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PHASE II TRIAL OF NIVOLUMAB, AN ANTI-PD-1 MONOCLONAL ANTIBODY, AS A NOVEL NEOADJUVANT PRE-SURGICAL THERAPY FOR LOCALLY ADVANCED ORAL CAVITY CANCER

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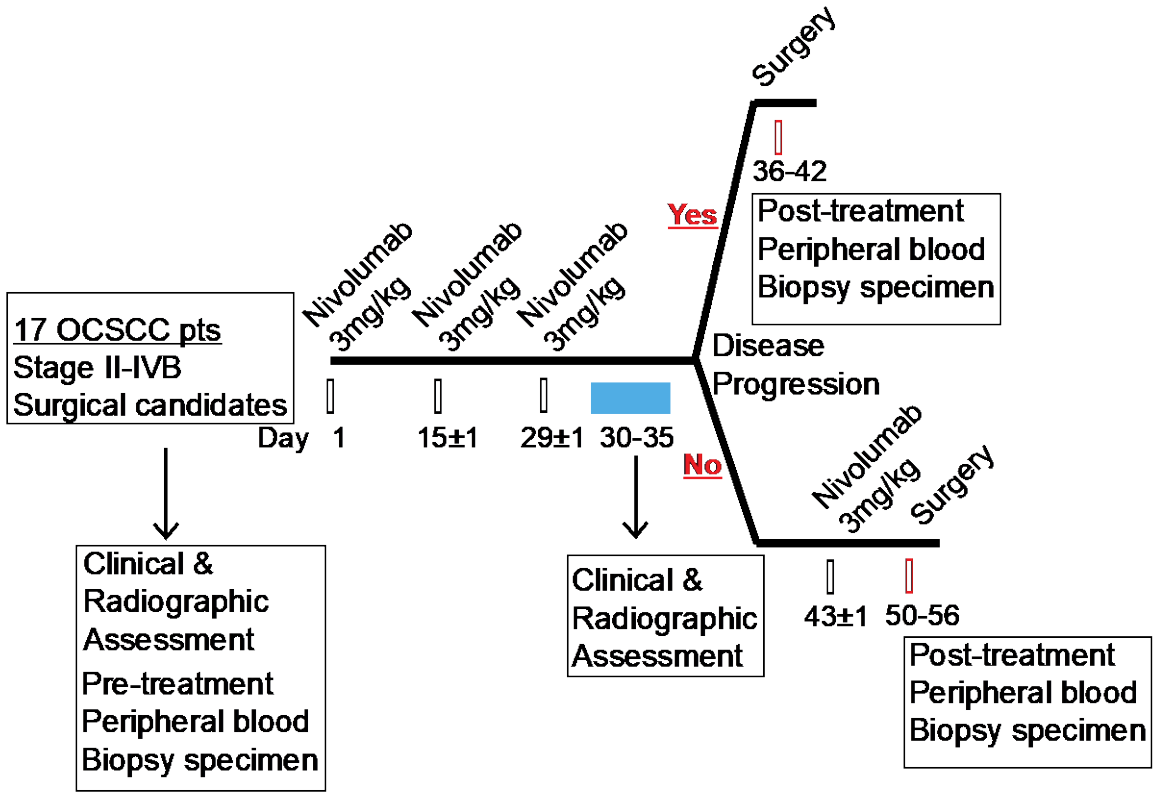
DEFINITIONS OF TERMS USED

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
AST	aspartate transaminase
BMS	Bristol Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CBCD	complete blood count with differential
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
DILI	drug induced liver injury
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCC	Hollings Cancer Center
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HR	heart rate
IB	Investigator's Brochure
ICH	International Council of Harmonisation
IIT	Investigator Initiated Trial
IRB	Institutional Review Board
IV	intravenous
LFT	liver function test
MRI	magnetic resonance imaging
MUSC	Medical University of South Carolina
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
OCSCC	oral cavity squamous cell carcinoma
pCR	pathologic complete response
PET	positron emission tomography
PR	partial response
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SIS Unit	Sponsor-Investigator Support Unit
SOP	standard operating procedure
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman of child bearing potential

1 SCHEMA


17 OCSCC pts
Stage II-IVB
Surgical candidates
Nivolumab 3mg/kg
Nivolumab 3mg/kg
Nivolumab 3mg/kg
Day 1
15±1
29±1
30-35
Disease Progression
Yes
Surgery
36-42
Post-treatment Peripheral blood Biopsy specimen
No
Nivolumab 3mg/kg
Surgery
43±1
50-56
Post-treatment Peripheral blood Biopsy specimen
Clinical & Radiographic Assessment
Pre-treatment Peripheral blood Biopsy specimen
Clinical & Radiographic Assessment

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To determine the pathological overall response rate (PR+CR) of neoadjuvant pre- surgical PD-1 inhibition in patients with surgically amenable oral cavity cancer.

2.2 SECONDARY OBJECTIVES

- To evaluate the systemic and intratumoral immune activation following PD-1 blockade.
- To determine immune reactivity to autologous OCSCC.

2.3 EXPLORATORY OBJECTIVES

- To compare genomic sequencing of patients before and after therapy with Nivolumab.

3 BACKGROUND

3.1 CLINICAL BURDEN OF HNSCC

Over 300,000 patients develop squamous cell carcinoma of the oral cavity (OCSCC) worldwide and nearly half of these patients die from the disease each year [1]. The development of regional metastases in oral cavity cancer decreases the 5-yr survival by 50%, and therefore advanced OCSCC portends a poor prognosis with estimated survival rates at 5 years ranging from 35-45% [2, 3]. Treatment of advanced oral cavity cancer often requires complex, multimodality therapy, employing surgical resection followed by post-operative radiation, with the addition of cisplatin-based chemotherapy for patients with high-risk of failure [4]. Despite these comprehensive treatment strategies, OCSCC recurs in 25-48% of patients [3, 5, 6]. Additionally, advances in reconstructive procedures have improved post-operative function of oral cavity cancer patients but these surgeries continue to be associated with significant morbidity including disfigurement, speech and swallowing deficits, and tracheostomy or gastrostomy tube dependence. Given the poor prognosis, high recurrence rates, and associated post-operative morbidities observed in OCSCC, it is evident new strategies are needed to treat and aid in the management of OCSCC [7, 8].

