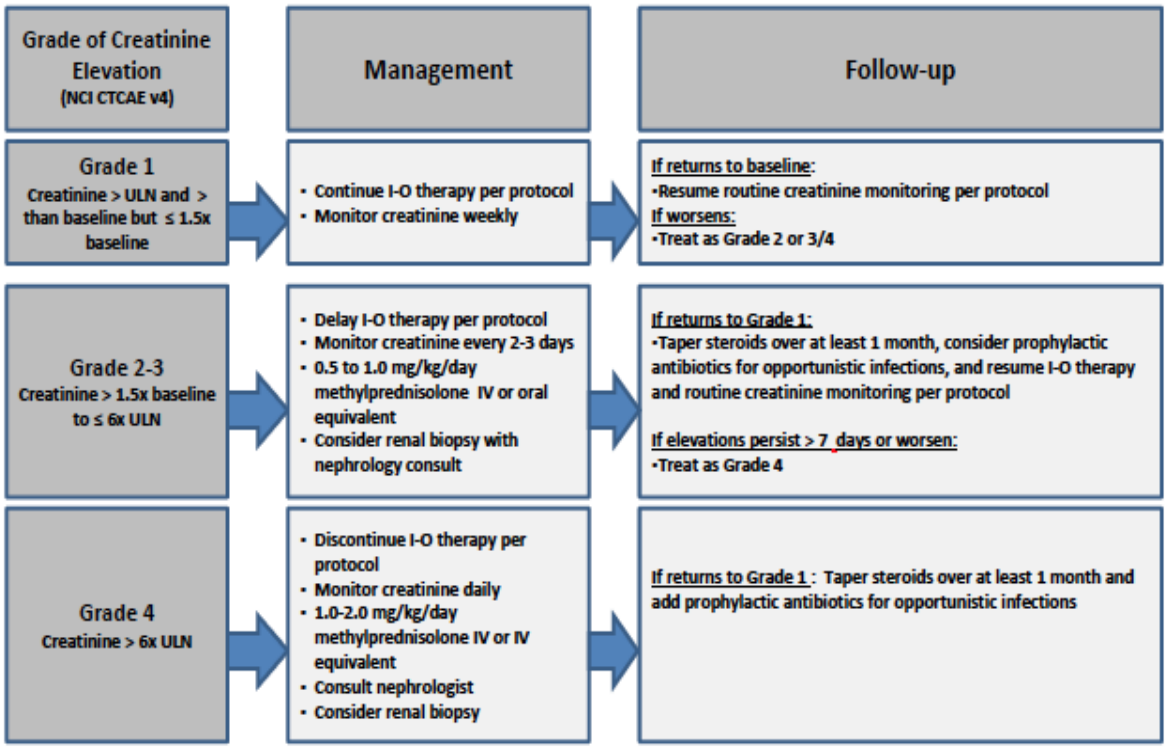


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

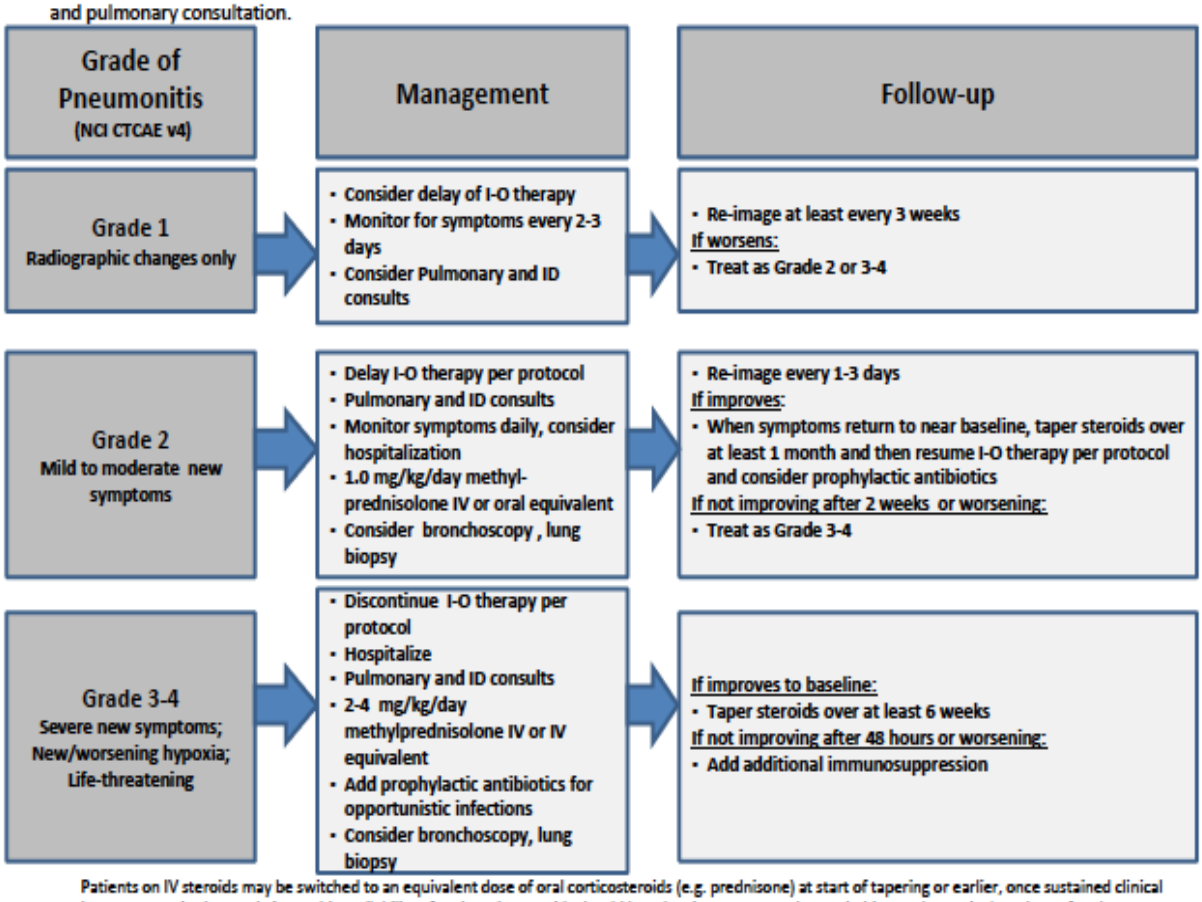


