ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA3161

A Phase III Randomized Study of Maintenance Nivolumab versus Observation in Patients with Locally Advanced, Intermediate Risk HPV Positive OPSCC

Rev. Add1

STUDY CHAIR:	Nabil F. Saba, MD
STUDY STATISTICIAN:	Yue Zheng, MS
TRANSLATIONAL SCIENCE CO-CHAIR:	Christine H. Chung, MD
LABORATORY CO-CHAIRS:	Joseph Califano, MD
	Alexandra Valsamakis, MD, PhD
IMAGING CO-CHAIR:	Rathan M. Subramaniam, MD, PhD, MPH
Rev. Add3 RADIATION ONCOLOGY CO-CHAIR:	Zain Husain, MD
MEDICAL ONCOLOGY CO-CHAIR	Ammar Sukari, MD
IMAGING STATISTICIAN:	Fenghai Duan, PhD
Rev. Add4 HEAD AND NECK COMMITTEE IMAGING CHAIR:	Rathan M Subramaniam, MD, PhD, MPH
HEAD AND NECK COMMITTEE CHAIR:	Barbara Burtness, MD

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STUDY PARTICIPANTS	***ACTIVATION DATE***
Rev. Add1 **ALLIANCE /** Alliance for Clinical Trials in Oncology	June 20, 2019
NRG / NRG Oncology	Addendum #1
SWOG / SWOG	Addendum #2
	Addendum #3
NCTN GROUP STUDY CHAMPIONS	Addendum #4
ALLIANCE: Alan Ho, MD, PhD	Addendum #5
Rev. Add3 **NRG:** Christina Henson, MD	
SWOG: Barbara Burtness, MD	

Agents	**IND#**	**NSC#**	**Supply**
Nivolumab (BMS-936558, MDX-1106, ONO-4538)	126146	748726	NCI
Cisplatin	IND Exempt	119875	Commercial

IND Sponsor: DCTD, NCI

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STUDY CHAIR

Nabil F. Saba, MD
Emory University School of Medicine
1365 Clifton Road, C2110
Atlanta, GA 30322
Tel: 404-778-3126
Fax: 404-778-5676
Email: nfsaba@emory.edu

Rev. Add3

STUDY CHAIR LIAISON (SCL)

Rev. Add1

Ms. Allyson Anderson
Winship Cancer Institute
Emory University Midtown
550 Peachtree St. NE
Atlanta, GA 30308
Tel: 404-6861794
Fax: 404-686-4537
Email: allyson.anderson@emory.edu

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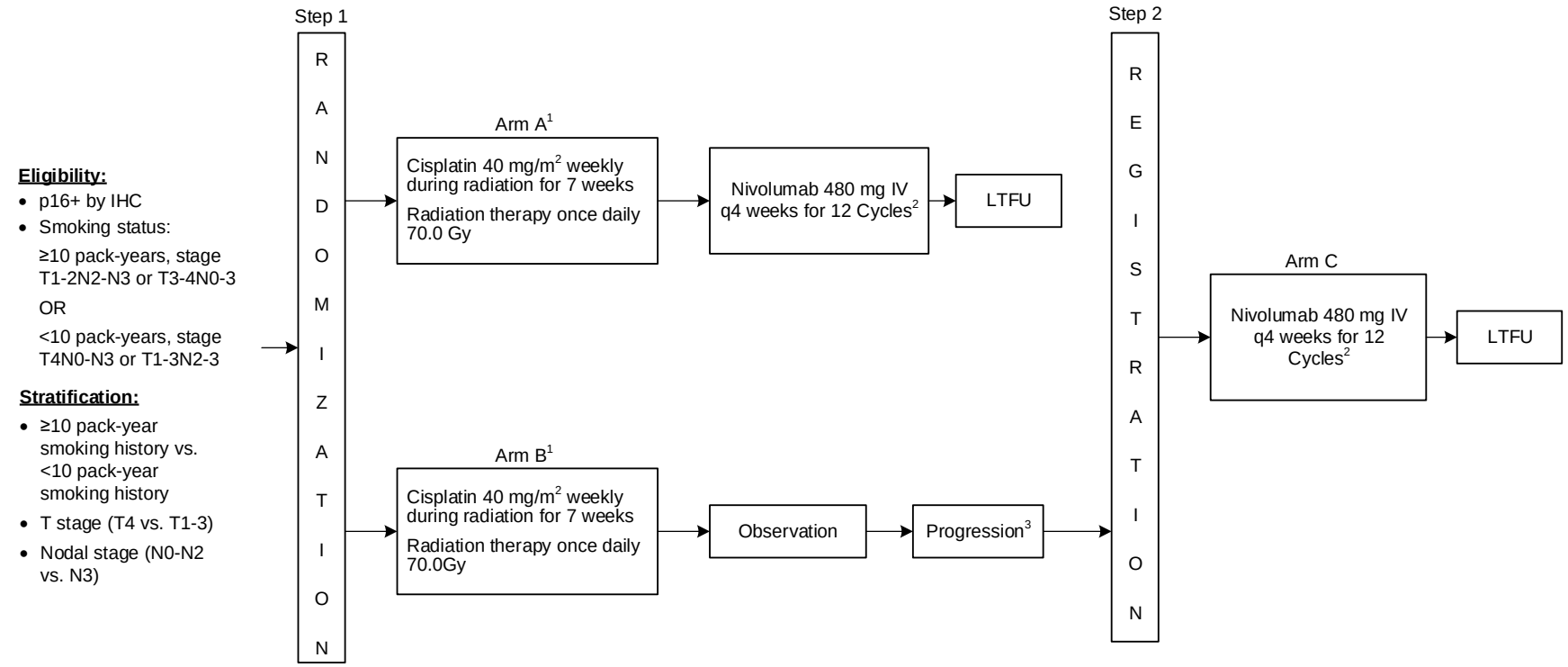
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Schema



1. Submit tissue for PD-L1 testing.
2. Cycle length = 28 days
3. Patients who were randomized to observation will be offered the option to cross over if they have clearly documented progression by the RECIST criteria and tissue-proven progression within 12 months from the end of cisplatin/radiation therapy.

1. Introduction

1.1 HPV Positive Oropharyngeal Carcinoma OPSCC

There has been a marked increased incidence of oropharyngeal squamous cell carcinoma (OPSCC), a subtype of squamous cell carcinoma of the head and neck (SCCHN), in recent decades due to increased incidence of high risk human papillomavirus (HPV)-related OPSCC [1-5]. Overall survival (OS) is substantially better among patients with HPV-driven OPSCC compared to HPV-negative disease [6, 7]. In one trial, detection of high risk HPV DNA in the tumors was noted as an independent prognostic variable for survival. Patients with HPV-driven OPSCC including all risk categories had a 3-year OS rate of 82.4%, compared to 57.1% among patients with HPV-negative tumors (P<0.001 by the log-rank test) [8, 9]. After adjustment for age, race, tumor and nodal stage and tobacco exposure, there was a 58% reduction in the risk of death. Nonetheless, a substantial number of patients with HPV-related OPSCC succumb to their disease. The risk of death significantly increases for the HPV-related with each additional pack-year of tobacco smoking, as well as increases in nodal stage. Based on data from ECOG 1308 (E1308), survival of patients with the intermediate risk (T4, N2, N3 or >10 pack-year smokers) category is inferior to that predicted by the model proposed in the Ang landmark NEJM paper [8]; HPV-driven OPSCC is therefore a heterogeneous disease as far as outcome and curability. A non-anatomic factor such as smoking is an important prognostic factor that is not incorporated in the AJCC version 8 staging system [10, 11]. Clearly patients with T4 or N2-N3 disease or smokers of more than 10-pk-year seem to be at the highest risk for death with an estimated 4-year OS of 68%. Patients with T3N3 or T4N2-N3 are at especially high risk with a 4-year survival of 51% [10]. Tobacco use is also an independent prognostic factor for survival. In an analysis of close to 900 patients with OPSCC, the intermediate risk HPV-positive group was defined as either patients with at least a 10 pack year smoking history, or patients with T4, N2-N3 disease regardless of smoking history [10]. In this group, the 3-year survival was 70%. It is of note also that the development of metastatic disease continues to occur as far as 5 years out from the completion of concurrent therapy, unlike the occurrence of distant metastases in the HPV-negative group which plateaus at 2 years following definitive therapy. Applying a maintenance approach in a group of patients at protracted risk of relapse is of clear interest [10,20].

Targeted immunotherapy promoting anti-tumor T-cell activity initially demonstrated improved survival and durable objective responses in advanced melanoma [12]. As PD-L1 expression is observed in close to 68% of SCCHN patients regardless of HPV status [13][14], targeting PD-1/PD-L1 in SCCHN was also a rational approach for study. Initially, pembrolizumab was studied in a Phase Ib study in patients with recurrent/metastatic disease [15]. In this study a significant clinical benefit with a response rate of close to 18% as well as a prolonged PFS was noted in heavily pretreated patients. Furthermore, the benefit was comparable between HPV-positive and negative groups. Pembrolizumab is now approved for use in recurrent or metastatic platinum refractory disease. In addition, the results from Checkmate-141, a phase III trial randomizing patients with recurrent or metastatic platinum-refractory SCCHN to nivolumab versus investigator's choice of chemotherapy, has shown a doubling of the 1-year OS (36.0% versus 16.6%, p= 0.0101); this occurred regardless of p-16 status [16].

1.2 Rationale for maintenance therapy in the intermediate risk HPV positive disease:

The aforementioned data clearly indicate that improving therapeutic outcome for patients with intermediate-risk HPV-related SCCHN is warranted. The clinical benefit from immune checkpoint inhibitors in the recurrent metastatic setting may be reflected in a prolonged stabilization of disease, raising interest in employing them as a form of maintenance therapy [15]. Further recent evidence indicated that nivolumab maintained function and improved symptoms in heavily pre-treated patient population making its use in a maintenance setting, following concurrent definitive therapy attractive (Harrington et al, Lancet Oncology 2017). These practice-changing results have opened the door to further investigate the role of nivolumab in HPV-related SCCHN especially the higher risk group. Given the noted significant activity in the HPV positive group, PD-1 inhibitors may play a significant role in prolonging survival in this patient population. This is further supported by the fact that HPV-positive OPSCC are associated with large numbers of PD-1–positive infiltrating T cells making the use of PD-1 inhibitors attractive in eradicating residual disease [17,18].

1.3 Rationale for selected approach and trial design

Several trials in the definitive setting have introduced immune check-point inhibitors in the treatment and maintenance of SCCHN, yet none have not focused on the biologically distinct disease that is HPV-related OPSCC. Even though, when it comes to trials of de-intensification focusing exclusively on HPV-positive disease seems to be the case in several clinical trials, focusing on the locally advanced intermediate risk HPV-positive OPSCC, is a current rarity among the currently developed studies. This proposal will have the advantage of focusing on HPV-positive intermediate risk OPSCC, with a specific focus on maintenance therapy in addition to providing robust, biologically significant correlative studies in this patient population. This will open the door for an in-depth analysis of the biology of HPV-related disease, biomarkers predictive of progression (saliva, blood, and genomic analysis) in addition to the possible influence of the introduction of checkpoint inhibitors on these biomarkers and disease outcome. We believe this trial constitute a departure from current studies, which are focused on locally advanced disease with HPV-driven and HPV-negative disease seeking an early signal; we believe we are in a unique position to answer an important question for a disease that has a distinct biology and behavior and to answer the crucial question of whether intensification of therapy through the addition of a PD-1 inhibitor is warranted in this group of relatively healthier patients.

The randomization upon enrollment will also provide an edge over some of the current pharma trials that are trending towards randomization following completion of concurrent therapy; patients with disease progression will therefore be included in the intent to treat analysis. In addition, the proof or lack of proof for the role of a pure maintenance approach can be potentially practice changing and is currently not being evaluated in other cooperative group trials in SCCHN.

Our current projections take into account the patients who required salvage surgery with longer follow-up based on data from E1308 (looking at the same population), data from RTOG-0129 as well as RTOG-0522. Data from RTOG-0522 and RTOG-0129 indicate a projected PFS of close to 73% in patients with high/intermediate risk HPV related OPSCC; however, both RTOG-0522 and RTOG-0129 included lower risk patients (also in Galloway et. al, PFS is defined

at time of neck dissection so that data set may not accurately reflect our patients in EA3161); it is rather challenging to retrieve data specific for T4 or N3 or smokers with HPV-related OPSCC from either RTOG-0129 or RTOG-0522. Looking at AJCC 8 as well as the ICON-S data, the N3 or T4 HPV positive patients have a 5 year OS of 57-59 %; in addition, these patients had 3-year PFS rate of 61% based on E1308 which provides a more accurate representation of this higher risk group. We therefore believe that there is clear room for improvement for this relatively high risk HPV-related disease. As far as the patients with initial disease progression, we agree that randomization at study entry would circumvent the exclusion of these patients from the overall analysis; we have therefore planned to randomize at study entry as indicated, avoiding any selection of a more favorable group of patients in either arm.

1.4 Radiation Therapy for the intermediate risk HPV positive disease:

Radiation therapy forms the treatment backbone for a majority of patients with locally advanced HPV+ oropharyngeal cancer. This is likely even more so in the population targeted in this trial, which enriches for T4 or N3 disease, where radiation is often favored due to concerns about organ preservation, functional outcomes, and potentially high rates of extranodal extension. Radiation therapy is most commonly delivered to a dose of 70 Gy in 2 Gy daily fractions with 5 fractions delivered per week over 7 weeks. This is usually given with a concurrent radiosensitizer such as cisplatin. Accelerated approaches to radiation, i.e. finishing the course in 6 or fewer weeks, appear to improve control rates at the cost of higher toxicity when radiation is given alone, however in a Phase III study of accelerated radiation with cisplatin based chemotherapy (RTOG 0129), acceleration failed to improve outcomes. Thus, in this study, standard fractionation will be used.

Several Phase II studies have examined dose de-escalation to 54-60 Gy, but largely for what would be considered low risk (T1-2N0-1) disease, with a minimal smoking history. It should be noted that “intermediate-risk HPV-driven disease,” is a relatively novel designation, and thus outcomes for this subgroup of patients have not been typically reported as a codified group. Still, the data suggest that distant metastases are the most common cause of demise in HPV-positive patients. This appears to hold true in T4 or N3 patients where the 3-year rate of distant metastases is 24% while the 3-year locoregional failure rate is 18% (O’Sullivan JCO 2013) [27]. Additionally, multiple large institutional series have demonstrated that smoking history correlates with the risk of distant metastases, particularly in the case of current active smokers (Maxwell CCR 2010, Weller Head and Neck 2017) [28, 29]. Taken together, this suggests that the approach taken in this study of adjuvant immunotherapy following locoregionally directed chemoradiation, in hopes of decreasing distant metastases and improving overall survival is a rational one.