3.2 BENEFITS OF NEOADJUVANT TREATMENT

Neoadjuvant therapy is now being applied in multiple cancer types and has provided a new paradigm in the treatment of patients with breast and esophageal cancer in terms of overall and disease-free survival [9-12]. In the case of unresectable HNSCC, neoadjuvant chemotherapy has been applied prior to definitive radiotherapy or chemoradiotherapy with significant response rate in several phase II and III studies [13-15]. The results from these clinical trials support the concept that neoadjuvant treatment can be considered as a novel therapeutic strategy for the treatment of advanced HNSCC. Neoadjuvant chemotherapy prior to definitive surgery has been explored for the treatment of HNSCC with high rates of initial response ranging from 30-40% but a recent meta-analysis of 28 randomized trials revealed a modest survival benefit of only 6%[16-18]. Neoadjuvant treatment prior to definitive

surgery has been shown to determine clinical efficacy and define molecular biomarkers predictive of response and has been tested in several studies including one at our own institution investigating the mTOR inhibitor, Rapamycin [16, 19-21]. In general, the potential benefits of effective neoadjuvant therapies include 1) the assessment of clinical response to novel, mechanism-based treatment options which can decrease tumor burden and thus reduce the extent of surgery [17]; 2) the exploration of molecular changes in cancer cells and surrogate tissues, such as blood, may provide valuable biomarkers to identify patients that may benefit the most from new targeted therapies [22]. A clinical response to neoadjuvant chemotherapy has prognostic value in multiple cancers, as pathologic complete response at the time of surgery is a recognized and validated surrogate marker for good clinical outcome [23, 24].

3.3 IMMUNOTHERAPY IN HNSCC

Because of the combination for the need of new therapies and the benefits of a neoadjuvant treatment strategy, the possibility of immunotherapeutic approaches for HNSCC patients has gained interest. Unfortunately, HNSCC patients have profound immune defects that are associated with a worse outcome and have been attributed to tumor production of inhibitory mediators and tumor-induced immune inhibitory cell populations [25-30]. Programmed Death receptor I (PD-1) and its ligand (PD-L1) appear to contribute to this immune dysfunction as 50-60% lymphocytes from HNSCC patients have upregulated PD-1 expression and PD-1 blockade enabled lymphocyte proliferative reactivity to stimulation and indirectly overcame immune unresponsiveness by modulating immune inhibitory populations, including T regulatory cells [30-33]. Furthermore, tumor PD-L1 expression has been associated with improved objective response and clinical benefit in multiple tumor types [34]. Since 60-80% of OCSCC express PD-L1, it is anticipated PD-1 blockade will benefit 20-25% of patients with OCSCC [30, 33, 34]. Most recently the Checkmate 141 Phase III trial revealed in patients with treatment-resistant and rapidly progressive head and neck carcinoma that nivolumab treatment was associated with an improved 12-month overall survival of 36%, compared with 17% in the Investigator Choice arm [40, 41].

3.4 STUDY RATIONALE

Our past clinical trials with HNSCC patients have shown the feasibility of pre-surgical targeted or immunotherapy followed by multi-modality treatments combining surgery and adjuvant therapy leading to an improvement in recurrence free survival [35-37]. A similar multi-modality treatment is being proposed in this application to overcome immune lethargy by Nivolumab treatment to block PD 1 between the time of OCSCC diagnosis and surgical treatment. This duration of time will allow for the administration of three doses of Nivolumab given on Days 1, 15 and 29. The primary objective of the proposed study is to determine the efficacy of neoadjuvant PD-1 inhibition in patients with oral cavity cancer undergoing definitive surgical resection. In addition to assessing the clinical efficacy of Nivolumab, secondary objectives will be to analyze the effectiveness of PD-1 antibodies at

restoring the immune reactivity in the peripheral blood as well as stimulating intratumoral immune activity. The rationale for this approach is based on the overexpression of lymphoid PD 1 in the HNSCC environment along with our prior demonstration of the feasibility of pre-surgical immune modulatory treatment or targeted mTOR therapy having positive post-surgical clinical effectiveness [30, 35, 36, 38]. Additionally, blocking PD 1 prior to surgical excision will allow restoration of immune competence to not only enable pre surgical immune responsiveness to HNSCC, but also post-surgical immunological surveillance for residual cancer.

We hypothesize 25-30% overall response rate (PR+CR) in patients with OSCC, and these patients will reveal a systemic and intratumoral response following anti-PD-1 therapy along with immune reactivity to autologous OCSCC.

4 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Patients eligible for study participation must meet all of the following criteria

1. Newly diagnosed histologically proven locoregional OCSCC without evidence of distant metastases and a clinically determined T-stage of 2-4 (based on AJCC Staging Manual v.7 guidelines),

   OR

   Recurrent or persistent histologically proven locoregional OCSCC that was initially treated with surgery alone, and a clinically determined recurrent T-stage of 2-4 (based on AJCC Staging Manual v.7 guidelines).

   Note – OCSCC includes the subsites of oral tongue, floor of mouth, gingiva, retromolar trigone, and buccal mucosa.
   Note – To allow sufficient tumor tissue for the immunological analyses, patients with T-stage 1 OCSCC will be excluded

2. Greater than or equal to 18 years of age
3. ECOG performance status of 0 or 1
4. Screening labs must meet the following criteria and must be obtained within 14 days prior to registration:
   - WBC $\geq$ 2,000/μL
   - Absolute Neutrophil Count $\geq$1,500/μL
   - Platelets $\geq$ 100 X 10^3/μL
   - Hemoglobin $\geq$ 9.0 g/dL

- Serum creatinine $\leq$ 1.5 X ULN or CrCl $\geq$ 40mL/min (if using the Cockcroft-Gault formula below):

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

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

- AST/ALT $\leq$ 3 x ULN
- Total Bilirubin $\leq$ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

5. Reproductive Status:

   WOCBP must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

   Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception with a failure rate of less than 1% per year for a period of 31 weeks after the last dose of investigational product.

   WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 consecutive months of amenorrhea in a woman over 45.

   Women of childbearing potential must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to registration

   Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) and azoospermic men, are not required to use contraception.

   See appendix A for acceptable methods of contraception.

4.2 EXCLUSION CRITERIA

Patients eligible for study participation CANNOT meet any of the following criteria

1. Prior immunotherapy or treatment with another anti PD 1 agent
2. Prior chemotherapy including Cetuximab or radiation therapy
3. Previous severe hypersensitivity reaction to another monoclonal antibody
4. Women who are pregnant, lactating or expecting to conceive
5. Men who are expecting to father children within the research period
6. Known history of HIV or AIDS
7. Positive test for HBV sAg or HCV antibody indicating acute or chronic infection

8. Concomitant malignancies except cutaneous squamous cell carcinoma or basal cell carcinoma
9. Unresectable primary tumor or regional disease; presence of distant metastases.
10. History of pneumonitis or interstitial lung disease
11. Active, known or suspected autoimmune disease. Note: Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger
12. Presence of condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease

4.3 INCLUSION OF WOMEN AND MINORITIES

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

4.4 SUBJECT REGISTRATION

The SIS Unit will provide subject registration services for the study. After obtaining signed informed consent and completion of required baseline assessments, eligible subjects will be registered. All study subjects will undergo an eligibility audit prior to registration. A unique subject number will be assigned to each patient. A registration confirmation will be emailed to the enrolling study team at the time of registration. This confirmation will include the subject's assigned cohort dose level and study ID number. Registrations may occur between 8AM and 5PM EST, Monday through Friday. Registrations may take place outside of this timeframe if prior arrangements are made.