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

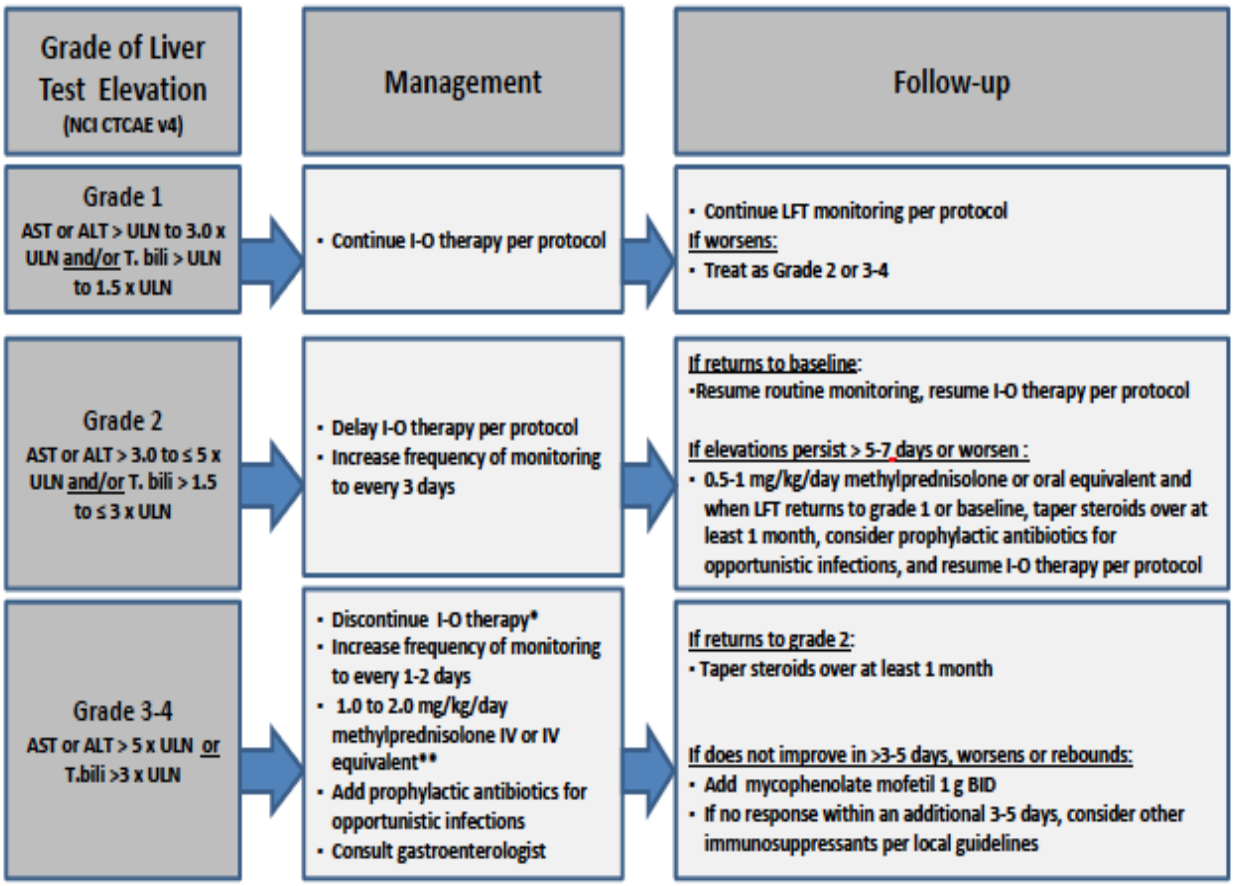