1.5 Post Chemoradiation Therapy PET Response Assessment Method – ‘Hopkins Criteria’

The interpretation of 12 week post concurrent chemoradiation therapy FDG PET/CT scan will be based on structured qualitative assessment (‘Hopkins Criteria’)[30,31]. This is a five point scale with blood pool and liver as reference standard and accommodates FDG uptake due to post radiation inflammation. Score 1 and 2 will be interpreted as negative FDG PET/CT, score 3 represent FDG uptake likely due to post radiation inflammatory uptake (also considered

negative for residual tumor) and score 4 and 5 represent as positive FDG PET/CT for residual tumor. The interpretation criteria is based on 214 patient study (HNSCC) who had a post therapy FDG PET/CT for therapy assessment. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of the therapy assessment were 68.1%, 92.2%, 71.1%, 91.1%, and 86.9%, respectively. Among the HPV-positive patients (n = 123), there was a significant difference in PFS (hazard ratio [HR], 0.14; 95% confidence interval, 0.03-0.57; P = 0.0063) and OS (HR, 0.01; 95% confidence interval, 0.00-0.13; P = 0.0006) between the patients who had a score negative for residual tumor versus positive for residual tumor. A similar significant difference was observed in PFS and OS for all patients.

2. Objectives

2.1 Primary Objectives

2.1.1 To assess the efficacy of concurrent definitive therapy followed by nivolumab compared with concurrent definitive therapy followed by observation in terms of overall survival (OS). Rev. Add3

2.2 Secondary Objectives

2.2.1 To further assess the efficacy of nivolumab compared with observation in terms of:

2.2.1.1 To evaluate treatment effect within the subset of patients tested as PD-L1+

2.2.1.2 To evaluate the prognostic effect of baseline saliva and/or plasma HPV status

2.2.1.3 To evaluate the prognostic effect of mutation burden among patients on the Nivolumab arm Rev. Add3

2.2.1.4 To evaluate the association of 12-week post therapy FDG PET/CT OS and PFS.

2.2.1.5 To establish the prognostic value of SUV max of primary tumor or neck nodal metastasis of baseline FDG PET/CT for OS (and/or PFS).

2.2.1.6 To correlate SUV max of primary tumor or nodal metastasis of baseline FDG PET/CT with PD-L1 expression (positive vs. negative).

2.2.1.7 To compare the PET based therapy response assessment (Hopkins criteria) to the RECIST 1.1 assessment at 12 week post chemoradiation therapy, for patients who have a PET/CT scan at 12 weeks.

2.2.2 To assess the efficacy of concurrent definitive therapy followed by nivolumab in terms of progression free survival (PFS) Rev. Add3

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria for Step 1 Randomization

_____ 3.1.1 Age ≥ 18 years.

_____ 3.1.2 ECOG performance status of 0 or 1.

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_____ 3.1.3 Patients must have oropharynx cancer (AJCC 8) that is p16-positive by immunohistochemistry OR p16 equivocal by IHC and HPV positive by in situ hybridization with the following criteria:

≥10 pack-years, stage T1-2N2-N3 or T3-4N0-3 (less than 10 pack-years is considered a non-smoker)

OR

<10 pack-years, stage T4N0-N3 or T1-3N2-3.

_____ 3.1.4 Patients must not have known hypersensitivity to nivolumab or compounds of similar chemical or biologic composition.

_____ 3.1.5 Patients with a history of allergic reactions attributed to platinum-based chemotherapy agents are excluded.

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_____ 3.1.6 Patients must not have had prior systemic therapy, radiation treatment or surgery for p16 positive OPSCC.

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NOTE: Patients who had resection of T1 or T2 carcinoma with no radiation or chemotherapy are eligible if surgery was done 5 years prior to enrollment.

_____ 3.1.7 Patients must not have received previous irradiation for head and neck tumor, skull base, or brain tumors.

_____ 3.1.8 Patients must not receive investigational agents within 4 weeks of enrollment or at any time while on study.

_____ 3.1.9 Patients with evidence of distant metastases or leptomeningeal disease (LMD) are excluded.

_____ 3.1.10 Patients with uncontrolled inter-current illnesses which in the opinion of the investigator will interfere with the ability to undergo therapy including chemotherapy are excluded.

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_____ 3.1.11 Patients with a history of prior or second malignancy are excluded, with the exception of curatively treated non-melanoma skin cancer, or curatively treated cervical cancer; additionally, patients curatively treated for malignancy who remain disease-free at >2 years of follow up, are not excluded.

_____ 3.1.12 Baseline organ and marrow parameters (must be obtained ≤ 2 weeks prior to randomization).

- ANC ≥ 1500/mm^3 ANC: _____Date of test: _____
- Hgb ≥ 8.0 g/dL Hgb: _____Date of test: _____
- Platelet count ≥ 100,000/mm^3

  Platelet count: _____ Date of test: _____
- Creatinine clearance of ≥ 60 ml/min.

  Creatinine clearance: _____Date of test: _____

  Creatinine clearance may be measured or calculated. If calculating, creatinine clearance, use the Cockroft-Gault formula:

  (140 – Pt. age) x (Pt. weight in kg)/(72 x patient's serum creatinine) (for females, multiply the result by 0.85)

Actual, not ideal, body weight will be used.

_____ 3.1.13 Baseline liver function parameters (must be obtained ≤ 2 weeks prior to randomization):

- Total bilirubin within 1.5 times the normal limits

  ULN: _____ Total Bilirubin: _____ Date of test: _____
- SGOT (AST) or SGPT (ALT) within 2.0 times the normal limits AND Alkaline Phosphatase within 2.0 times the normal limits

  ULN: _____ AST/ALT: _____ Date of test: _____

  ULN: _____ Alk Phos: _____ Date of test: _____

_____ 3.1.14 Patients must not be pregnant or breast-feeding as chemotherapy, radiation, and immunotherapy may have possible teratogenicity

effects; in addition, complications from pregnancy may interfere with the ability of patients to have an uninterrupted therapy.

All patients of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.

A patient of childbearing potential is any patient, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of child bearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

Rev. Add3 _____ 3.1.15 Patients of childbearing potential must use an accepted and effective method of contraception or abstain from sexual intercourse for at least one week prior to the start of treatment, and continue for 5 months after the last dose of protocol treatment. Patients must also not donate ova during this same time period.

_____ 3.1.16 Patients must have measurable disease as defined in Section 6.1.

_____ 3.1.17 Patients must have tumor measurements with CT of neck and CT of chest (or CT of neck and FDG PET/CT if standard of care) within 4 weeks prior to Step 1 randomization.

Rev. Add3 _____ 3.1.18 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue disease, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjogren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

_____ 3.1.19 Patients 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 (precipitating event).

Rev. Add3 _____ 3.1.20 Patients must not have a condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone equivalents) or other immunosuppressive medications which are expected to continue during Nivolumab administration. Inhaled or topical steroids and adrenal replacement doses >10 mg/day prednisone equivalents are permitted in the absence of active autoimmune disease.

Rev. Add4 _____ 3.1.21 Patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undectable on suppressive therapy, if indicated.

Rev. Add4 _____ 3.1.22 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

_____ 3.1.23 Patients with a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) must have no detectable viral load on a stable antiviral regimen.

Rev. Add3 _____ 3.1.24 Patients must not be receiving any other investigational agents.

_____ 3.1.25 Patient must not have a baseline clinically significant hearing loss, which in the opinion of the investigator would preclude the use of cisplatin.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3.2 Eligibility Criteria for Step 2 Registration

_____ 3.2.1 Patients must have progression per RECIST criteria AND tissue-proven progression on Arm B treatment within 12 months after completion of radiation therapy.

_____ 3.2.2 ECOG performance status of 0 or 1.

_____ 3.2.3 Patients must not have known hypersensitivity to nivolumab or compounds of similar chemical or biologic composition.

_____ 3.2.4 Patients must not have received non-protocol anti-cancer therapy after completion of radiation and chemotherapy.

_____ 3.2.5 Baseline organ and marrow parameters (must be obtained ≤ 2 weeks prior to registration).

- ANC ≥ 1500/mm^3 ANC: _____Date of test: _____
- Hgb ≥ 8.0 g/dL Hgb: _____Date of test: _____
- Platelet count ≥ 100,000/mm^3

  Platelet count: _____ Date of test: _____

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- Creatinine within institutional limits of normal.

  Creatinine: _____Date of test: _____

_____ 3.2.6 Baseline liver function parameters (must be obtained ≤ 2 weeks prior to registration):

- Total bilirubin within 1.5 times the normal limits

  ULN: _____ Total Bilirubin: _____ Date of test: _____

- SGOT (AST) or SGPT (ALT) within 2.0 times the normal limits AND Alkaline Phosphatase within 2.0 times the normal limits

  ULN: _____ AST/ALT: _____ Date of test: _____

  ULN: _____ Alk Phos: _____ Date of test: _____

_____ 3.2.7 Patients must not be pregnant or breast-feeding as chemotherapy, radiation, and immunotherapy may have possible teratogenicity effects; in addition, complications from pregnancy may interfere with the ability of patients to have an uninterrupted therapy.

All patients of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

A patient of childbearing potential is any patient, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of child bearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

Rev. Add3 _____ 3.2.8 Patients of childbearing potential must use an accepted and effective method of contraception or abstain from sexual intercourse for at least one week prior to the start of treatment, and continue for 5 months after the last dose of protocol treatment. Patients must also not donate ova during this same time period.

Rev. Add4 _____ 3.2.9 Patients must have measurable disease as defined in Section 6.1 at the time of documented progression.

NOTE: For patients that have undergone salvage surgery for disease recurrence, measurable disease is not required at the time of registration to Step 2.

_____ 3.2.10 Patients must have tumor measurements with CT of neck and CT of chest (or CT of neck and FDG PET/CT if standard of care) within 4 weeks prior to Step 2 registration.

Rev. Add4 **NOTE:** Patients that have undergone salvage surgery for disease recurrence prior to Step 2 are not required to have measurable disease post-resection, but must have CT of neck and CT of chest (or CT of neck and FDG PET/CT if standard of care) after salvage surgery and within 4 weeks prior to step 2 registration to establish a baseline prior to Nivolumab.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration and Randomization Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;

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- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);

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- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact or with consenting privileges);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance). Additional information can be found on the

CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

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For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;

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- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To

participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website https://www.ctsu.org using your CTEP-IAM username and password
- Click on the Protocols in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA3161
- Click on Documents, select the Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Requirements For EA3161 Site Registration:

- IROC Credentialing Status Inquiry (CSI) Form - this form is submitted to IROC Houston when verification of credentialing status is needed. See Section 5.1.5.

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- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.

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Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website, go to the Regulatory Section and select Regulatory Submission

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

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Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on the Regulatory at the top of your screen;
- Click on the Site Registration; and
- Enter your 5-character CTEP Institution Code and click on Go
- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

NOTE: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to registration.

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The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Treatment should start within 2 weeks after registration.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

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Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

4.1 Randomization to Step 1 Randomization

4.1.1 Protocol Number

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4.1.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender

- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.5 Stratification Factors

≥ 10pack-year smoking history vs. < 10pack-year smoking history.

T stage (T4 vs. T1-3).

Nodal stage (N0-N2 vs. N3).

4.2 Registration to Step 2 Registration

4.2.1 Protocol Number EA3161

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4.2.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.2.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

4.3 Additional Requirements

4.3.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office.

4.3.2 Biological specimens are to be submitted as indicated in Section 10.

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4.3.3 Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (LabAdmin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on

the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

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4.3.4 Digital RT and Image Data Submission Using TRIAD

Along with the submission of Digital RT plans, Standard of Care Whole Body and Dedicated Head and Neck 18F-FDG PET/CT scans and diagnostic CT (with intravenous contrast) of the neck and chest (if chest was performed) will be collected by the ACR Core Laboratory. All imaging studies are to be submitted to the ACR Core Laboratory via TRIAD.

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.
- All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, please contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or call 703-390-9858.

4.4 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA3161 Forms Completion Guidelines.

5. Treatment Plan

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5.1 Administration Schedule

Overall Summary:

Patients will be randomized at study entry to nivolumab post concurrent therapy (Arm A) versus observation post concurrent therapy (Arm B). During concurrent therapy, cisplatin will be administered on a weekly basis in conjunction with radiation treatment for 7 weeks. Thereafter, patients randomized to Arm A will receive nivolumab as a single agent for 12 cycles starting within 4-8 weeks of completion of cisplatin/radiation therapy. Patients randomized to Arm B will go on to observation, however, they will be offered the option to cross-over to Arm C to receive nivolumab if they have clearly documented progression by the RECIST criteria and tissue-proven progression within 12 months from the end of cisplatin/radiation therapy.

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If patient consent is given, tissue from the standard of care biopsy (or salvage surgery) at time of progression, will be submitted for research. This biomarker analysis will help shed more light on the biology of patients with HPV-driven disease who have progression of cancer following exposure to radiation and chemotherapy.

Salvage Surgery:

Patients on both Arm A and B who have residual tumor or residual neck nodes following concurrent cisplatin/radiation therapy will be considered for salvage surgery. This need for salvage surgery will be determined by the treating investigators.

For patients who have surgery and who were randomized to nivolumab (Arm A), nivolumab will be resumed no later than 6 weeks following surgical resection and will continue for the total number of 12 treatments.

NOTE: Evidence of residual disease at 12 weeks that is salvageable by surgery does not count as tumor progression.

There are two circumstances in which a patient randomized to Arm B (observation) may have salvage surgery and cross over to Arm C:

(1) At 12 weeks post cisplatin/radiation for residual disease

Patients randomized to Arm B (observation) who have salvage surgery at 12 weeks will continue observation. These patients may be offered cross over to Arm C only when RECIST progression is documented following salvage surgery.