5 STUDY INTERVENTION

5.1 NIVOLUMAB ADMINISTRATION

Nivolumab will be given every two weeks at a dose of 3mg/kg will be administered as a 60 minute IV infusion (+/- 10 minutes). Study drug will be administered on an outpatient basis. Subjects may be dosed no less than 12 days from the previous dose of drug.

REGIMEN DESCRIPTION			
Agent	**Dose**	**Route**	**Schedule**
Nivolumab	3mg/kg	IV	Cycle 1 = Day 1 Cycle 2 = Day 15 Cycle 3 = Day 29 Response assessment

			Cycle 4 = Day 43 if stable disease or response after day 29.

The dosing calculations should be based on the actual body weight at baseline. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. **There will be no dose reductions allowed**.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. 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 1 mg/mL). Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 5.3.

5.2 SURGICAL RESECTION

Between days 28-35, subjects will be evaluated for disease progression through clinical and radiographic tumor assessment, and for toxicity by history, physical and clinical labs. In the event of disease progression, subjects will proceed to definitive surgical resection between days 36-42 and no later than 50 days after randomization. If disease is stable or response is observed, subjects will have the fourth administration of nivolumab on Day 43 (+/- 1 day) followed by definitive surgical resection on day 50-56 and no later than 60 days randomization.

5.3 PRE AND POST MEDICATIONS

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, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v. 4.0 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)

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

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

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

- **For Grade 3 or Grade 4 symptoms:** (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory 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 (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

6 DOSE MODIFICATIONS

Dose reductions or dose escalations are not permitted. Dose delays due to adverse events are not permitted. If an AE occurs causing a missed dose, the subject will stop the nivolumab administration schedule and proceed to surgery. Dose delays for other reasons are allowed with prior approval from the Sponsor-Investigator.

6.1 MANAGEMENT ALGORITHMS

Immuno-oncology agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs 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 AEs: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms can be referenced in the Nivolumab IB. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

6.2 DISCONTINUATION CRITERIA

Subjects may discontinue study treatment at any time. Subjects may be removed from study for any of the following reasons:

- Radiographic disease progression that is not amendable to resection
- Clinical disease progression that would not benefit from surgery
- Inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study drugs
- Completion of protocol treatment.
- Death
- Subject non-compliance
- 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, hypersensitivity reactions, infusion reactions, and endocrinopathies:
        - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
        - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement **do not** require discontinuation

        - Grade 3 drug-related laboratory abnormalities **do not** require treatment discontinuation except those noted below
            - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
            - Any drug-related 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
    - Grade 4 lymphopenia or leukopenia
    - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Principal Investigator.

7 CONCOMITANT THERAPY

7.1 PERMITTED MEDICATIONS – USE WITH CAUTION

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

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

8 STUDY ASSESSMENTS

8.1 GENERAL GUIDELINES

- Screening evaluations are to be done within 14 days of registration with the following exceptions:

  - informed consent, hepatitis B and C testing, and radiographic disease assessments to be done within 28 days of registration
  - serum pregnancy test must be done within 24 hours prior to registration
- After registration, subjects should begin study drug within 72 hours.
- On study assessments to be completed +/-3 days, radiographic assessments will be completed within +/- 7 days.

8.2 PREGNANCY TEST FOR WOCBP

A serum pregnancy test is required within 24 hours prior to registration. If day 1 is more than 24 hours after the screening pregnancy test, the pregnancy test must be repeated prior to day 1 of drug administration. A pregnancy test is also required at day 29 and prior to surgery. After discontinuation from nivolumab these should be repeated at approximately 30 days and approximately 70 days.

8.3 BASELINE ASSESSMENTS:

- Medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, BP, HR, temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be performed within 14 days prior to registration. Concomitant medications will be collected from within 14 days prior to the first dose through the study treatment period.
- Laboratory assessments will be done within 14 days prior to registration and are to include: CBCD, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, calcium, Magnesium, Sodium, Potassium, Chloride, phosphate, LDH, glucose; TSH, free T3, and free T4.
- The following baseline local laboratory assessments to be done within 28 days prior to registration: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).
- **After patients are entered into this study**, the clinical team will oversee collection of primary tumor biopsy if not previously performed.

8.4 RADIOGRAPHIC ASSESSMENT:

- Initial evaluation will include PET/CT or CT scan of the head and neck to assess local and regional disease extent. PET/CT or CT of the chest, abdomen, and pelvis will also be utilized to assess for distant disease.
- MRIs may be substituted in place of PET/CT or CT scan for clinical reasons such as subject intolerance of intravenous contrast material.
- The same method of assessment (i.e. CT, MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- RECIST 1.1 guidelines will be used.
- Restaging scans of the head and neck will be performed following the 3rd cycle between Days 29-36
- If tumor cannot be visualized on radiology exam, caliper measurement should be used.

8.5 CLINICAL TUMOR ASSESSMENT:

- Primary tumors will be assessed for progression using caliper measurement on prior to registration and following the third cycle of treatment Day 29-36. Caliper measurements are only required if tumor cannot be visualized on radiology exam.
- Tumors will be photographed at time of clinical assessment on day 1 and following the third cycle of treatment for a qualitative assessment of possible effects on reduction in tumor size, necrosis, erythema/inflammation, and vascularity. Standard flash or endoscopic digital photography may be used depending on the site and accessibility for photography.
- Following completion of the trial, two blinded head and neck tumor surgeons (Photograph Examiner #1 and #2) will review the photographs separately. Each examiner will record estimated size, percent increase or decrease, and anatomic descriptive terms related to change in size, shape, texture, and color over time from the photographs.

8.6 ON STUDY ASSESSMENTS

- Toxicity assessments will be continuous during the treatment phase. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.03.
- On-study weight, ECOG performance status, and vital signs should be assessed at each on-study visit prior to dosing. Vital signs should also be taken as per institutional standard of care. Oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be assessed at each on-study visit prior to dosing. The start and stop time of the study therapy infusions should be documented.
- Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, the changes should be reported as AEs.
- Laboratory testing prior to each dose: Within 72 hours prior to re-dosing to include CBCD, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase.
- Thyroid function testing should be done every 6 weeks (every 3 cycles) for subjects receiving nivolumab.
- A minimum of five and a maximum of seven 5-mL tubes of peripheral blood will be collected for correlative studies. See section 12 for more details.
- Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.
- If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with

possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity.