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

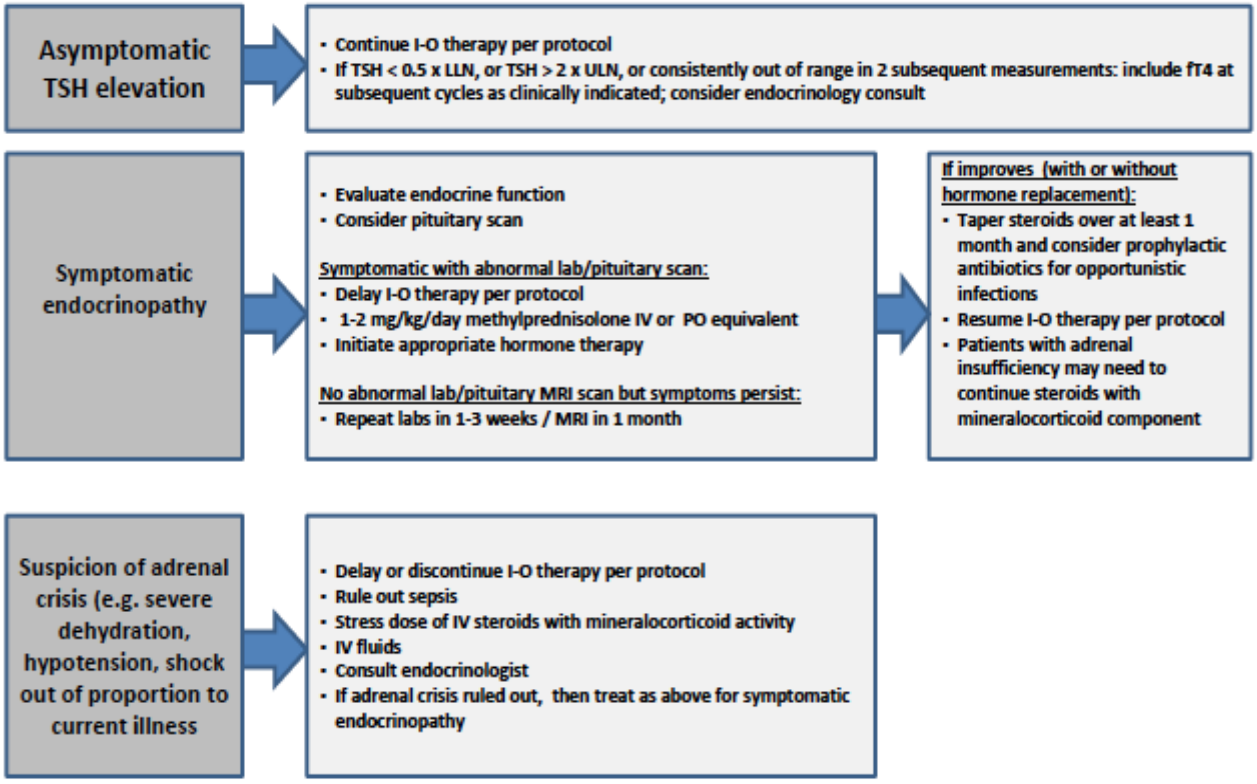
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