(2) Greater than 12 weeks post cisplatin/radiation for disease recurrence

If progression by RECIST criteria is present and documented on scans subsequent to a negative 12-week post-therapy scan, and salvage surgery is determined by the treating investigator to be feasible and indicated, salvage surgery is permitted. Following salvage surgery undertaken for disease recurrence documented after the 12-week scan, such patients are eligible to cross over to Arm C. Salvage surgery must be done before crossing over in this case. These patients will not require further tissue confirmation of progression as tissue from their salvage surgery will provide this confirmation.

5.1.1 Treatment Arm A

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Patients will receive concurrent therapy of cisplatin and radiation for 7 weeks. Cisplatin will be administered (+/- 2 days) as 40mg/m2 weekly, over one hour during a 5 days/week radiation schedule with 70 Gy of radiation administered once daily. See Section 5.1.4 for details regarding RT schedule. Maintenance therapy with nivolumab will initiate within 4-8 weeks after completion of concurrent therapy of cisplatin/RT. Nivolumab will be administered at 480 mg IV q4 weeks for 12 cycles thus completing a total of one year of maintenance therapy provided there is no evidence of disease progression (or for other compelling reasons that in the opinion of the investigator warrants discontinuation of nivolumab; such reasons include but are not limited to, significant toxicity deemed related to nivolumab, or a significant deterioration in the patient's health warranting discontinuation of therapy). See Section 5.4.

Cisplatin administration will require hydration. Any preexisting dehydration should be corrected.

Hydration Requirements

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre- and post-cisplatin hydration is achieved and renal function remains adequate. One suggested regimen consists of administering cisplatin in 500 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consist of NS at 500 cc/hr x 1 liter and post-cisplatin hydration consist of 1/2 NS + 10 meq KCl/liter + 1 gram magnesium sulfate/liter + 25 grams mannitol/liter at 500 cc/hr for at least one hour, followed by additional hydration at the discretion of the investigator.

Antiemetics

It is suggested that patients receive antiemetic therapy, acute and delayed, including dexamethasone, 5-HT3 serotonin receptor antagonists and aprepitant, according to published ASCO guidelines. However, the specifics of the regimen are at the discretion of the treating physician, provided adequate control is achieved. One potential regimen consists of 20 mg of oral or IV dexamethasone and an oral or IV 5-HT3 antagonist (such as 2 mg oral or 10 mcg/kg IV granisetron, or 8 mg oral or IV ondansetron) on the day of cisplatin administration. Followed by additional antiemetics consisting of oral dexamethasone and scheduled 5-HT3 serotonin receptor antagonists on days 2-5. For example, 8 mg orally, twice daily for days 2 and 3, and then 4 mg orally, twice daily for days 4 and 5, especially if aprepitant is not given. Aprepitant should be used with caution when combined with dexamethasone due to the possibility of a drug interaction with dexamethasone via CYP3A4 pathway. On the day of chemotherapy administration, the dose of dexamethasone must be reduced by 50%, if aprepitant is given. Antiemetics can vary as long as it does not contradict protocol language.

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Manitol administration is allowed with cisplatin and is left to the discretion of the treating centers.

It is suggested that patients be evaluated by speech and swallow therapy and provided with swallowing exercises during and following concurrent therapy.

Oral care for patients with mouth rinses is strongly encouraged during radiation therapy; management of pain is also encouraged and left at the discretion of the treating physicians.

5.1.2 Treatment Arm B

Patients will receive concurrent therapy of cisplatin and radiation for 7 weeks. Cisplatin will be administered as 40mg/m2 weekly during a 5 days/week radiation schedule with 70 Gy of radiation administered once daily. See Section 5.1.4 for details regarding RT schedule. Following the completion of the 7 weeks of concurrent therapy of cisplatin/RT, the patient will go on to observation.

5.1.3 Treatment Arm C

Patients who were randomized to observation will be offered the option to cross over if they have clearly documented progression by the RECIST criteria and tissue-proven progression within 12 months from the end of cisplatin/radiation therapy. If consent is given, tissue from the standard of care biopsy at time of progression will be submitted for research.

After progression and registration to Step 2, Nivolumab will be administered at 480 mg IV q4 weeks for 12 cycles starting within 2 weeks of Step 2 registration. Patients will complete a total of one year of therapy provided there is no evidence of disease progression (or for other compelling reasons that in the opinion of the investigator warrants discontinuation of nivolumab; such reasons include but are not limited to, significant toxicity deemed related to nivolumab, or a significant deterioration in the patient's health warranting discontinuation of therapy).

5.1.4 Radiation Dose and Timing

Treatment should start within 2 weeks of registration. Radiation should start on a Monday (preferred), or Tuesday, or Wednesday.

Intensity Modulated Radiation Therapy (IMRT) and Image-Guided Radiation Therapy (IGRT) are required for this study. Proton therapy is not permitted.

IMRT/IGRT will be given in 35 fractions over 7 weeks, 5 fractions per week. Missed treatments due to holidays or logistical reasons can be compensated by delivering fractions given twice in one day, with a minimum inter-fraction interval of 6 hours, or by treating on weekends.

5.1.4.1 Equipment

Modality: Accelerator x-ray beams with nominal energy of at least 4 MV shall be used. Accelerators must be capable of delivering treatment using multileaf collimation.

Cyberknife treatment is not allowed. Proton therapy is not allowed.

Intensity Modulated Radiation Therapy (IMRT) is mandatory for this study. Guidelines developed by the NCI for the use of IMRT in clinical trials should be followed. (See the IROC Rhode Island website, www.irocri.qarc.org).

Calibration: All therapy units used for this protocol shall have their calibrations verified by the IROC Houston QA Center.

5.1.4.2 CT Simulation

CT simulation will be required in all patients. A thermoplastic mask shall be used for patient immobilization (shoulders along with head strongly encouraged, although an alternative method of ensuring reproducible shoulder position is acceptable) for both CT-simulation and for each daily treatment. IV contrast simulation is strongly recommended in all patients (unless renal function prohibits contrast). If an institution does not perform IV contrasted simulations then it is acceptable to perform a non-contrasted simulation provided a diagnostic CT with contrast can be fused to the simulation CT. Slice thickness of ≤ 3mm is required. The patient should be simulated and immobilized with the neck extended in a position that will be reproducible on a daily basis. The scan should at a minimum extend from the top of the orbits to the aortic arch.

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5.1.4.3 Image Fusion

Fusion of other studies (MRI, PET/CT) to the treatment planning CT is permitted to help aid in volume delineation.

5.1.4.4 Target Volume Delineation

Table 1: Clinical Target Volume Nomenclature and Description.

Standard Name	Description	Structure Requirement
GTV_70	Primary tumor and involved nodes	**Required**
CTV_70	GTV + 5 mm margin, excluding anatomic boundaries to tumor spread	**Required**
PTV_70	CTV-to-PTV (3-5mm margin depending on institutional reproducibility)	**Required**
PTV_70_Eval	PTV minus OARs, subtract 3 mm from the skin when needed	**Required when applicable**
CTV_63	CTV to receive 63 Gy (high risk elective nodes)	**Required when applicable**
PTV_63	CTV-to-PTV (3-5mm margin depending on institutional	**Required when applicable**

Standard Name	Description	Structure Requirement
	reproducibility)	
PTV_63_Eval	PTV minus OARs, subtract 3 mm from the skin when needed	**Required when applicable**
CTV_56	CTV to receive 56 Gy (low risk elective nodes)	**Required when applicable**
PTV_56	CTV-to-PTV (3-5mm margin depending on institutional reproducibility)	**Required when applicable**
PTV_56_Eval	PTV minus OARs, subtract 3 mm from the skin when needed	**Required when applicable**

Gross Tumor Volume (GTV): The GTV_70 will encompass the primary tumor volume and involved lymph nodes designed in concordance with physical exam findings, endoscopic findings, as well as imaging studies. FDG-PET may assist in GTV localization, but GTV contours should not be based solely on PET given uncertainties regarding the edge of the PET signal and the tumor border. Involved nodes are defined as those >1.5 cm in long axis or >1cm in short (axial) axis. Nodes of any size with radiologic evidence of necrosis or extranodal extension (ENE) are to be considered involved. Smaller nodes located in close proximity to either the primary site and/or other grossly involved nodes, or those demonstrating significant PET uptake may be considered involved.

Clinical Target Volume (CTV): The CTV_70 represents a 5mm isotropic expansion of the GTV_70. CTVs should be edited along natural barriers to spread such as air cavities, bone, fascial planes, and the external body contour.

Additionally, elective nodal CTVs for coverage of microscopic nodal disease include a CTV_63 for high risk subclinical nodes, such as the ipsilateral node positive hemineck, and a CTV_56 for low risk subclinical nodes, such as the uninvolved contralateral hemineck.

Planning Target Volume (PTV): Will consist of a minimum of 3mm and a maximum of 5mm in all directions to define each respective PTV (PTV 70, PTV 63, PTV 56). The PTV margin should be based on the set-up reproducibility at each institution.

Generally speaking, the PTV should not extend beyond the skin, unless the skin was involved with tumor, in which case the application of bolus material over this portion of the PTV should be considered. Additionally, it is allowable to define 2 PTV's for a given CTV. The first would be a planning PTV can extend beyond the skin surface and is used for planning treatment segments. The second would

be the PTV Evaluation (PTV_Eval), which does not reach the skin surface within 3 mm and is used for evaluation of the dose volume histogram to determine if treatment goals have been met.

For some patients, a PTV will overlap critical organs. When a PTV overlaps a critical OAR (spinal cord and/or brainstem) and its associated PRV, the PTV_Eval should be modified to exclude the OAR.

5.1.4.5 Unilateral Treatment

Unilateral neck treatment is allowed on the study if it is in the institution's established practice, and it meets the clinical criteria described below. Unilateral neck treatment is recommended in the case of well lateralized tonsillar primaries, defined as those with <1cm extension into soft palate or base of tongue, who have no posterior pharyngeal wall extension, and who also are N0 or N1 with a single lymph node < 3cm.

Unilateral treatment may be offered to subjects with N1 disease with < 3 nodes confined to level II as long as the primary site is lateralized as defined above.

Bilateral treatment is mandatory for N2 or N3 tumors, as well as those arising from the soft palate, tongue base or posterior pharyngeal wall.

5.1.4.6 Description of at risk nodal volumes

The nodal levels to be included in the nodal CTVs are detailed in the table below.

Table 2: Nodal level to be included in the elective nodal CTVs

Nodes*	**Ipsilateral Neck**	**Contralateral Neck****
N0-N1 (single node < 3 cm)	II-IV 1b(for oral cavity extension) RP (lateral RP nodes for posterior pharyngeal wall involvement, soft palate involvement)	II- IV RP (lateral RP nodes for posterior pharyngeal wall involvement, soft palate involvement)
N1 (2 or more nodes)	II-V 1b(for oral cavity extension or extensive adenopathy) retrostyloid nodes (for any patient with level II nodal involvement) lateral RP nodes medial RP nodes (if lateral RP nodes involved)	II-IV RP (lateral RP nodes for posterior pharyngeal wall involvement, soft palate involvement)

Nodes*	Ipsilateral Neck	Contralateral Neck**
N2	II-V 1b (for oral cavity extension or extensive adenopathy) retrostyloid nodes (for any patient with level II nodal involvement) lateral RP nodes medial RP nodes (if lateral RP nodes involved)	According to N stage in contralateral neck
N3	Ib-V retrostyloid nodes (for any patient with level II nodal involvement) lateral RP nodes medial RP nodes (if lateral RP nodes involved)	According to N stage in contralateral neck

*definitions of the lymph node levels can be found in Gregoire Radiother Oncol 2014.

**patients who are eligible for omitting radiation to the contralateral neck are discussed above.

5.1.4.7 IMRT techniques: Dose-Painting versus Cone-Down

IMRT will utilize a dose painting technique (differential daily doses to different target volumes using a single IMRT plan throughout the course of treatment, i.e. 2 Gy per day for PTV_70, 1.8 Gy per day for PTV_63, and 1.6 Gy per day for PTV_56) rather than by using sequential cone-down IMRT plans.

5.1.4.8 Management of low neck

Head and neck irradiation utilizing IMRT will be used to treat the entire neck. The clinical target volume (CTV) [upper and lower neck and primary tumor bed] is irradiated with IMRT. There is no match line between upper and lower portions of the regions at risk.

Treatment with a matched AP/PA lower neck field is not allowed.

5.1.4.9 IMRT Planning

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTVs and critical normal structures. An “inverse” treatment plan using computerized optimization shall be used. The treatment aim will be the delivery of radiation to the PTVs and minimizing dose to critical structures and non-involved tissue. All plans shall be normalized such that at least 95% of the volume of the PTV is covered by the prescribed isodose surface.

5.1.4.10 Tissue Heterogeneity

The dose calculation algorithm shall take into account the effect of tissue heterogeneities. The method used for tissue heterogeneity calculations shall be reported. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

A list of acceptable algorithms to account for tissue heterogeneity correction can be found at http://irochouston.mdanderson.org/RPC/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf

5.1.4.11 Time-Dose Considerations

Treatment will be delivered once daily, 5 fractions per week over 7 weeks. Treatment breaks, should be taken only if necessary and should not exceed 5 treatment days. The reason(s) for the break must be clearly recorded in the treatment record. Any treatment break(s) exceeding two (2) treatment days for reasons other than toxicity/illness will be considered a protocol deviation. The reason for the missed treatment(s) must be disclosed in the copy of the patient's treatment record submitted to IROC Rhode Island.

5.1.4.12 Definition of Organs at Risk

The following critical structures should be carefully outlined, and attempts should be made to minimize doses to these structures. Structures must be named for RT data submission exactly as listed in the table below (Table 3). Resubmission may be required if labeling does not match the standard name listed.

Standard Name	Description	Necessity
SpinalCord	Spinal Cord	**Required**
SpinalCord_PRV05	Planning Risk Volume of 5mm margin around Spinal Cord	**Required**
BrainStem	Brain Stem	**Required**
BrainStem_PRV05	Planning Risk Volume of 5mm margin around Brain Stem	**Required**
OpticNrv_L	Left Optic Nerve	**Required**
OpticNrv_R	Right Optic Nerve	**Required**
OpticChiasm	Optic Chiasm	**Required**
Parotid_L	Left Parotid	**Required**
Parotid_R	Right Parotid	**Required**

Standard Name	Description	Necessity
Cavity_Oral	Oral Cavity	**Required**
Lips	Lips	**Required**
Mandible	Mandible	**Required**
OARPharynx	Uninvolved posterior pharyngeal wall plus adjacent constrictor muscles	**Required**
Esophagus	Cervical Esophagus	**Required**
Larynx_SG	Glottic/SupraGlottic Larynx	**Required**
Glnd_Submand_L	Left Submandibular Salivary Gland	**Required**
Glnd_Submand_R	Right Submandibular Salivary Gland	**Required**
External	Patient contour encompassing all patient anatomy with a single contour on each slice	**Required**
E-PTV	All tissue excluding the PTVs	**Required**

Definitions

All of the following structures are to be contoured according to the guidelines below:

Spinal Cord: The spinal cord begins at the cranial-cervical junction (i.e. the top of the C1 vertebral body). Superior to this is the brainstem. The spinal cord should be contoured until approximately T3-T4. The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined which is equal to the spinal cord + 5 mm in each dimension, irrespective of the use of IGRT for margin reduction.

Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined, which is equal to the brainstem + 5 mm in each dimension, irrespective of the use IGRT for margin reduction.

Lips: The definition of the lips is self-explanatory.

Oral Cavity: The oral cavity will be defined as a structure inclusive of the anterior one half to two thirds of the oral tongue/floor of mouth, buccal mucosa, and palate.

Parotid Glands: Parotid glands are defined based on the treatment planning CT scan, and include both the superficial and deep lobes.

OARPharynx: This is defined as the “uninvolved” posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). Areas of overlap with the PTVs should be excluded.

Cervical Esophagus (Esophagus): This is defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.

Glottic/Supraglottic Larynx (Larynx_SG): The GSL begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

Mandible (Mandible): The mandible includes the entire bony structure from TMJ through the symphysis.

Unspecified Tissue outside of the Targets (E-PTV): This will be defined as all tissue located between the skull base and thoracic inlet excluding all PTVs and defined normal structures within the external contour of the patient.

5.1.4.13 Prioritization for IMRT planning:

1. Spinal Cord
2. Brainstem
3. PTV70
4. PTV63
5. PTV3 56
6. OARpharynx
7. Parotid gland contralateral to primary tumor site
8. GSL
9. Esophagus
10. Lips
11. Oral cavity
12. Parotid gland ipsilateral to primary tumor site
13. Mandible
14. Unspecified tissue outside targets

5.1.4.14 Compliance Criteria

All treatment plans are to be normalized so that 95% of the PTV1 volume is covered by 70 Gy. Plan evaluation criteria are given in the table below.

NOTE: An Unacceptable Deviation results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal

and additional treatment planning optimization is recommended.

Table 4: Target volumes and OAR Constraints

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
PTV_70 or PTV_Eval_70	D95%[Gy]	>=70	>=69
	V95%[%]	>99	>=90
	D0.03cc[Gy]	<=77	<= 82
E-PTV	D1cc[Gy]	< 74	<=77
PTV_63	D95%[Gy]	>=63	>=59.9
PTV_56	D95%[Gy]	>=56	>=50.4
SpinalCord_PRV05	D0.03cc[Gy]	<= 50	<= 52
BrainStem_PRV05	D0.03cc[Gy]	<= 54	<=56
OpticNrv_L or OpticNrv_R	D0.03cc[Gy]	<= 54	<=56
OpticChiasm	D0.03cc[Gy]	<=54	<=56

Table 5: Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	Deviation Unacceptable
Overall Treatment time	< 50 days	50-54 days (without a medically appropriate indication for delay)	> 54 days (without a medically appropriate indication for delay)
Interruptions	0-2	2-4	> 4

Table 6: Recommended dose acceptance criteria for other normal tissue but not to be used for plan score

Name of Structure	Recommended dose acceptance criteria
Parotid_L or Parotid_R	Mean[Gy] <26 (for at least one parotid)
Lips	Mean[Gy] <20
Larynx_SG	Mean[Gy] <45
OARPharynx (excluding PTVs)	Mean[Gy] <45
Glnd_Submand_L or Glnd_Submand_R (contralateral)	Mean[Gy] <39
Cavity_Oral (non-involved oral cavity)	Mean[Gy] <30
	D0.03cc[Gy] <60
Esophagus	Mean[Gy] <30
	D0.03cc[Gy] <60
Mandible	D0.03ccMax[Gy] <70
Cochlea	Max [Gy] <35

5.1.4.15 Replanning

On occasion, due to weight loss or shrinkage of lymphadenopathy, substantial changes in the patient anatomy can occur during the treatment. This can lead to inadequate immobilization as the mask from the original CT simulation may be seen to fit poorly. Additionally, this may have implications on the dose distribution as well. In these situations, it is recommended that a new mask be created and a repeat CT simulation be performed to assess the planned dose distributions on the current anatomy. Whether replanning is necessary will be up to the treating physician. It should be noted however, that the target volumes should be similar to the initial plan and not be adjusted for treatment response, except to respect distinct anatomic barriers such as the external body contour, muscle, or fascial planes that were initially uninvolved by disease.

5.1.4.16 Image Guided Radiation Therapy (IGRT)

Daily IGRT is mandated for this study. IGRT credentialing is required. Sites that have been previously approved for head and neck IGRT credentialing will not have to repeat credentialing for this study.

IGRT may be achieved using any one of more of the following techniques:

- Orthogonal kilovoltage (KV) images
- Linear-accelerator mounted kV and MV conebeam CT images
- Linear-accelerator mounted MV CT images

5.1.4.17 Radiation Therapy Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE).

Grade 3 therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about one half to two thirds of patients. Nutritional evaluation prior to the initiation of therapy is highly recommended. In the absence of substantial pretreatment dysphagia and associated weight loss of > 10% body weight, prophylactic PEG tube insertions are not recommended. If performed, placement of a feeding tube should be recorded on the appropriate case report form in RAVE, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

5.1.5 Credentialing Requirements

Institutions using IMRT must be credentialed prior to delivery of radiation therapy on any protocol patient. Credentialing requirements are listed in the table below. Institutions previously credentialed for use of IMRT in clinical trials need not repeat the credentialing for this trial.

Web Link for Credentialing Procedures and Instructions:
http://irochouston.mdanderson.org

RT Credentialing Requirements	Treatment Modality	Key Information
	IMRT	
Facility Questionnaire	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	To determine if your institution has completed the requirements for this study, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Phantom Irradiation	X	The IMRT head and neck phantom provided by the IROC Houston QA Center must be successfully irradiated. Instructions for requesting and irradiating the phantom may be found on the IROC Houston website (http://irochouston.mdanderson.org). Tomotherapy and Cyberknife treatment delivery modalities must be credentialed individually.

RT Credentialing Requirements	Treatment Modality	Key Information
	IMRT	
IGRT Verification Study	X	Institutions planning to use PTV margins of 3 mm must be credentialed for bony landmark IGRT by IROC Houston. Find details on the IROC Houston QA Center website (http://irochouston.mdanderson.org) Institutions that have previously been approved for IGRT may not need to repeat credentialing.
Institution		Institutions will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and ECOG-ACRIN Headquarters that all desired credentialing requirements have been met.

5.1.6 QA Documentation

5.1.6.1 **Submission of Digital Radiation Therapy Data**

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps (see Section 4.3.4 for details). Additional information is available at:

http://triadhelp.acr.org/ClinicalTrials/NCISponsoredTrials.aspx

Use of SFTP will also be accepted as an alternate method of data submission on this study. See the instructions for submission of data via SFTP on the IROC Rhode Island website under Digital Data.

Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data.

5.1.6.2 **Required Documentation and Timelines**

Within 3 days of the start of radiotherapy for each patient, the following data shall be submitted:

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Copies of the pretreatment diagnostic imaging and copies of the operative and pathology reports must also be submitted.
- Treatment planning system summary report that includes the monitor unit calculations, beam

parameters, calculation algorithm, and volume of interest dose statistics.

- Dose prescription for the entire treatment
- RT-1 Dosimetry Summary Form

Within one week of the completion of radiotherapy, the following data shall be submitted:

- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas
- RT-2 Radiotherapy Total Dose Record Form
- If there are any changes in the patient's status (i.e. early discontinuation of protocol therapy, delay in starting radiotherapy, or break in radiotherapy) these should be communicated in writing to IROC Rhode Island.

Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist
IROC Rhode Island QA Center
Phone: (401) 753-7600
Email: physics@qarc.org

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5.2 Adverse Event Reporting Requirements

All toxicity grades described in this protocol and all reportable adverse events on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

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ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to protocol treatment.
Unlikely	The AE is *doubtfully related* to protocol treatment.
Possible	The AE *may be related* to protocol treatment.
Probable	The AE is *likely related* to protocol treatment.
Definite	The AE is *clearly related* to protocol treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the

protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.2.3 Mechanisms for Adverse Event Reporting

Routine reporting: Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA3161 forms packet for instructions on what, where and when adverse events are to be reported routinely.

Expedited reporting: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provides information and instructions regarding expedited adverse event reporting.

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5.2.4 Expedited Adverse Event Reporting Procedure

This protocol is a Medidata Rave-CTEP-AERS Integration study.

The general procedures outlined below describe how to report an Adverse Event (AE) requiring expedited reporting on an Integration study.

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline/once protocol treatment initiates must be reported in Medidata Rave, according to the instructions on the EA3161 Adverse Event/ Late Adverse Event Form. These forms are available for each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period.

All AEs that occur prior to enrollment/ prior to the start of protocol treatment must be recorded in Medidata Rave on the EA3161 Baseline Adverse Events Form only and should not be included in the Rave CTEP=AERS Integration or on the Adverse Events Form located in the Treatment Folders in Rave unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process to determine if expedited reporting is required, the staff must verify the following on the EA3161 Adverse Event/Late Adverse Event Form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

NOTE: The site must reports AEs in Rave at the time the Investigator learns of the event.

NOTE: If an AE reported on the EA3161 Adverse Events/Late Adverse Events Form is modified, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the site must then submit the AE for rules evaluation by completing the Expedited Reporting Evaluation Form. Both NCI and EA3161 protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for all AEs that meet expedited reporting requirements. The site must then complete the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation Form.

In the rare occurrence that Internet connectivity is disrupted, a 24-hour notification is to be made by telephone to:

- The AE team at ECOG-ACRIN (857-504-2900) – for all arms
- CTEP at 301-897-7497 for Arms A and C
- The FDA at 1-800-FDA-1088 for Arm B

Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website.

NCI guidelines for SAE reporting and then CTEP-AERS application are available on the CTEP website http://ctep.cancer.gov.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301-897-7404) for Arms A and C and FDA (800-332-0178) for Arm B in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.5 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event

- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol EA3161 and outline the specific expedited adverse event reporting requirements for study EA3161.

5.2.6 Steps to determine if an adverse event is to be reported in an expedited manner – Arms A and C

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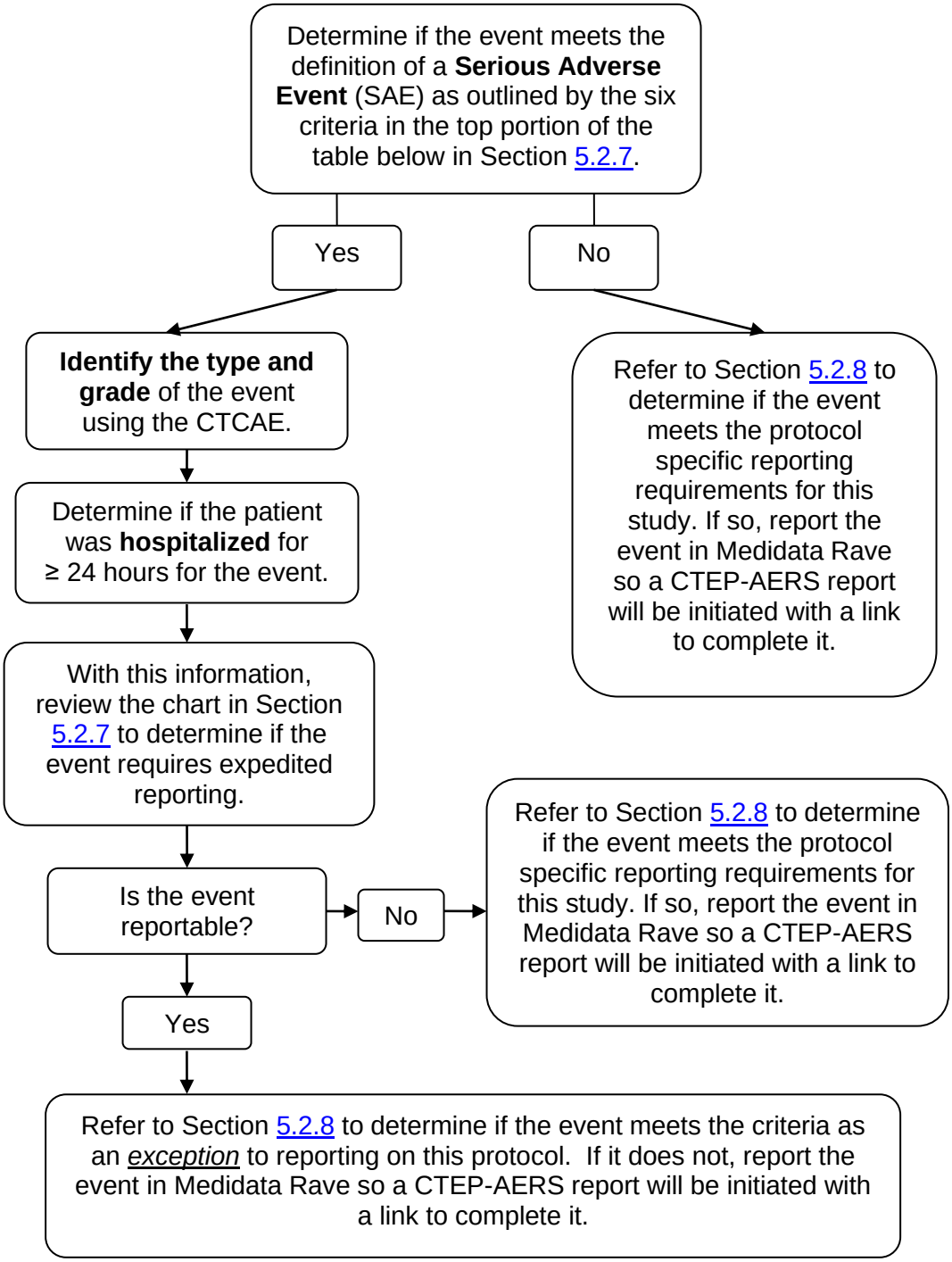
5.2.6.1 Guidelines for reporting adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).