- **<u>At the time of surgery</u>**, portions of the excised HNSCC tissues that are not required for clinical purposes (existing material) will be used for correlative research. See section 12 for more details.
- Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

8.7 OFF STUDY AND FOLLOW UP

8.8 SUBJECTS WILL BE FOLLOWED EVERY 3 MONTHS (+/- 15 DAYS) FROM THE DATE OF SURGERY UNTIL PROGRESSION OR UNTIL DEATH, WHICHEVER COMES FIRST, FOR A MAXIMUM OF 12 MONTHS AFTER THE LAST SUBJECT HAS BEEN REGISTERED TO THE TRIAL. AES WILL BE RECORDED FOR 6 WEEKS AFTER SURGERY. AES CAN BE REPORTED THROUGH REGULAR CLINIC VISITS OR OVER THE PHONE.

8.9 STUDY CALENDAR

Activity	Screening			Patient Registration	Nivolumab Administration[g]			If stable or response only:	Surgery[c, h]	Follow Up			
	Within 28 days of Registration	Within 14 days of Registration	Within 24 hours of registration		Day 1[i]	Day 15	Day 29	Day 43[c]	Day 36-42 or Day 50-56	30 days[d]	42 days[j]	70 days[d]	Q 3 months[b]
Informed consent	X												
History and Physical examination		X			X[a]	X[a]	X[a]	X[a]					
ECOG PS		X			X	X	X	X					
Vital signs, weight		X			X	X	X	X					
CBCD & CMP		X			X	X	X	X					
Mag, Phos		X			X	X	X	X					
HVB and HVC screening	X												
TSH, free T3, free T4		X			X			X					
LDH, amylase, lipase		X			X	X	X	X					
Serum Pregnancy test (WOCBP only)			X				X		X	X		X	
Assessment of Concomitant medications		X			X			X					
Adverse events assessment					X	X	X	X			X		
Tumor Photographs[k]					X		X						
Radiographic or Caliper Measurement Tumor Assessment[k]	X						X						
Survival Status and Disease Status[b]													X
Nivolumab Administration					X	X	X	X					
Surgery									X				
Tumor biopsy	**Any time after consent and prior to day 1 dose**								X				
Research blood collection[f]	**Any time after consent and prior to day 1 dose**								X				

a. Performed as clinically indicated
b. Follow up every three months (+/- 15 days) from the time of surgery until progression or death, for up to 12 months after the last subject has been registered to the trial.
c. If disease is stable or response is observed at days 28-35, subjects will have the forth administration of nivolumab on Day 43, followed by definitive surgical resection on day 50-56.
d. Serum pregnancy test to be done 30 days and 70 days after last drug administration.
e. AEs will be recorded for 6 weeks after surgery.

f. A minimum of five and a maximum of seven, 5-mL tubes of peripheral blood will be collected for correlative research in purple top tubes. See section 12 for more details about tumor biopsy and research blood collection.
g. Nivolumab may be administered +/- 1 day
h. Surgery is to be performed any time between Days 36-42 for patients whose disease has progressed and no later than 50 days after randomization or between Days 50-56 for patients who have stable disease or response, with surgery to be no later than 60 days after randomization.
i. Screening labs done within 72 hours of day 1 do not need to be repeated.
a. AEs will be assessed up to 6 weeks after surgery and may be assessed through clinic notes and/or reported via phone.
b. See section 8.5 Clinical Tumor Assessment for more information.

9 DRUG INFORMATION - NIVOLUMAB

9.1 DRUG ORDERING AND ACCOUNTABILITY

BMS is supplying study drug. Please see the pharmacy manual for instructions on how to order study drug from BMS.

9.2 PRODUCT DESCRIPTION AND DOSAGE FORM

Nivolumab (BMS-936558-01) Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL.

- **Other names**: MDX-1106, ONO-4538 and antiPD-1.
- **Potency:** 100mg/Vial (10mg/mL)
- **Primary Packaging (volume)/Label type:** Carton of 5 or 10 vials
- **Secondary packaging (Qty)/Label type:** 10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.
- **Appearance:** clear to opalescent, colorless to pale yellow liquid. May contain particles

9.3 STORAGE CONDITIONS:

Investigational product must be stored at 2-8 degrees C (36-46 degrees F) and protected from light and freezing.

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.
For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions"

9.4 LABELING:

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

9.5 HANDLING AND DISPENSING

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Please refer to the current version of the Investigator Brochure and/or shipment reference sheets for additional information on storage, handling, dispensing, and infusion information for nivolumab.

9.6 DESTRUCTION

Sponsor/Investigator drug destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the Sponsor SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for BMS to review throughout the clinical trial period as per the study agreement.

If conditions for destruction cannot be met, please contact BMS.

It is the Sponsor Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10 DEFINITION OF ENDPOINTS

10.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is objective response rate: pathologic complete response + pathologic partial response. Objective response rate: the sum of patients with either a pCR defined as no invasive and no in situ residuals present in the surgical specimen or partial pathologic response defined at least a 30% reduction in the size of the lesion in the surgical specimen. The reduction in size will be determined by comparing the pretreatment clinical measurements (the sum of the greatest axial measurement obtained radiographically, or using calipers if necessary, at the time of initial evaluation) with the final pathologic measurements. Partial response has been chosen as an efficacy endpoint because of the two stage design and small sample size of the proposed trial (*i.e.* a objective response must be observed in at least 1 patient in first nine to proceed with the second stage). The proposed study is based on the current available head and neck squamous cell carcinoma data and is not powered to assess an objective response rate defined as pathologic complete response + major pathologic response.

10.2 SECONDARY EFFICACY ENDPOINTS

Immune capability will be measured as follows:

1. Levels of Treg cells in pre and post treatment peripheral blood will be evaluated using immunostaining for CD4 and flow cytometric analysis of Foxp3. Differences will be calculated (absolute change and percentage change) between pre and post treatment measures.
2. Levels of activated T-cells in peripheral blood will be assessed using flow cytometry for expression of CD69, IFN γ, T-bet and ICOS in CD4+ cells. Differences will be calculated (absolute change and percentage change) between pre and post treatment measures.

3. Intratumoral immune activity assessed by levels of immune stimulatory cytokines including IL-2, IFN γ, and IL-12 or inhibitory cytokine, IL10 and TGF-beta, in OCSCC tumor lysates will be measured flow cytometrically by cytokine bead array. Differences will be calculated (absolute change and percentage change) between pre and post treatment measures.

Immune reactivity against autologous OCSCC will be measured by T cell responsiveness of their pre and post treatment peripheral blood following a challenge with autologous OCSCC.

1. Expression of IFN γ, IL-2 (Th1 responses) and IL 10 (Th2 responses) in CD4+ cells from peripheral blood of patients following PD-1 inhibition therapy will be compared between pre-treatment peripheral blood samples and post-treatment samples from the same patient.
2. Expression of CD8+ cells expressing granzyme B (cytolytic response) from peripheral blood of patients following PD-1 inhibition therapy will be compared between pre-treatment peripheral blood samples and post-treatment samples from the same patient.