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

Updated 05-Jul-2016

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.

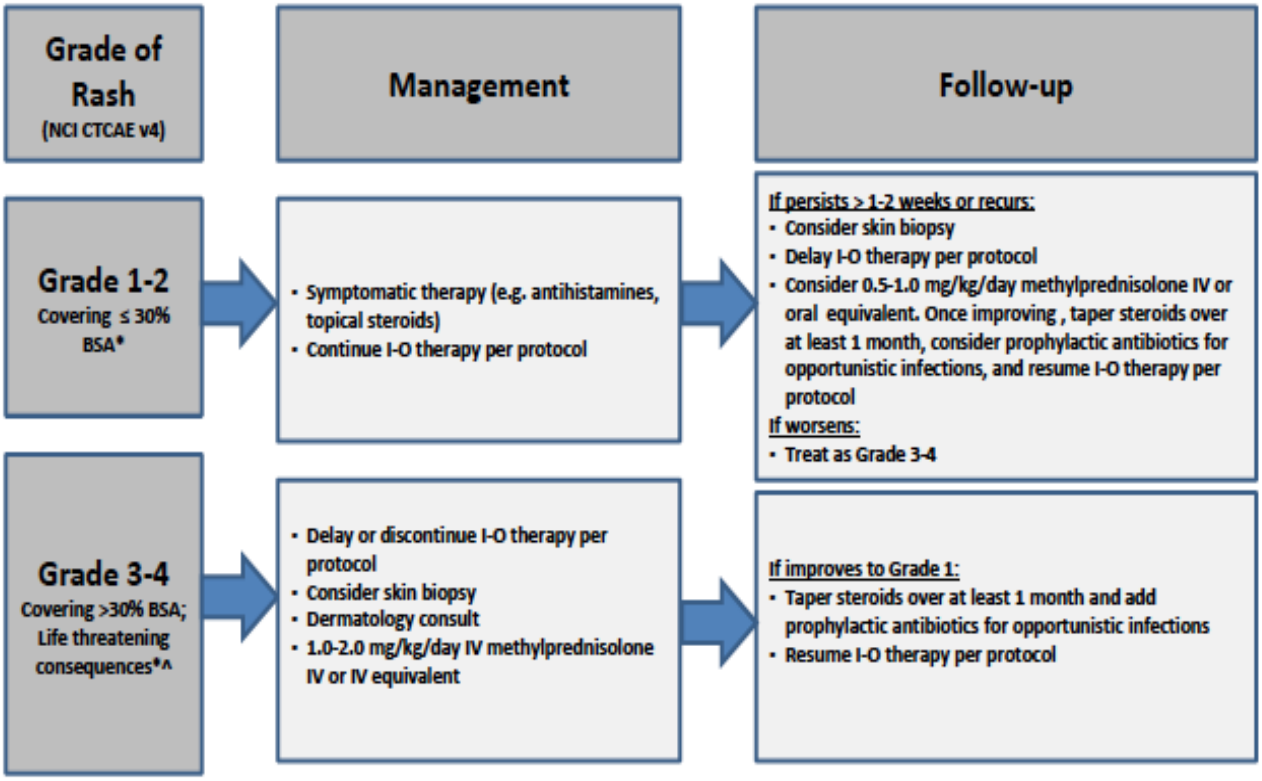


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

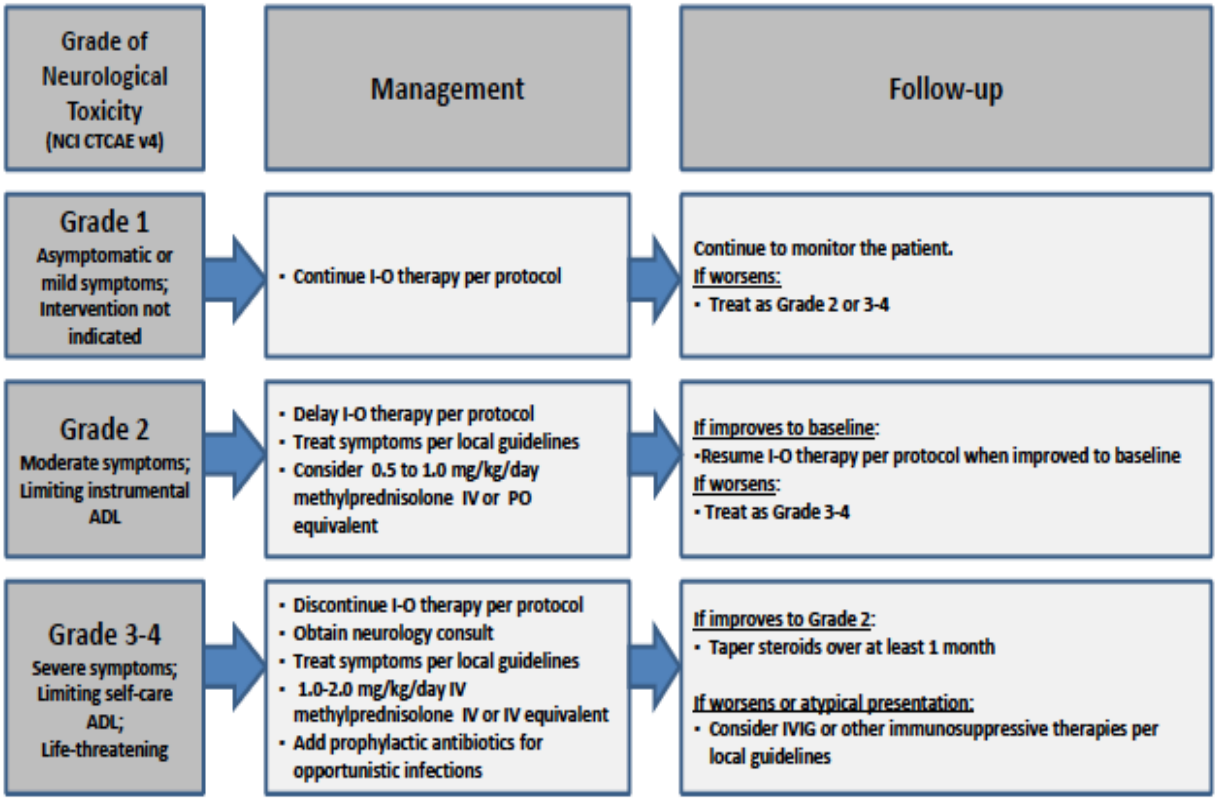
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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.

Updated 05-Jul-2016

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.

Updated 05-Jul-2016

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