- Site must determine if an event meets expedited reporting requirements so that the AE will be entered into Medidata Rave, triggering a CTEP-AERS report, within the mandated timeframes outlined in Section 5.2.7.
- Do not initiate the CTEP-AERS report via the CTEP-AERS website.
- We encourage all sites to confirm the Rules Engine assessment with the charts and tables below.
- Once the CTEP-AERS is completed, ECOG-ACRIN, the NCI, and all appropriate regulatory agencies will be notified of the event in an expeditious manner.


Determine if the event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.2.7.
Yes
No
Identify the type and grade of the event using the CTCAE.
Refer to Section 5.2.8 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in Medidata Rave so a CTEP-AERS report will be initiated with a link to complete it.
Determine if the patient was **hospitalized** for ≥ 24 hours for the event.
With this information, review the chart in Section 5.2.7 to determine if the event requires expedited reporting.
Is the event reportable?
No
Refer to Section 5.2.8 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in Medidata Rave so a CTEP-AERS report will be initiated with a link to complete it.
Yes
Refer to Section 5.2.8 to determine if the event meets the criteria as an *exception* to reporting on this protocol. If it does not, report the event in Medidata Rave so a CTEP-AERS report will be initiated with a link to complete it.

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5.2.6.2 Guidelines for reporting adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.7, OR the protocol specific requirements in Section 5.2.8 AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported in CTEP-AERS accessed via Medidata Rave even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.7 Expedited Reporting Requirements for Arm A and C on protocol EA3161

Investigational Agents: Nivolumab

Commercial Agents: Cisplatin, Radiation

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI in CTEP-AERS accessed via Medidata Rave within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.8 Additional instructions, requirements and exceptions for protocol EA3161

Additional Instructions

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.
- **Reporting a death on study**: A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

EA3161 specific expedited reporting requirements:

- **Infusion Reactions:** Any grade 3 and higher infusion reactions must be reported in CTEP-AERS accessed via Medidata Rave according to the timeframes outlined in the AE table in Section 5.2.7.
- **Treatment Delay**: Any delay in Nivolumab treatment lasting > 6 weeks that is related to the drug Nivolumab must be reported in CTEP-AERS accessed via Medidata Rave within 10 calendar days of learning of the delay. A treatment delay incident meeting these criteria must be reported as a grade 2 event under the CTCAE category 'General disorders and administration site conditions – Other, specify' and it must be specified as a treatment delay.
- **Long Term Adverse Events:** Any grade 3 or higher adverse event within the radiation field occurring beyond 12 weeks post radiation treatment (excluding events related to salvage surgery) must be reported in CTEP-AERS accessed via Medidata Rave according to the timeframes outlined in the AE table in Section 5.2.7. A long term adverse event incident meeting these criteria must be reported under the CTCAE category 'Injury, poisoning and procedural complications – Other, specify' and it must be specified as a long term adverse event within the radiation field.
- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on

nivolumab, or within 28 days of the female patient's last dose of nivolumab, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of the Investigator's knowledge. Please refer to Appendix VI for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EA3161 specific expedited reporting exceptions:

For study arms A and C, the adverse events listed below **do not** require expedited reporting:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event.

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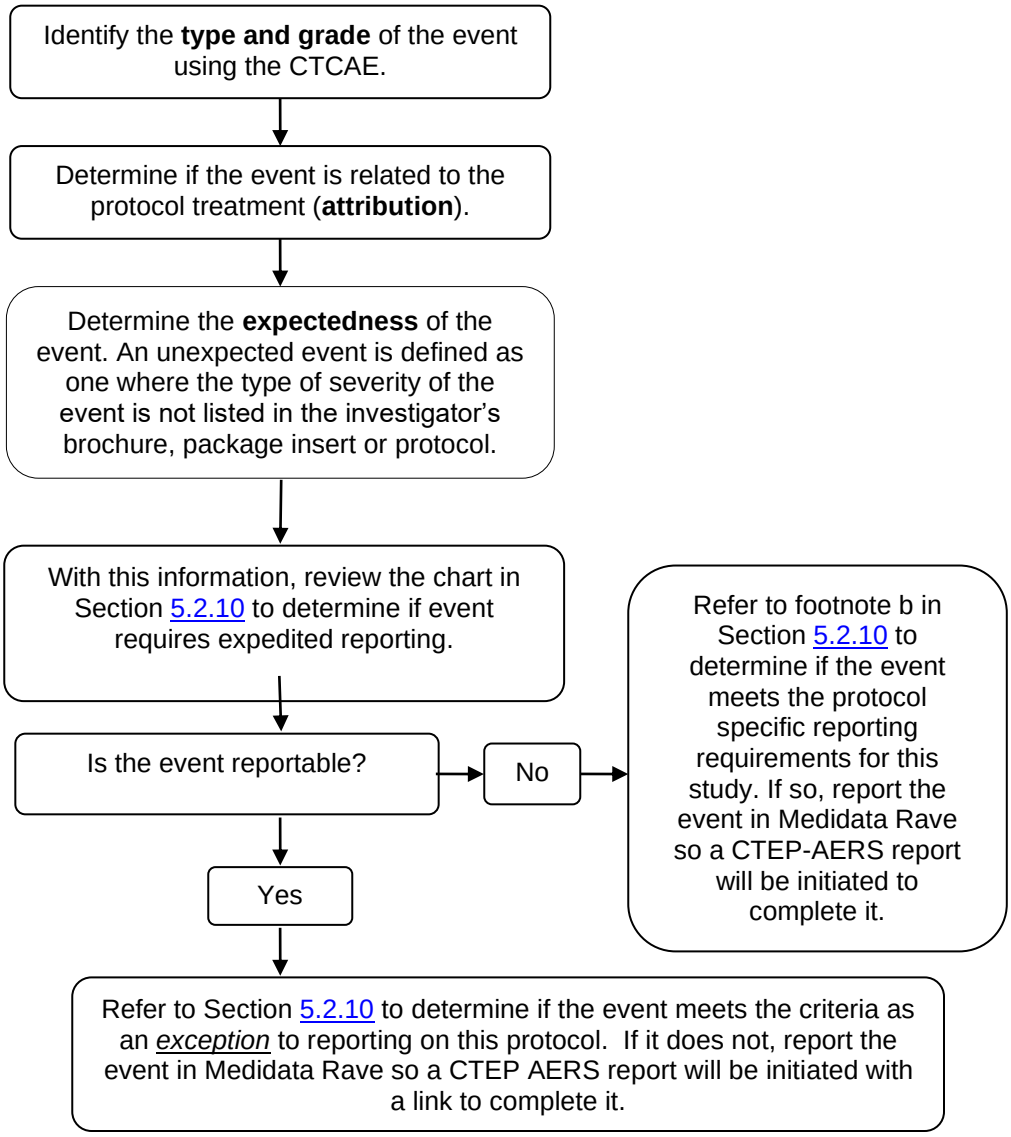
5.2.9 Steps to determine if an event is to be reported in an expedited manner – Arm B

- Site must determine if an event meets expedited reporting requirements so that the AE will be entered into Medidata Rave, triggering a CTEP-AERS report, within the mandated timeframes outlined in Section 5.2.10.
- Do not initiate the CTEP-AERS report via the CTEP-AERS website.
- We encourage all sites to confirm the Rules Engine assessment with the charts and tables below.
- Once the CTEP-AERS is completed, ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner


Identify the **type and grade** of the event using the CTCAE.
Determine if the event is related to the protocol treatment (**attribution**).
Determine the **expectedness** of the event. An unexpected event is defined as one where the type of severity of the event is not listed in the investigator's brochure, package insert or protocol.
With this information, review the chart in Section 5.2.10 to determine if event requires expedited reporting.
Is the event reportable?
No
Refer to footnote b in Section 5.2.10 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in Medidata Rave so a CTEP-AERS report will be initiated to complete it.
Yes
Refer to Section 5.2.10 to determine if the event meets the criteria as an *exception* to reporting on this protocol. If it does not, report the event in Medidata Rave so a CTEP AERS report will be initiated with a link to complete it.

5.2.10 Expedited Reporting Requirements for Arm B on protocol EA3161

Commercial Agents: Cisplatin, Radiation

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arm B

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "Disease progression" under the System Organ Class (SOC) "General disorder and administration site conditions". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: Any death that occurs > 30 days after the last dose of study treatment and is attributed possibly, probably, or definitely to the study treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported in CTEP-AERS accessed via Medidata Rave within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Long Term Adverse Events: Any grade 3 or higher adverse event within the radiation field occurring beyond 12 weeks post radiation treatment (excluding events related to salvage surgery) must be reported in CTEP-AERS accessed via Medidata Rave within 7 calendar days of learning of the event. A long term adverse event incident meeting these criteria must be reported under the CTCAE category 'Injury, poisoning and procedural complications – Other, specify' and it must be specified as a long term adverse event within the radiation field.

5.2.11 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA for Arms A and C. Any additional written AE information requested by NCI or ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and

procedures, to the Institutional Review Board responsible for oversight of the patient.

Rev. Add4

5.2.12 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported as follows:

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis expeditiously by initially reporting it PROMPTLY upon learning of the secondary malignancy on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the secondary malignancy requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event/Late Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

     NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).

     NOTE: We encourage all sites to confirm the Rules Engine assessment with the Second Primary reporting requirements outlined in this section.

3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted in CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) For Nivolumab (NSC 748726)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2069 patients. Below is the CAEPR for Nivolumab.

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported in CTEP-AERS accessed via Medidata Rave if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Version 2.5, June 10, 2023[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (lymphatic dysfunction)	
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves opthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)[3]	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (Immune-related hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma, sarcoidosis)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocytes decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (Immune-related nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))[3]	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Nivolumab being a member of class of agents involved in the inhibition of “immune checkpoints”, may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia

EAR AND LABYRINTH DISORDERS - Vestibular disorder

EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema

GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain

HEPATOBILIARY DISORDERS - Bile duct stenosis

IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)

INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection

INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)

VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

NOTE: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.4 Dose Modifications

IF A PATIENT EXPERIENCES SEVERAL TOXICITIES AND THERE ARE CONFLICTING RECOMMENDATIONS, PLEASE FOLLOW THE MOST CONSERVATIVE DOSE ADJUSTMENT RECOMMENDED (DOSE REDUCTION APPROPRIATE TO THE MOST SEVERE TOXICITY).

NOTE THAT THE DOSES WHICH HAVE BEEN REDUCED FOR TOXICITY MUST NOT BE RE-ESCALATED.

5.4.1 Dose Modifications for Nivolumab

Rev. Add4

NOTE: Dose reduction for Nivolumab is not permitted. The guidelines/management tables below include instructions for nivolumab dose holds for AE management.

Please also refer to the Nivolumab Investigator Brochure or Appendix III to the protocol for toxicity management algorithms which include specific treatment guidelines. The algorithm in section 5.4 should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study chair is recommended.

In all of the tables for dose modification and holds in this section, the guidelines are for adverse events thought at least possibly attributed to study drug. Generally we strongly encourage early evaluation while withholding drug, and appropriate treatment as indicated in the management tables and event specific guidelines. (Information)

Rev. Add1

(Follow guidance in section 5.4, Appendix III should be only used as a supplemental guidance).

Rev. Add3

Investigator's best judgment needs to be followed as dose reductions are guidelines.

ALL OTHER EVENTS	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below). Resume at same level at investigator discretion.
Grade 3	Hold until ≤ Grade 1 OR baseline and patient no longer on steroid treatment if initiated. (exceptions as noted below). Permanently discontinue for events with a high likelihood of morbidity or mortality with recurrent events. Resume at same level at investigator discretion.
Grade 4	Off protocol therapy
Recommended management: As clinically indicated	

Exceptions:

- 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 should go off protocol treatment.

- Any Grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose *
Grade 2	Hold* until ≤ Grade 1 resolved. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same dose level at investigator discretion
Grade 4	Off protocol therapy
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, toxic epidermal necrolysis (TEN), and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: see Skin AE management guidelines	

Liver Function AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold at investigator discretion until ULN or baseline. Resume at same dose level.
Grade 2	Grade 2 (> 3X UNL to 5X UNL) Hold until grade 1 (UNL- 3X UNL) or baseline. Resume at same dose level at investigator discretion.
Grade 3	Grade 3 (> 5X UNL to 20X UNL) Hold until grade 1 or baseline. Resume at same dose level at investigator discretion with return to grade 1 or baseline within 7 days without steroids. If persistent or steroids are required off protocol therapy.
Grade 4	Off protocol therapy
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate liver function test (LFT) changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis. Please note: Grades for liver function follow UNL rather than multiples of baseline.	
Recommended management: see Hepatic AE management algorithm	

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold until baseline. No change in dose.

Diarrhea/ Colitis	Management/Next Dose for Nivolumab
Grade 2	Hold until baseline. No change in dose
Grade 3	Resume at same dose level at investigator discretion if resolved to grade 1 within 7 days without steroids and no evidence of colitis. If persistent or steroids are required off protocol therapy.
Grade 4	Off protocol therapy
See GI AE Algorithm for management of symptomatic colitis. Patients with Grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require systemic steroids should be taken off study treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes C. diff, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

Pancreatitis Amylapse/Lipase	Management/Next Dose for Nivolumab
≤ Grade 1	Continue at same dose level if asymptomatic at investigator discretion
Grade 2	Continue at same dose level if asymptomatic at investigator discretion If symptomatic resume at same dose level when resolved.
Grade 3	Continue at same dose level if asymptomatic at investigator discretion Patients should have imaging study when clinically indicated (grade 3 symptomatic pancreatitis) before resuming treatment. Patients who develop diabetes mellitus should be taken off protocol therapy.
Grade 4	Hold until grade 2. Resume at same dose level at investigator discretion if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated Patients who develop grade 4 symptomatic pancreatitis or diabetes mellitus should be taken off protocol therapy.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as diabetes mellitus and diabetic ketoacidosis (DKA). Lipase elevation may occur during the period of steroid withdrawal and with other immune-mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis, please follow the Hepatic AE Management Algorithm.	

Pneumonitis	Management/Next Dose for Nivolumab
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO2. Resume no change in dose after pulmonary and/or infectious disease (ID) consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes nivoumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required.
Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes nivoumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off protocol therapy.