10.3 DEFINITION OF SECONDARY OUTCOMES/ENDPOINTS:

1. Increased immune capability will be defined as decrease in Treg population with subsequent increase in activated T cells population.
2. Immune reactivity will be defined as increased Th1 response and CD8+ cytolytic response following challenge to autologous OCSCC in post treatment peripheral blood relative to pretreatment peripheral blood samples.

10.4 SAFETY ENDPOINTS

Adverse events, assessed using the CTCAE v4, occurring between enrollment and 6 weeks following surgery will be collected.

11 STATISTICAL CONSIDERATIONS AND DETERMINATION OF SAMPLE SIZE

11.1 DEFINITION OF EVALUABLE PATIENTS

11.1.1 EVALUABLE FOR SAFETY

Any patient who receives one or more doses of nivolumab will be included in the safety population.

11.1.2 EVALUABLE FOR EFFICACY

Patients who receive at least two doses of nivolumab and undergo surgery will be included in the efficacy population.

11.1.3 EVALUABLE FOR IMMUNE ACTIVATION AND REACTIVITY

Patients who have received at least two doses of nivolumab and have both a pre-treatment and a post-treatment sample available for measuring immune markers will be included in the analyses for the secondary objectives of the study.

11.2 DATA ANALYSIS PLANS

11.2.1 PRIMARY OBJECTIVE

The clinical, radiographic and pathologic response rates will each be estimated with a 95% confidence interval, accounting for the two-stage design [41]. The null hypothesis is a 2% pathological response rate and the alternative is a 25% pathological response rate. If no patients respond in the first nine evaluable patients enrolled, the study will be terminated and we will conclude that there is not sufficient activity to reject the null hypothesis. The trial may pause enrollment after the first nine patients (if needed) to follow the ninth patient for a pathologic response. Note, however, that it is possible that an earlier patient may respond which would negate the need to stop enrollment (e.g. the 2nd patient may respond which would satisfy the criteria of at least one patient response in the first nine patients). If at least one patient has a pathologic response among the first nine evaluable patients enrolled, an additional eight patients will be enrolled. If two or more patients among 17 evaluable patients respond, we will reject the null hypothesis. The reported p-value will be based on two-stage design and any deviations from the intended sample size will be accounted for using the approach by Koyama and Chen [41]. Deviations from the planned sample size would only include the need for replacement patients in the event of a patient withdrawal following a single dose of Nivolumab secondary to toxicity or patient preference. If this were to occur these withdrawn patients would be excluded from the efficacy analysis. Only patients that receive at least 2 doses of Nivolumab will included in the efficacy analysis. Briefly, Koyama and Chen's approach adjusts the final results of the Simon two-stage design (point estimate, 95% confidence interval, and p-value) by considering the evaluation of the data at the end of the 1st stage of the design. Ignoring the two-stage nature of the design, the estimated response rate (i.e. number of responders divided by the total number of patients at the end of stage 2) tends to underestimate the true response rate. In addition, the p-value and 95% confidence interval based simply on the maximum likelihood estimate using the total number of responses and total sample size will not be valid if the futility stopping evaluation is ignored. The approach for implementing the adjustment can be found here: http://biostat.mc.vanderbilt.edu/wiki/Main/TwoStageInference

11.2.2 SECONDARY OBJECTIVES

Immune activation markers will be graphically displayed at baseline (pre-treatment) and at time of surgical resection, and summary statistics will be reported for baseline, follow-up and changes over time. Based on our prior studies a 50% increase in immune stimulatory cytokines and 50% decrease in Treg levels is anticipated.

Transformations will be taken as needed (e.g. log transform) to adhere to assumption of statistical methods. Comparisons of baseline vs. follow-up measures will be made using paired t-tests. Logistic regression will be used to evaluate the association between baseline immune markers and clinical response and to evaluate associations between changes in immune markers and response. Both absolute change and percentage change in markers will be considered

11.3 DETERMINATION OF SAMPLE SIZE

This study will enroll up to 19 patients. The Simon two-stage design is based on a total of 17 patients who are evaluable for efficacy. We may enroll up to 19 to allow for up to two patients to be inevaluable.

Without treatment, the rate of response would be expected to be very low (<2%). With treatment, we anticipate a meaningful pathological response rate of 25%. Using a Simon optimal two-stage design with alpha of 4% and power of 91%, we can detect this difference with a sample size of no more than 17 patients. In stage 1, 9 patients will be enrolled. If none respond, the study will be stopped. If one or more responds, we will continue to the 2nd stage and an additional 8 patients will be enrolled. If a total of 2 or more patients respond out of 17 we will reject the null hypothesis and conclude that treatment with Nivolumab results in a meaningful pathological response for patients with HNSCC.

11.4 SAFETY ANALYSIS

Adverse events occurring between enrollment and 6 weeks after surgery will be tabulated by type and grade. Adverse events that are at least possibly related to nivolumab will be tabulated separately.

Safety monitoring will occur continuously during the study. We anticipate nivolumab to be well-tolerated in this patient population and would anticipate a low (≤5%) rate of grade 3 and 4 adverse events that are at least possibly related to nivolumab. If there were strong evidence during the course of the trial that the rate of grade 3 and 4 adverse events was 25% or higher, we would stop the study. Using a likelihood-based approach, the study will stop if the likelihood ratio for a grade 3-4 AE rate of 25% vs. a grade 3-4 AE rate of 5% is 4 or higher. This is based on the binomial distribution. The stopping boundaries based on this approach are shown in the table below. Note that the upper limit on the sample size 19 due to the potential need to enroll up to 19 patients in the case of up to two patients inevaluable for response.

Stop the trial if:	Observed rate	Likelihood Ratio
2 of 3-9 pts have grade 3-4 AEs	22% - 67%	≥ 4.78
3 of 10-17 pts have grade 3-4 AEs	18% - 30%	≥ 4.57
4 of 18-19 pts have grade 3-4 AEs	21% - 22%	≥ 4.36

Additionally, if there is evidence that there is a delay in time to surgery due to adverse events, the study will be stopped. It would be considered acceptable if 5% or fewer of patients experienced a delay (i.e. greater than 3 weeks from their last dose of nivolumab.. A rate of delay of 10% or greater would be considered unacceptable. Given these assumptions and the use of a likelihood-based approaches as above (with a likelihood ratio of 4 or greater in favor of 20% causing study stoppage). The stopping boundaries are listed below:

Stop the trial if:	Observed rate	Likelihood Ratio
3 of 3-15 pts have a surgery delay	20% - 100%	≥ 4.20
4 of 9-19 pts have a surgery delay	21% - 25%	≥ 7.11

11.5 INTERIM ANALYSIS

There are no interim analyses planned for this study. However, given that the study design is a Simon two-stage design, the number of responses in the first nine patients will be evaluated and the study will be terminated after the ninth patient if none of these nine patients have achieved a clinical response.