Pneumonitis	**Management/Next Dose for Nivolumab**
Grade 4	Off protocol therapy
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified, including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary Adverse Event Management Algorithm	

Other GI Nausea Vomiting	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis, duodenitis, and other immune AEs or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment, patients should go off protocol therapy.
Grade 4	Off protocol therapy
Patients with Grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose.
Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume at same dose level.
Fatigue is the most common AE associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation.	

Neurologic events	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline.
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy).
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, and myasthenia gravis should be off study.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab**
≤ Grade 1	* Hold pending evaluation for evidence of adrenal insufficiency or hypophysitis. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment while evaluating the need for thyroid replacement.
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level
Grade 3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.
Grade 4	Off protocol therapy
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered Grade 3 events. Isolated thyroid or testosterone deficiency may be treated as Grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	
Recommended management: See Endocrine Management Algorithm	

Renal	**Management/Next Dose for Nivolumab**
≤ Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off protocol therapy

Infusion reaction	**Management/Next Dose for Nivolumab**
≤ Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off protocol therapy
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Fever	**Management/Next Dose for Nivolumab**
≤ Grade 1	Evaluate and continue at same dose level
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off protocol therapy
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever	

Fever	**Management/Next Dose for Nivolumab**
during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Cardiac*	**Management/Next Dose for Nivolumab**
< Grade 2	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop then treat as below.
Grade ≥ 2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus. May resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥ 2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off protocol therapy.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* NOTE: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

- Drug will be held for any indication suggestion of cardiac dysfunction of any grade pending evaluation
- Drug will be permanently discontinued for treatment related grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur
- Treatment as clinically indicated for cardiomyopathy

If treatment is delayed >6 weeks for an adverse event, the study chair must be consulted for any consideration of further therapy.

Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.

Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.

Any patients who require additional immune suppressive treatment beyond steroids should go off protocol therapy.

Patients requiring > two dose delays for the same event should go off protocol therapy.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 should be obtained to document baseline. However, if urgent steroid use is clinically required, steroid treatment should not be delayed for bloodwork.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Patients may be dose-delayed for evaluation and restarted depending on results.

Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator.

5.4.2 Dose modifications of Cisplatin during radiation therapy:

Patients will be examined and graded for subjective/objective evidence of developing toxicity weekly according to the CTCAE while receiving concurrent cisplatin with radiotherapy.

Treatment interruptions are allowed if there is symptomatic mucositis or skin reaction that, in the judgment of the clinician, warrants a break. For chemotherapy-attributable AEs requiring a break in treatment, resumption of concurrent cisplatin may begin when AEs have recovered to the levels specified below.

Chemotherapy should be discontinued in the event of more than 2 events requiring dose reduction (e.g. if grade 3 or greater non-hematologic or hematologic event occurs at the reduced dose of cisplatin, at 23 mg/m^2/week).

If an AE does not resolve to the levels specified in the sections below prior to the calendar week of the last radiation treatment then chemotherapy should be discontinued.

Cisplatin Dose Modifications for Hematologic Adverse Events during Concurrent Radiation

Starting Dose	Dose Level -1	Dose Level -2
40 mg/m^2	30 mg/m^2	23 mg/m^2

Chemotherapy must not be administered until the ANC is ≥ 1,000 mm^3 and platelets are ≥ 75,000 mm^3. If not, delay 7 days. Cisplatin should be held every week until the above ANC and platelet parameters are met. Dose reduction will need to occur after 2 occurrences of delays. Dose reductions when cisplatin is resumed after delay for low ANC or platelets will be as follows, based upon counts at time cisplatin was held. Hematologic growth factors for neutropenia or anemia are not allowed during concurrent cisplatin and radiation treatment.

Cisplatin Dose Modifications for Non-Hematologic Adverse Events during Concurrent Radiation:

Renal Adverse Events: Dose will be modified based on the serum creatinine prior to each cisplatin dose. If the serum creatinine is ≤ 1.5 mg/dL, creatinine clearance is not necessary for treatment with full dose. If the serum creatinine is > 1.5 mg/dL, a creatinine clearance should be obtained by urine collection or nomogram calculation (valid only if serum creatinine is not changing rapidly).

Cisplatin must not be administered until creatinine is ≤ 1.5 or creatinine clearance ≥ 50. Once the creatinine has met the above parameters, cisplatin may be restarted with the below modifications based on the creatinine at the time the cisplatin was held: In general, cisplatin should be held for weekly intervals (rather than restarting cisplatin later in the same week that a dose limiting AE is seen).

Cisplatin dose modifications for creatinine during concurrent radiation			
Creatinine		Creatinine clearance measured or calculated ml/min	Cisplatin dose reduction
≤1.5	or	≥50	No change
>1.5	and	40-49	One dose Level
		<40	Hold drug

Neurologic effect dose modifications of cisplatin:

Grade (CTCAE)	**Dose Reduction**
0-1	None
2	One dose level
3-4	Hold drug

Ototoxicity: Should patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. A neurologic deficit should be distinguished from a conductive loss from obstruction of the Eustachian tube leading to a middle ear effusion. Because no AE scale, including the CTCAE, has been validated in terms of correlation with clinically relevant hearing loss, there are no protocol mandates requiring dose reduction for audiogram-determined sensorineural hearing loss without an analogous clinical high grade (> grade 2) hearing loss. However, for clinical grade 3 or higher hearing loss, cisplatin should be held and for grade 2 clinical hearing loss, one dose level reduction should be implemented.

All Other Non-Hematologic Adverse Events Attributable to Cisplatin during Concurrent Radiation:

For all other non-hematologic adverse events in which toxicity is ≥ grade 2 (CTCAE), investigators are advised to evaluate and manage correctable issues promptly to prevent worsening of toxicity. For these events in which toxicity is ≥ grade 3, investigators should hold cisplatin, with weekly re-evaluation until AE grade falls to 0-1, then

restart cisplatin at one lower dose level. Note: Grade 3 mucositis is commonly experienced by head and neck cancer patients; the investigator generally would not hold the cisplatin.

Management of Cisplatin Adverse Events

Please refer to institutional policy and guidelines for irritation at the injection site and extravasation, which can occur with cisplatin administration.

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

Appendix III details required supportive care and management guidelines for immune-related toxicity.

5.6 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA3161 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered. Patients who require palliative radiation therapy may be considered to remain on study after discussion and approval by the study chair. Treatment with nivolumab should be halted during radiation therapy.
- Any dosing interruption lasting >6 weeks, with the following exceptions: Dosing interruptions >6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Disease progression

5.7 Treatment Past Progression

Rev. Add3

This applies to patients on Arm C of the study who are on nivolumab for recurrent disease and to patients on Arm A who develop reactive nonspecific radiologic changes.

NOTE: Progression, provided it meets radiologic criteria, will be counted as such regardless of the decision to continue nivolumab post documented progression.

A minority of subjects treated with immunotherapy may derive clinical benefit with either delayed responses, stable disease, or increased overall survival despite

Rev. Add3

initial evidence of progressive disease (PD) with nivolumab. In addition, a minority of patients on nivolumab may develop reactive changes that are nonspecific.

Patients may be permitted to continue treatment beyond initial RECIST 1.1-defined PD as long as they meet the following criteria:

- No more than 4 new lesions total sum of the longest diameter (SHORT diameter for LN) cannot exceed 40% of the initial sum including new lesions
- Patients must be clinically stable with no change in performance status due to disease progression
- No indication for immediate alternative treatment

Rev. Add3

- For patients on Arm A, who have non-specific radiologic changes, an FNA revealing no evidence of cancer is strongly recommended in order for patients to continue on nivolumab.
- Patient (assessed by the investigator) is showing clinical benefit and tolerates study drug. The assessment of clinical benefit should take into account whether the subject is clinically stable or deteriorating and while on nivolumab are likely or unlikely to receive further benefit from continued treatment.
- The time of progression is noted from the first assessment that exceeds standard criteria
- New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

5.8 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 10 years from the date of randomization.

6. Measurement of Effect

Rev. Add4

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, all patients on Arm A and patients on Arm C with measurable disease should be re-evaluated for response every 12 weeks and patients should be evaluated for progression on Arm B as clinically indicated. Patients on Arm C without measurable disease at the time of initiation of Nivolumab will also be re-evaluated every 12 weeks to assess for maintained disease control on Nivolumab.

For patients who have evidence of disease progression, the option of continuing nivolumab and repeating a scan in 4 weeks will be available to investigators to confirm progression. If the repeated 4 weeks scan reveals further progression the patient will be declared as having disease progression. If on the other hand the 4-weeks scan is stable or improved, the patient will not be deemed to have progression and may continue on therapy as per investigator's discretion.

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

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The

response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable Disease

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

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it is appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes

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

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the

largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

6.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before registration.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

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

Chest X-ray

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

Conventional CT and MRI

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image

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

PET-CT

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

Ultrasound

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

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

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

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression, See Section 6.1.4.3.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 12 weeks (84 days).

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD

Persistence of one or more non-target lesions.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.2). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

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

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if:

a) it increases in size to ≥ 15 mm in the short axis, or
b) there is new pathological confirmation that it is disease (regardless of size).

New effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

Rev. Add4

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions**	New Lesions*	Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR***/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 12 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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

For Patients with Only Non-Measurable Disease (i.e., Non-Target Disease)

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

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

6.1.4.5 Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Stable Disease

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

7. Study Parameters

Rev. Add4

7.1 Therapeutic Parameters

1. At baseline, scans need to be performed within 4 weeks prior to randomization.
2. Pre-study CBC (with differential and platelet count) should be done ≤ 2 weeks before randomization at Step 1 and registration to Step 2.
3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ 2 weeks before randomization at Step 1 and registration to Step 2 – unless specifically required on Day 1 as per protocol.

Rev. Add1

Test	**Prior to Step 1 Randomization**	**Arms A and B – At Every dose of cisplatin, before agent is administered**	**Arms A and B – Every 2 doses of cisplatin**	**Arms A, B, and C – 12 weeks after radiation and every 12 weeks while on nivolumab or observation for 12 months**	**Prior to Step 2 Registration (Arm C)**	**Arms A and C With each dose of nivolumab on each arm**	**Arms A, B, and C - Follow-up after completion of therapy for 10 years**
History and Physical[8]	X	X		X	X	X	
Weight and ECOG PS	X	X		X	X	X	
Tumor measurement with CT of Neck plus CT of Chest or CT of Neck plus FDG PET/CT	X[6]			X[4,6]	X[9]		X[7]
CBC with Differential[1]	X	X			X	X	
Chemistry profile with Mg	X	X			X	X	
Toxicity assessment	X		X	X		X	
EKG, CPK, troponin, echocardiogram	X[3]	X[3]					
Pregnancy Test[2]	X				X		
TSH						X[5]	

1. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle of cisplatin. For maintenance Nivolumab a window of 48 hours are allowed between laboratory collection and infusion. Buccal rinse can be collected +/- 3 days of lab collections.

Rev. Add1

2. Blood or Urine pregnancy test (patients of childbearing potential). All patients of childbearing potential must have a negative pregnancy test performed within 14 days prior to randomization at Step 1 and registration to Step 2. A repeat pregnancy test must be done < 48 hours prior to the first date of treatment with Nivolumab on both Arms A and C with results available prior to treatment.
3. EKG, CPK, troponin, and echocardiograms should be conducted only as clinically indicated for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs. For patients with evidence of congestive heart failure (CHF), myocardial infarction (MI), cardiomyopathy, or myositis, further cardiac evaluation, lab tests and cardiology consultations, including EKG, CPK, troponin, and echocardiogram should be conducted as clinically indicated.

Rev. Add4

4. Continue every 12 weeks (+/- 2 weeks) until end of Nivolumab therapy or progression on Nivolumab (Arms A and C). Scans for patients on observation (Arm B) should be conducted every 12 weeks (+/- 2 weeks) as clinically indicated.
5. Every 8 weeks while on nivolumab.
6. FDG PET/CT to be performed if standard of care. CT of chest is not needed at baseline or 12 weeks post therapy if FDG PET/CT is performed.

Rev. Add4

7. Follow-up scans are to be performed as clinically indicated at a recommended frequency of every 3-6 months following completion of therapy for first 3 years from the date of Step 1 registration. Yearly scans are suggested, if clinically warranted, for 10 years post Step 1 registration. No specific requirements for follow up if patient is more than 10 years from date of Step 1 registration.

Rev. Add1

8. History and Physical exams (+ 2 days) are mandatory each visit for Cisplatin and Nivolumab treatment. Allow for (+/- 7 days) for administration of Nivolumab and allow for (+/- 2 days) for administration of Cisplatin.

Rev. Add4

9. CT of neck and CT of chest (or CT of neck and FDG PET/CT if standard of care) must be done within 4 weeks prior to Step 2 registration to Arm C. Tumor measurements are not required for patients that have undergone salvage surgery for disease recurrence prior to Step 2 but scan still must be performed.

7.2 Biological Sample Submissions

Rev. Add1

Specimens are to be submitted (+/- 7 days) as outlined in Section 10 per the applicable patient consent. The biological materials will be used in the correlative studies described in Section 11.

Material	Prior to Start of Treatment	12 weeks post completion Cis/RT	9 months post completion Cis/RT	Progression	**Ship To:**
MANDATORY: Submit from all patients that are participating on the trial.					
FFPE tumor tissue[1]	X				E-A CBPF
Rev. Add1 **SCIENTIFIC STUDIES:** Submit from patients who have answered "Yes" to "*I agree to provide additional specimens for research.*"					
Plasma from (2) EDTA tubes, residual cells[2, 4]	X	X	X		E-A CBPF
Whole blood, ACD tube[4]	X				
Buccal rinse[4]	X	X	X		
FFPE tumor tissue[3]				X	

1. Submit within 4 weeks of registration to trial.
2. Processing instructions provided in Section 10.
3. Submit within 4 weeks of collection.
4. To order kits for blood and buccal specimens, follow the instructions outlined in Appendix VII.

8. Drug Formulation and Procurement

8.1 Availability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Site can request an initial 5 vials of nivolumab once a patient is randomized to the nivolumab arm.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

NCI Supplied Agent(s) – General Information

NOTE: Under no circumstances can commercially supplied **OPDIVO™** be used or substituted for the NCI-supplied **nivolumab.**

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov/forms) or by calling the PMB at 240-276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each agent on this protocol.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.2 Cisplatin

Refer to the FDA-approved package insert for more information about cisplatin.

8.2.1 Other Names

Cis-diaminedichloroplatinum Cis-diaminedichloroplatinum (II), diaminedichloroplatinum, cis-platinum, platinum, Platinol, Platinol-AQ, DDP, CDDP, DACP, NSC 119875 R R

8.2.2 Classification

Alkylating agent

8.2.3 Mode of Action

Inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanisms include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

8.2.4 Storage and Stability

Intact vials of cisplatin are stored at room temperature. Solutions diluted with saline solution are stable for up to 72 hours at room temperature. Due to the risk of precipitation, cisplatin solutions should **not** be refrigerated.

8.2.5 Dose Specifics

40 mg/m^2 IV x 7 weeks

8.2.6 Preparation

The desired dose of cisplatin is diluted with 250-1000 ml of saline solution.

Varying concentrations of 0.225-5% sodium chloride may be used. To maintain stability of cisplatin, a final sodium chloride concentration of at least 0.2% is recommended.

8.2.7 Route of Administration

Cisplatin is administered as an intravenous infusion over 60 minutes.

8.2.8 Incompatibilities

Amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, thiotepa. Cisplatin may react with aluminum which is found in some syringe needles or IV sets, forming a black precipitate.

8.2.9 Compatibilities

Admixture: aztreonam, carmustine, cefazolin, cephalothin, droperidol, etoposide, floxuridine, hydroxyzine, ifosphamide, leucovorin, magnesium sulfate, mannitol, potassium chloride.

Y-site: Allopurinol, bleomycin chlorpromazine, cimetidine, cyclophosphamide, dexamethasone, diphenhydramine, doxapram, doxorubicin, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, heparin, hydromorphone, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, ranitidine, sargramostim, vinblastine, vincristine, vinorelbine.

Consult your pharmacist regarding specific concentrations

8.2.10 Availability

Commercially available as a 1 mg/ml solution in 50 and 100 mg vials. Vials of lyophilized powder are no longer commercially available, but may be obtained directly from the manufacturer for chemoembolization use.

8.2.11 Side Effects

Please refer to Cisplatin package insert.

8.2.12 Nursing/Patient Implications

1. Prior to administration, assess:
   A. Labs: CBC with differentials, platelet count, BUN, creatinine.
   B. Urine output: 100-150 ml/hr for at least 4-6 hours.
   C. Signs of ototoxicity or neurotoxicity.
2. Administer supportive medications:
   A. Premedicate with antiemetics – prophylaxis with a 5 – HT3 receptor antagonist and dexamethasone (+/- aprepitant) is standard.
   B. Hydration
   C. Diuretics - may be ordered.
3. Observe for signs of allergic reaction.

8.2.13 References

Alberts DS. Carboplatin versus cisplatin in ovarian cancer. Semin Oncol 1995;22(5 Suppl 12):88-90.

Bonomi P. Platinum/etoposide therapy in non-small cell lung cancer. Oncology 1992;49(Suppl 1):43-50.

Dabholkar M, Reed E. Cisplatin. Cancer Chemother Biol Response Modifiers 1993;14:86-97.

Fram RJ. Cisplatin and platinum analogues: recent advances. Curr Opin Oncol 1992;4:1073-9.

Garrow GC, Johnson, DH. Treatment of "good risk" metastatic testicular cancer. Semin Oncol 1992;19:159-65.

Markman M. Current status of intraperitoneal therapy for ovarian cancer. Curr Opinion Obstet Gynecol 1993;5:99-104.

Ozols RF, et al. Advanced ovarian cancer. Dose intensity. Ann Oncol 1993;(4 Suppl 4):49-56.

Saxman S. Salvage therapy in recurrent testicular cancer. Semin Oncol 1992;19:143-7.

Wheeler RH, Spencer S. Cisplatin plus radiation therapy. J Infusional Chemother 1995;5:61-6.

ECOG 6/96

8.3 Nivolumab (NSC748726)

In this study, nivolumab is considered investigational.

8.3.1 Other Names

Opdivo, BMS-936558; MDX1106

8.3.2 Classification

Anti-PD-1MAb

8.3.3 Mode of Action

Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

8.3.4 Description

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

8.3.5 How Supplied

Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

8.3.6 Storage and Stability

Vials of Nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing, and shaking.

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Shelf-life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

Unopened vials can be stored at room temperature (up to 25 ºC, 77ºF) and room light for up to 48 hours.

8.3.7 Dose Specifics

Refer to Section 5.1 for specific dosing of nivolumab.

8.3.8 Preparation

Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

8.3.9 Route of Administration

Intravenous infusion. Do not administer as an IV push or bolus injection. Nivolumab is infused over 30 minutes. See Section 5.1.

8.3.10 Method of Administration

Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter. See Section 5.1.

8.3.11 Potential Drug Interactions

The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes

across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

8.3.12 Side Effects

See Section **Error! Reference source not found.**

8.3.13 Nursing/Patient Implications

No incompatibilities between Nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed.

Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter.

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Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Patients must also not donate ova during this same time period.

8.3.14 References

Nivolumab IB, Version 17, 27-Jun-2018

9. Statistical Considerations

9.1 Statistical Considerations

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This section incorporates design change from the original Phase II/III design to a Phase III design with overall survival (OS) as the primary endpoint.

This is a randomized phase III study to evaluate the efficacy of concurrent definitive chemo radiation therapy (CRT) followed by nivolumab maintenance compared with concurrent definitive CRT followed by observation, in patients with intermediate risk HPV+ oropharynx cancer >= 10 pk-yr smoking history, stage T1-2N2-N3 or T3-4N0-3, OR < 10 pk-yr smoking history, stage T4N0-N3 or T1-3N2-3 (AJCC8)). Patients will be randomized to receive either CRT followed by nivolumab or CRT followed by observation (subsequent salvage surgery are allowed on both arms). Randomization will be stratified by smoking history (>=10pk-yr vs. <10pk-yr smoking history), T stage (T4 vs. T1-3), and Nodal stage (N0-N2 vs. N3). Randomized treatment will be assigned using a permuted blocks within strata with dynamic balancing on institution (with main institutions combined with their affiliate networks for balancing).

9.2 Sample Size Considerations

Overall Survival (OS) is defined as the time from randomization to death from any cause. Patients that have not had an event reported at analysis will be censored at their date of last follow-up. The comparison of OS will use log rank test stratified by the randomization stratification factors, and will be intent-to-treat analyses. A total of 636 patients will be randomized (as of January 22, 2021, 130 patients are randomized; an additional 506 patients will need to be randomized). Assuming accrual rate is 10 patients per month, accrual will take approximately 64 months, and full information of 196 deaths is expected with 41 months additional follow-up. This gives 82% power for a log rank test at one-sided alpha level of 0.025, to detect a hazard reduction of 35% on the nivolumab arm, compared to observation (corresponding to 2-yr OS of 86% vs. 90.7%, assuming exponential distribution). The total accrual number 636 here reflects a slight inflation of the sample size (~6%), based on the Lachin-Foulkes correction, to adjust for an estimated ~3% patients on the nivolumab arm with early progressions who may or may not proceed to receive nivolumab.

9.3 Interim Monitoring

Feasibility

Two interim analyses will be performed to monitor the proportion of patients who are randomized to the nivolumab arm but unable to receive it, due to early progression or any other reasons. First analysis will be performed after the first 50 patients who are randomized to nivolumab (~100 total patients randomized) have been followed for >=5 months (nivolumab is to start within 4 weeks after completion of concurrent therapy, plus some time for maintenance treatment data to come in). Second analysis will be performed after 100 patients randomized to nivolumab (~200 total patients randomized) have been followed for >=5 months. In the initial design, it was specified that if, in either analysis, the observed proportion of patients who have not started nivolumab is >=10%, feasibility of the study will be discussed with CTEP.

The first interim feasibility analysis was performed in preparation for the Spring 2021 DSMC meeting. Of the first 50 patients who were randomized to nivolumab, 7 (14%) did not receive it. After discussing this result with CTEP, it was decided that at the time of the second interim feasibility analysis, the proportion of patients randomized to the nivolumab arm who do not receive it will be estimated and the rate shared with the study team and CTEP. At that time, an increase (maximum 20%) in the accrual goal and total information to adjust for nonadherence will be considered. The adjustment will be based on the Lachin-Foulkes method, with both the total enrollment and total information increased by a factor of 1/(1-R)^2, where R is the proportion not starting nivolumab. The decision whether to implement this change will be made jointly by the study team and CTEP based primarily on feasibility. If more than 10% of the planned information under the current design is available at that time, then the study statistician will not participate in this discussion.

Efficacy Interim Monitoring

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Three efficacy analyses (two interim and one final) for OS are planned. To preserve the overall type I error rate, critical values used in the interim analyses will be determined using a truncated version of the Lan-DeMets error spending rate function corresponding to the O'Brien-Fleming boundary. Interim analyses will correspond to scheduled ECOG-ACRIN Data Safety Monitoring Committee meetings. The following tables give the boundary estimates at the expected analysis times.

OS Efficacy Interim Monitoring

Time from Study Start (Years)	Information Time	Events Under H_1	Truncated O-F Boundary
5.5	0.50	99	2.9626
7.0	0.75	148	2.3599
8.7	1.00	196	2.0147

Harm and Inefficacy Interim Monitoring

OS will be monitored for early stopping for harm. At 25% information, the DSMC may consider stopping the study for harm if the lower bound of a 95% confidence interval in the hazard ratio (nivolumab/observation) is above 1.

Inefficacy monitoring for OS is scheduled to start approximately after 46% of the full information becomes available with repeated analyses at each semi-annual DSMC meeting. Linear 20% Inefficacy Boundary (LIB20) proposed by Boris Freidlin et al (2010) will be used. At each interim analysis, if the estimated hazard ratio is larger than the cut-off value given in the LIB20 boundary, DSMC may recommend that the study be terminated for futility.

9.4 Secondary Endpoints

Progression-Free Survival (PFS) will be compared between the two arms. PFS is defined as the time from randomization to the earliest event defined as time from randomization to date of progression, second primary tumor from the head and neck region, or death. Progression will be defined using RECIST 1.1 criteria. In the scenario that a patient on the nivolumab arm is allowed to continue nivolumab after RECIST PD is documented (Section 6), and the subsequent

scan did not confirm PD, this will not be considered as PD and patient disease status will continue to be followed. Patients without documented progression/second primary cancer or death reported will be censored at the time of their last disease evaluation. The comparison of PFS will use stratified log rank test and will be intent-to-treat analyses. A secondary analysis counting salvage surgery as events will also be performed.

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Treatment effect on OS and PFS will be evaluated among both the PD-L1+ subset (roughly 90% of all randomized patients) and the PD-L1- subset. Confidence intervals (CI) will be calculated. We anticipate ~85% all randomized patients will have PD-L1 data, among whom 90% will be PD-L1+. The prognostic effect of baseline PD-L1 expression (positive vs. negative) on OS and PFS will be evaluated as well. Even though it is anticipated that the number of patients in the PD-L1 negative subgroup might be limited, which will be reflected by the width of the corresponding CI, this subgroup analysis will still provide important information for treatment benefits regarding PD-L1 score. The interaction between PD-L1 and treatment will also be evaluated in a Cox proportional hazards model.

Another secondary objective is to evaluate the prognostic effect of baseline saliva and/or plasma HPV status (positive vs. negative) on OS and PFS. Based on Ahn et.al (2014), 7%, 11% and 18% patients had saliva HPV+, plasma HPV+, and saliva or plasma HPV+, respectively. Assuming 85% of all randomized patients have HPV data available, and an overall OS event rate of 31% and 64% for PFS, the study will have ~81% power to detect a hazard ratio of 1.66 for OS and 1.45 for PFS (saliva or plasma HPV+ vs. saliva and plasma HPV-), respectively, at two-sided alpha level of 0.05. Saliva and plasma HPV status at 12 weeks and 9 months following completion of concurrent therapy will also be analyzed regarding effect on outcome.

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Mutation burden before and after treatment will be evaluated using whole exome sequencing of baseline tissue sample and samples obtained at the time of progression. Rizvi et.al (2016) suggest higher nonsynonymous mutation burden in tumors is associated with better outcome in patients with non-small cell lung cancer treated with pembrolizumab. In our study, assuming 80% patients on the nivolumab (n=298) have baseline mutation burden data available, and an overall event rate of 27% for OS and 55% for PFS, there is ~80% power to detect a hazard ratio of 1.87 for OS and 1.55 for PFS (lower mutation burden vs. higher mutation burden), respectively, at two-sided alpha level of 0.05. Lower vs. higher mutation burden will be defined using the median value as cut-off. The interaction between mutation burden and treatment will also be evaluated in a Cox proportional hazards model. Mutation burden change between baseline and progression will also be analyzed as an exploratory objective.

9.5 Imaging endpoints

9.5.1 Primary aim

9.5.1.1 To establish the association of a negative (standardized qualitative) 12 week post therapy (cisplatin + RT) FDG PET/CT with OS (and/or PFS) for patients who have a PET/CT scan at 12 weeks.

9.5.2 Secondary aims

9.5.2.1 To establish the prognostic value of SUVmax of primary tumor or neck nodal metastasis of baseline FDG PET/CT for OS (and/or PFS).

9.5.2.2 To correlate SUVmax of primary tumor or nodal metastasis of baseline FDG PET/CT with PD-L1 expression (positive vs. negative).

9.5.2.3 To correlate the post therapy (cisplatin + RT) FDG PET/CT with saliva or plasma levels of HPV DNA collected at the time of the standard 3 months PET/CT scan as well as 6 months later (i.e. 9 months post therapy) for both the observation and Nivolumab groups.

9.5.2.4 To compare the PET based therapy response assessment (Hopkins criteria) to the RECIST 1.1 assessment at 12 week post chemoradiation therapy, for patients who have a PET/CT scan at 12 weeks.

9.5.3 Statistical Considerations for Imaging

The definition of negative and positive 12 week post therapy FDG PET/CT is detailed in Section 6.1.4. In particular, we will use the standardized FDG PET/CT response assessment for head and neck cancer – Hopkins Criteria. The PET scan results will not be used for decision making but for correlative research analysis; clinical decision making about salvage surgery will be left for the treating centers and local PIs.