12 CORRELATIVE STUDIES

After patients are entered into this study, the clinical team will oversee collection of primary tumor biopsy if not previously performed and peripheral blood at the onset of the study prior to initiating treatment. Prior to surgical resection, peripheral blood will again be collected in an effort to measure pre- and post-treatment immune reactivities. At each blood draw, each patient will have peripheral blood drawn into a minimum of five and a maximum of seven 5-ml purple top tubes. Portions of the excised HNSCC tissues that are not required for clinical purposes (existing material) will be used in addition to the peripheral blood for immunological assessments. The peripheral blood and HNSCC tissues will be used to assess immunological responsiveness to the immunotherapy (see "Correlative Research" below)

12.1 EVALUATION OF THE SYSTEMIC AND INTRATUMORAL IMMUNE ACTIVATION FOLLOWING PD-1 BLOCKADE:

Increased immune capability will be defined as follows:

a. Reduced levels of Treg cells in pre and post treatment peripheral blood will be evaluated using immunostaining for CD4 and flow cytometric analysis of CD3 and Foxp3.
b. Increased levels of activated T-cells in peripheral blood will be assessed using flow cytometry for expression of CD69, IFN-γ, T-bet and ICOS in $CD4^+$ cells.
c. Intratumoral immune activity assessed by increased levels of immune stimulatory cytokines including IL-2, IFN-γ, and IL-12 or inhibitory cytokine, IL10 and TGF-beta, in OCSCC tumor lysates will be measured flow cytometrically by cytokine bead array.

12.2 DETERMINING IMMUNE REACTIVITY TO AUTOLOGOUS OCSCC:

Immune reactivity against autologous OCSCC will be measured by T-cell responsiveness of their pre and post treatment peripheral blood following a challenge with autologous OCSCC.

a. Following a challenge with autologous OCSCC, increased expression of IFN-γ, IL-2 (Th1 responses) and decreased IL-10 (Th2 responses) in $CD4^+$ cells from peripheral blood of patients following PD-1 inhibition therapy will be compared to pre-treatment peripheral blood samples from the same patient.
b. Following a challenge with autologous OCSCC, Increased expression of $CD8^+$ cells expressing granzyme B and perforin (cytolytic response) from peripheral blood of patients following PD-1 inhibition therapy will be compared pre-treatment peripheral blood samples from the same patient.

12.3 GENOMIC SEQUENCING

Genomic sequencing will be done on samples collected prior to the start of therapy and after the completion of therapy (at the time of surgery). The samples will be linked to the patients by a unique study ID. Results of genomic sequencing will not be shared with subjects and the results of the sequencing will not alter clinical decisions. The genomic sequencing correlative study is optional.

13 ADVERSE EVENT REPORTING REQUIREMENTS

13.1 PURPOSE

AE data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AE are reported in a routine manner at scheduled times during a trial. Additionally, certain AEs must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe routine and expedited AEs reporting for this protocol.

Throughout the study, the Investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safety of the drug under investigation.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

13.2 DEFINITION OF SERIOUS ADVERSE EVENT

An SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject 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.)
- Potential DILI is also considered an important medical event.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

The following hospitalizations are not considered SAEs for this protocol:

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

Potential Drug Induced Liver Injury (DILI)

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 SAEsPotential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times 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 AST/ALT 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.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form [provided upon request from BMS]in accordance with SAE reporting procedures.

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. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Overdose

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

13.3 SAE REPORTING

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to the SIS Unit and BMS within 24 hours.

SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form:

SAE Email Address: **WORLDWIDE.SAFETY@BMS.COM**
SAE Facsimile Number: 609-818-3804

All SAEs reports (including follow up reports) must be reported to the SIS Unit via REDCap (redcap.musc.edu)

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

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

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study including periodic reconciliation.

Any event that is both serious and unexpected must be reported to the 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.

Reportable 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/

The SIS Unit will be responsible for submitting the SAEs to the FDA and other regulatory agencies/oversight committees as required.

All SAEs should simultaneously be faxed or e-mailed to BMS at:
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

13.4 DEFINITION OF 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 subject administered an investigational (medicinal) product 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 AEs. The casual relationship can be one of the following:

Definitely related:	An adverse event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. The event must be definite pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary and feasible.
Possibly related:	An adverse event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Not related:	An adverse event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying diseases provide plausible explanations.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

13.5 NONSERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The collection of non-serious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

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

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 subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

Any significant worsening of a pre-existing condition 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 nonserious or serious AE, as appropriate, and reported accordingly.

13.6 DEFINITION OF SEVERITY

Adverse events will be graded according to the revised NCI CTCAE v. 4.03. If toxicities are not defined by the NCI CTCAE v. 4.03, the intensity of each adverse event should be graded as outlined below:

GRADE 1	MILD: Sign or symptom noticeable, but does not interfere with normal daily activities.
GRADE 2	MODERATE: Sign or symptom sufficient to interfere with normal daily activities.
GRADE 3	SEVERE: Sign or symptom is incapacitating, with inability to perform daily activities.

GRADE 4 LIFE-THREATENING: sign or symptom poses immediate risk of death to this patient.

13.7 DOCUMENTATION OF ADVERSE EVENTS

The Investigator will monitor and/or ask about or evaluate AEs using non leading questions at each visit or evaluation. The occurrence of all AEs will be documented in the CRF with the following information, where appropriate:

- AE name or term
- When the AE first occurred (start date)
- When the AE stopped (stop date), (or an indication of "ongoing")
- How long the AE persisted (optional)
- Severity of the AE
- Seriousness
- Actions taken
- Outcome
- Investigator opinion regarding the relationship of AE to the study drug(s)

14 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with ICH CGP, the FDA, local IRB policies and in compliance with the protocol. The protocol, any amendments and the subject informed consent will received IRB approval before initiation of the study or implementation of any protocol change.

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

14.1 INFORMED CONSENT

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Informed consent will be obtained by personnel who are qualified by education, training and experience to perform the task. The Sponsor-Investigator will not use the services of study personnel for whom sanctions have been invoked where there has been scientific misconduct or fraud.

Investigators 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. The approved consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

14.2 INSTITUTIONAL REVIEW

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46)

15 MONITORING

The SIS Unit will be responsible for the monitoring of study subject data and records; monitoring will be performed centrally. The SIS Unit will be responsible for forwarding any applicable reports to the HCC DSMC for review.

The SIS Unit will conduct patient eligibility audit reviews for all patients prior to patient registration. During the course of the study, subjects will be selected for an audit at least once a year. Progress reports will be submitted to the HCC DSMC at least once a year.

15.1 PROTOCOL DEVIATIONS

For the purposes of this study, a **protocol deviation** is any variance from the protocol involving a subject or subjects that is not approved by the IRB prior to its initiation or implementation, and occurs when a member of the study team departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval. Protocol Deviations have special reporting requirements. Any protocol deviation and any supporting documentation will be submitted to the SIS Unit within 10 days of notification as outlined in the Operations Manual for this study.

15.2 DATA SAFETY MONITORING BOARD

The HCC DSMC will have oversight of the protocol. The HCC DSMC will meet at a minimum on a semi-annual basis to review the audits and progress reports for this IIT.

In addition, all protocol deviations and SAEs as defined above will be reviewed by the HCC DSMC at monthly meetings. As new protocol deviations or serious adverse events are reported to the SIS Unit, the SIS Unit will review these reports for form completion and follow up if more information is warranted. The SIS Unit will forward the event report to the HCC DSMC so that the information can be reviewed at the next available DSMC meeting. During the DSMC review, the DSMC can make recommendations for any further study action. The SIS Unit will maintain a copy of the DSMC approval letters for each event reviewed for this study within the site's central study file and will distribute to the participating site, if applicable.

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APPENDIX A: ACCEPTABLE FORMS OF CONTRACEPTION

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. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- 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.

LESS EFFECTIVE METHODS OF CONTRACEPTION

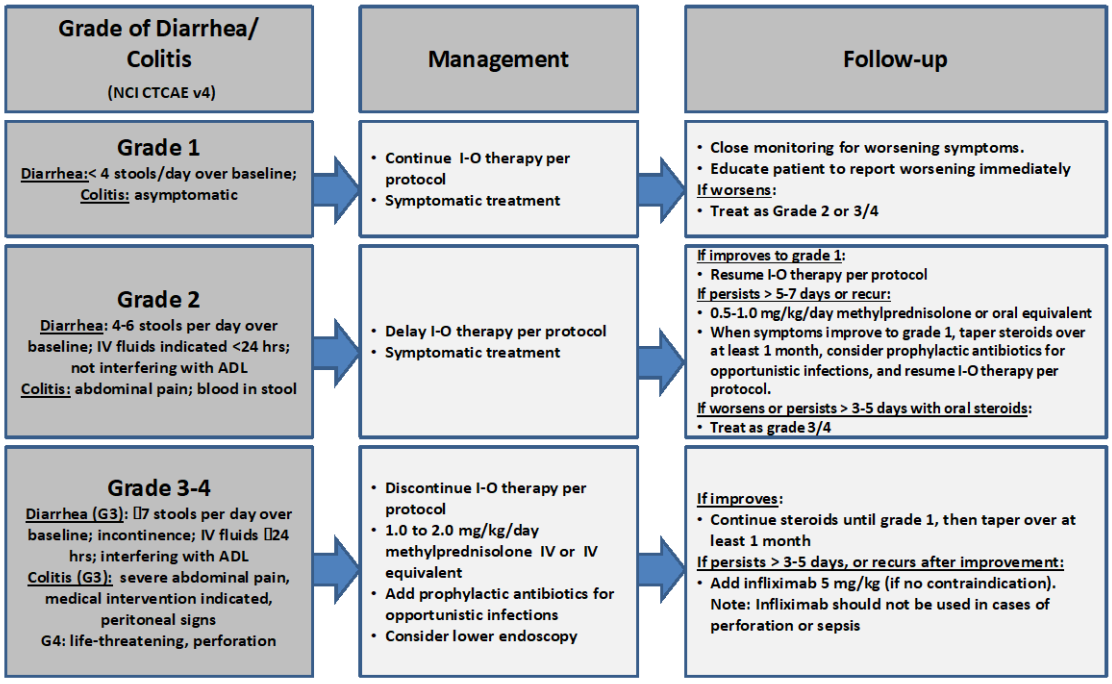
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom
- A male and female condom must not be used together

APPENDIX B: MANAGEMENT ALGORITHMS

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

GI Adverse Event Management Algorithm

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

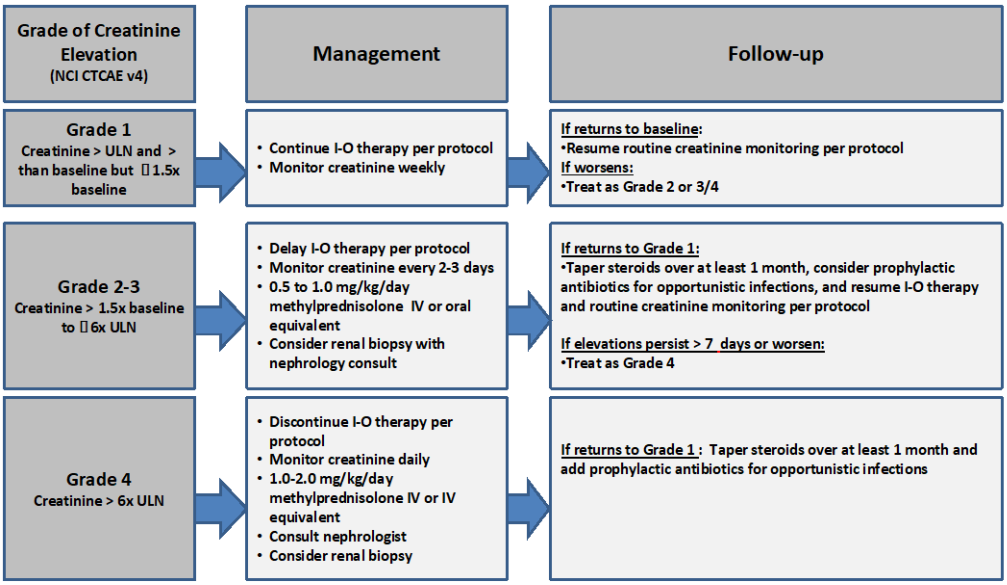


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

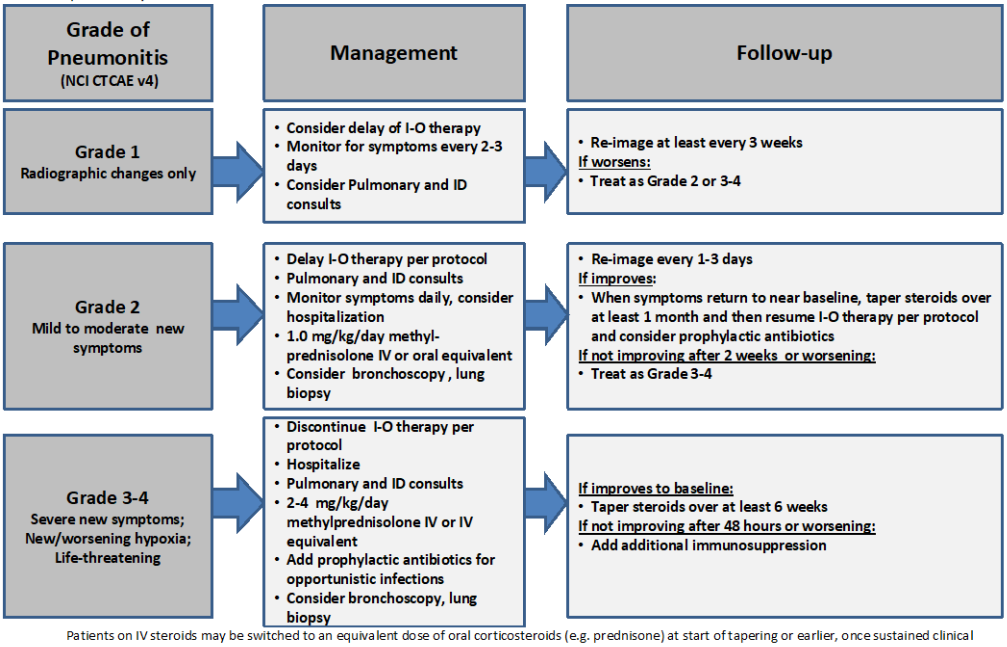


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

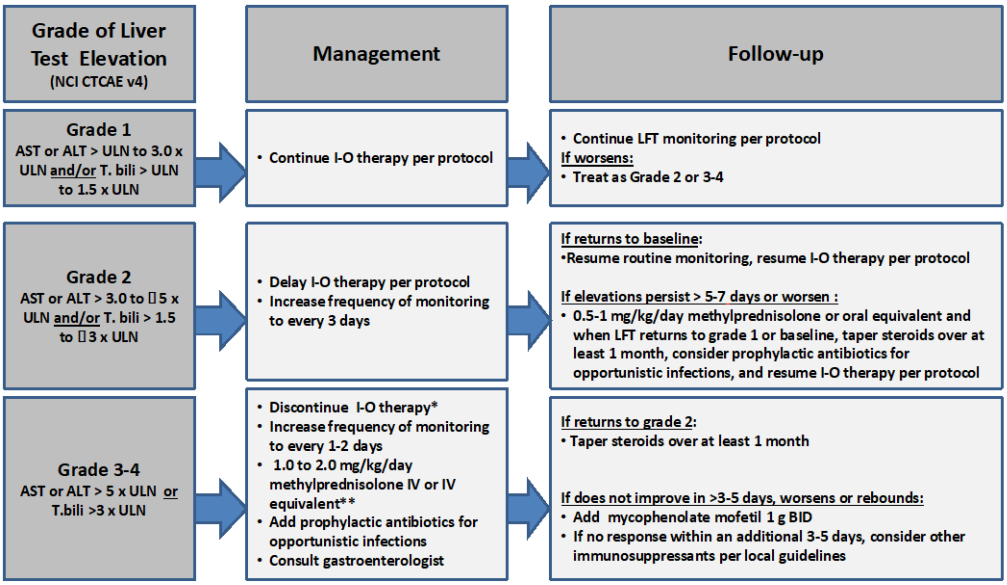


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

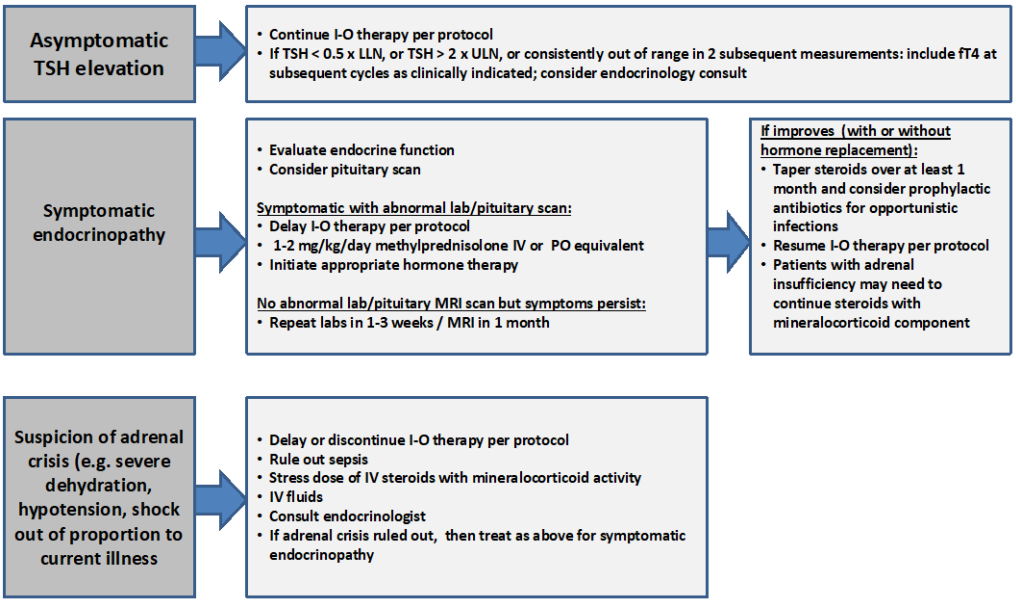
***I-O therapy may be delayed rather than discontinued if AST/ALT 8 x ULN or T.bili 5 x ULN.**

**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.

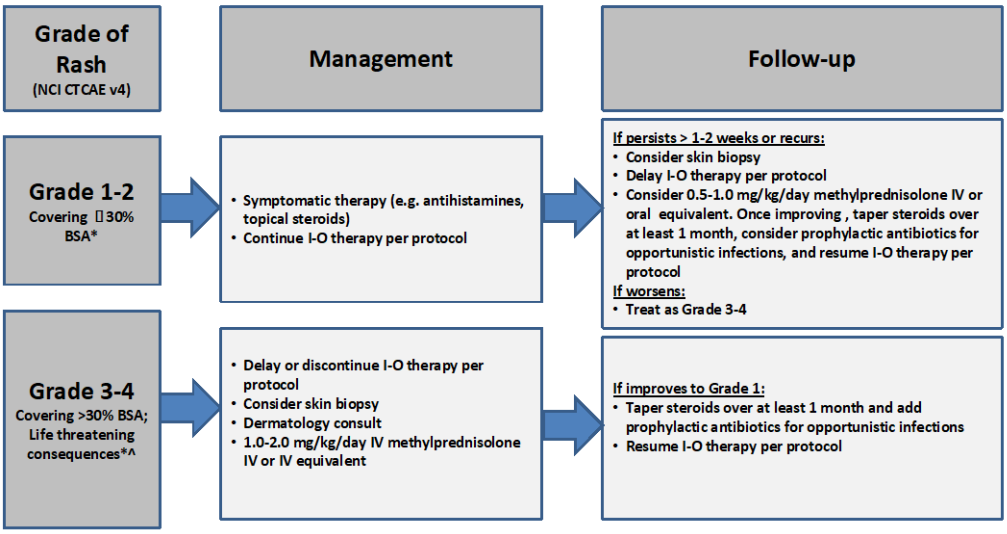


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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