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The primary imaging aim is to associate the dichotomized FDG PET/CT (positives (scores 4-5) versus negatives (scores 1-3)) with OS (196 events out of 702 patients). Of note, patients with Score 3 will be categorized into the negative group. The rate of negatives is assumed to be 80%, which is close to the response rate of CR and PR. Out of 636 accrued eligible patients for the treatment aim, we expect 90% of them to have the FDG PET/CT scans. The accrual completes in about 64 months and the follow-up is 41 months. Thus, we will have the 90% power to detect the hazard ratio of 0.53 (i.e., the ratio of hazard rate in PET negatives to the one in PET positives). With the power of 80%, we can adequately detect the hazard ratio of

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0.59. The proportion surviving in PET positives (control) is assumed to be 0.61, given that the overall survival is about 71%. The significance level is 0.05 (one-sided). The calculation was done by PASS 2021[ref] (using the module of Logrank Tests – input Proportion Surviving for Two Survival Curves). In terms of the analysis plan, we will use Kaplan-Meier method and Cox regression for the survival outcome analyses, and Chi-square testing or Pearson correlation testing for the secondary correlation analyses. The effect of treatment will be assessed as a covariate in these analyses. If needed, the above analyses will be performed separately within each arm to avoid the confounding effect from the treatment. Kappa statistic will be applied to evaluate the agreement between PET based therapy response

assessment (Hopkins criteria) and RECIST 1.1 assessment at 12 weeks post chemoradiation therapy.

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9.6 Gender and Ethnicity

Based on previous data from E1308 the anticipated accrual in subgroups defined by gender and race is:

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	15	0	0	15
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	29	0	0	29
White	29	512	7	44	592
Total	29	556	7	44	636

1. The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Specimen Submissions

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Representative tumor tissue specimens should be submitted for use in the correlative study described in Section **Error! Reference source not found.**. Additional tissue, as well as blood and buccal specimens, should be submitted for future unknown studies, as per the appropriate patient consent.

All specimens must be labeled with the ECOG-ACRIN protocol number, the patient's initials and ECOG-ACRIN sequence number, the collection date, and the type of sample. For pathology materials, it is strongly recommended that full patient names be provided.

KITS: Kits are available for the collection and submission of blood and buccal samples. Starter kits are NOT available. Kits are to be ordered after patient has consented to participate in the trial and has been determined to be eligible to register. To order kits follow the instructions outlined in Appendix VII. Kits will arrive within 3-5 working days from when the order is placed.

All specimens must be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS) Web Application (Section 10.4) and submitted with an STS generated shipping manifest.

10.1 Collection and Submission Guidelines

See Section 7.2 for a table summarizing the submission requirements.

10.1.1 Pathology Materials

Guidelines for pathologists are provided in Appendix I.

10.1.1.1 Tissue submissions:

Please submit fixed, paraffin-embedded tumor tissue blocks at the time points indicated below.

- Pre-Trial Diagnostic
  - **MANDATORY:** All patients on study
  - Specimens are to be submitted within 4 weeks following registration to the trial
- Progression

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  - **CONSENTING PATIENTS:** Those that have answered "Yes" to "I agree to provide additional specimens for research."
  - Specimens are to be submitted within 4 weeks following collection

NOTE: If blocks are not available for submission, the following alternative is to be submitted: 1 H&E (from the source block), 1-2 core punches (4 mm minimum) and 20 unstained slides (5 microns thick). Slides, including the H&E, are to be numbered consecutively in the order cut.

10.1.1.2 Forms

The relevant pathology and surgical reports must accompany all tissue submissions to the CBPF:

- Copy of the diagnostic or surgical Pathology Report
- Other Immunologic and cytologic reports
- STS generated shipping manifest for all submitted tissue.

10.1.2 Additional Specimens

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Submit for CONSENTING PATIENTS: Those that have answered "Yes" to "*I agree to provide additional specimens for research.*"

Ship Frozen →

10.1.2.1 Plasma, and residual cells

- Time points:
  - Prior to start of treatment
  - 12 weeks post end of Cisplatin/Radiation treatment
  - 9 months post end of Cisplatin/Radiation treatment

1. At each time point specified, draw two (2) 10mL EDTA vacutainers (purple top tubes)
2. BLOOD MUST BE PROCESSED WITHIN TWO (2) HOURS OF DRAWING BLOOD
3. Spin blood collection tubes at 2,500 x g for 10min, balance centrifuge if necessary
4. Aliquot the top plasma layer (2-4 cc) into the labeled 3 ml. cryovial tube. Be careful to leave at least 1-1.5 ml of plasma over the cell layer, making sure not to collect the "Buffy Coat", and aliquot top plasma layer into the cryovial freezer tubes. You may need to use up to 4-5 cryovial tubes to aliquot the plasma from two blood collection tubes.
5. Store the tubes in their respective sites at -80°C

Ship Ambient →

10.1.2.2 Whole Blood, ACD DNA

- Time points:
  - Prior to start of treatment

1. At each time point specified, draw one (1) 8.5mL ACD DNA vacutainer.
2. Ship at ambient the day of collection

Ship Frozen →

10.1.2.3 Buccal Rinse

- Time points:
  - Prior to start of treatment
  - 12 weeks post end of Cisplatin/Radiation treatment
  - 9 months post end of Cisplatin/Radiation treatment

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1. In a specimen cup, pour 10 ml of sterile 0.9% sodium chloride solution, mouth wash, or sterile saline. Instruct patient to swish and gargle in an alternating fashion for 10 seconds and then spit the liquid back into the cup.
2. Decant saliva sample from saliva cup to labeled 15 ml conical tube. Spin down in centrifuge at 2,500 x g for 10 minutes.

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3. Confirm there is a white cell pellet in the bottom of the tube. Carefully decant most of the supernatant into a sink, leaving about 1 mL of fluid and the cell pellet intact.
4. Using a sterile pipette, re-suspend the pellet in the remaining solution. Divide the suspended pellet equally between two cryovial tubes.
5. Store at -80^0 C until ready to ship frozen.

10.2 Shipping Procedures

All submissions are to be shipped to the ECOG-ACRIN Central Biorepository and Pathology Facility.

The pathology materials are to be submitted as outlined above. Tissue samples are to be shipped at ambient (use a cool pack in warm weather).

It is requested that the frozen samples be batched and shipped frozen on dry ice (at least 5 pounds) on a quarterly basis. Samples from different time points and different patients are to be packaged separately and clearly marked within the shipment. Frozen and the ambient fluid shipments are to be made SUNDAY THROUGH THURSDAY only via overnight courier. Do not ship samples the day before a Holiday.

Shipping manifest generated from the ECOG-ACRIN STS system must accompany the samples.

Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506

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10.3 Use of Specimen in Research

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but is not limited to, extraction of plasma, serum, DNA and RNA.

The appropriate materials will be distributed to investigators for the research study described in Section **Error! Reference source not found.**.

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined research study, will be retained in an ECOG-ACRIN-designated central

repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility. Specimens will be de-identified prior to distribution for any approved research studies.

If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

10.4 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Any case reimbursements associated with specimen submissions will not be credited if specimens are not logged into STS. Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu .

Study Specific Notes:

If the STS is unavailable, the Generic Specimen Submission Form (#2981) is to be used as a substitute for the STS shipping manifest. The completed form is to be faxed to the receiving laboratory the day the samples are shipped. Indicate the Lab on the submission form:

- ECOG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

10.5 Planned Future Studies

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The following studies are intended future studies. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked tissue, blood or buccal samples will include the appropriate background, experimental plans with assay details including assay validation data, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

- Saliva and plasma HPV16 DNA based risk assessment
- Determination of tumor mutation burden to predict nivolumab response

10.6 Sample Inventory Submission Guidelines

Inventories of all samples submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for the will be submitted by the laboratory to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

Rev. Add1 **11. Specimen Analyses: Laboratory Research Study**

Pre-trial diagnostic tissue is required to be submitted for the baseline PD-L1 assessment. This assessment will be performed by Cancer Genetics, Inc.

11.1 PD-L1 Immunohistochemistry (MANDATORY)

This mandatory assessment will be performed retrospectively on the pre-trial diagnostic tumor FFPE to evaluate the prognostic effect of baseline PD-L1 expression. This analysis will be performed under the direction of Narasimha Marella, PhD at Cancer Genetics, Inc. The lab is a CLIA certified commercial laboratory that is experienced with the assay. The DAKO PD-L1 IHC 28-8 PharmDx kit will be utilized.

Tumor PD-L1 membrane expression will be evaluated centrally by means of immunohistochemical testing (Dako North America) on initial biopsies with the use of a rabbit antihuman PD-L1 antibody (clone 28–8, Epitomics). PD-L1 positivity will be expression of $\geq$ 1%. Scoring will be done based on the evaluation of a minimum of 100 tumor cells.

Patients will be evaluated as either PD-L1 positive and negative based on the test performed by the lab. Assessment of benefit to patients based on their PD-L1 status is a secondary endpoint goal of the study.

Immune checkpoint blockade, inhibitors of programmed cell-death receptor (PD-1) and its associated ligand (PD-L1), have demonstrated promising results. PD-L1, typically expressed on the surface of healthy cells, binds PD-1 on primed cytotoxic T cells thereby inhibiting cell-mediated attack. Purportedly, the expression of this ligand on tumor cells confers protection against immune-mediated attacks on tumor cells and may account for their particularly malignant potential. Thus, anti-PD-L1 (or anti-PD-1) monoclonal antibodies would inhibit PD-L1 binding to PD-1 and allow T cell activity at this immune checkpoint. Data also suggests that there does appear to be antitumor activity in patients with multiple tumor types, including esophageal, gastroesophageal junctional and gastric cancers, with the use of immunotherapeutic agents and that combination therapy with a CTLA-4 antibody (ipilimumab) and a PD-1 inhibitor (nivolumab) results in better outcomes that nivolumab monotherapy in patients with metastatic disease.

Additionally, this method has been used very reliably in head and neck squamous cell carcinomas as was published in the landmark NEJM paper[32]. More specifically, data from pre-specified exploratory analysis of the Checkmate 141 clinical trial showed that tumor PD-L1 expression, as detected by PD-L1 IHC 28-8 pharmDx in patients with squamous cell carcinoma of the head and neck, was associated with improved overall survival for patients who were randomized to nivolumab. Further details of this methodology is provided in the following online publication: Cogswell JP et al, Cancer immunotherapy by disrupting PD-1/PD-L1 signaling[33].

As not all patients respond to PD-1/PD-L1 inhibitors, predicting the likelihood of response to treatment would aid in appropriate patient selection for these drugs. Immunohistochemistry (IHC) biomarker assays for respective PD-1/PD-L1 inhibitors were designed to screen for the presence of specific PD-1/PD-L1

epitopes, of which the DAKO Pharm Dx 28-8 clone is the FDA approved companion diagnostic for nivolumab.

11.2 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates.

12. Electronic Data Capture

Please refer to the EA3161 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol and patient specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website (http://ctep.cancer.gov/reporting/cdus.html).

12.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

1. Simard EP, Torre LA, and J. A, *International trends in head and neck cancer incidence rates: Differences by country, sex and anatomic site.* Oral Oncol, 2014. **Feb 12th**(S1368-8375(14)00032-3. doi: 10.1016/j.oraloncology.2014.01.016. [Epub ahead of print]).
2. D'Souza G, K.A., Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML., *Case-control study of human papillomavirus and oropharyngeal cancer.* N Engl J Med 2007. **356**: p. 1944-56.
3. Saba NF, G.M., Ward K, Flowers C, Ramalingam S, Owonikoko T, Chen A, Grist W, Wadsworth T, Beitler JJ, Khuri FR, Shin DM, *Gender and ethnic disparities in incidence and survival of squamous cell carcinoma of the oral tongue, base of tongue, and tonsils: a surveillance, epidemiology and end results program-based analysis.* Oncology, 2011. **81**(1): p. 12-20.
4. Lau HY, et al., *Prognostic significance of p16 in locally advanced squamous cell carcinoma of the head and neck treated with concurrent cisplatin and radiotherapy.* Head Neck 2011. **Feb;33(2):251-6.**

5. Ragin CC and T. E, *Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis.* Int J Cancer 2007. **Oct 15;121(8):1813-20.**
6. Chaturvedi AK, E.E., Anderson WF, Gillison ML, *Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States.* J Clin Oncol, 2008. **26**: p. 612-9.
7. Ragin CC, T.E., *Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis.* Int J Cancer, 2007. **121**: p. 1813-20.
8. Ang KK, H.J., Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML, *Human papillomavirus and survival of patients with oropharyngeal cancer.* N Engl J Med, 2010. **363**(1): p. 24-35.
9. Nichols AC, et al., *HPV-16 infection predicts treatment outcome in oropharyngeal squamous cell carcinoma.* Otolaryngol Head Neck Surg., 2009. **Feb;140(2):228-34**.
10. O'Sullivan B, et al., *Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis.* J Clin Oncol, 2013. **Feb 10;31(5):543-50.** .
11. Huang SH, et al., *Refining American Joint Committee on Cancer/Union for International Cancer Control TNM stage and prognostic groups for human papillomavirus-related oropharyngeal carcinomas.* J Clin Oncol, 2015. **Mar 10;33(8):836-45.**
12. Seiwert, T.Y., et al., *A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV–associated head and neck (H/N) cancer.* J Clin Oncol, 2014 (suppl; abstr 6011). **32:5s**.
13. Swanson MS and Sinha UK, *Rationale for combined blockade of PD-1 and CTLA-4 in advanced head and neck squamous cell cancer—review of current data.* Oral Oncology 2015. **Jan;51(1):12-5.**
14. Kim HS, et al., *Association Between PD-L1 and HPV Status and the Prognostic Value of PD-L1 in Oropharyngeal Squamous Cell Carcinoma.* Cancer Res Treat., 2015. **Sep 15.**
15. Zandberg DP and S. SE, *The role of the PD-L1:PD-1 pathway in squamous cell carcinoma of the head and neck.* Oral Oncol 2014. **Jul;50(7):627-32.**
16. Gillison ML, et al., *Nivolumab (nivo) vs investigator's choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): CheckMate-141.* AACR 2016 abstract # CT099, 2016.
17. Badoual C, et al., *PD-1-expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV-associated head and neck cancer.* Cancer Res., 2013. **Jan 1;73(1):128-38.**
18. Melkane AE, et al., *Human papillomavirus prevalence and prognostic implication in oropharyngeal squamous cell carcinomas.* Head Neck, 2014. **Feb;36(2):257-65.**
19. Rosenthal DA, H.P., Giralt J, Bell D, Raben D, Liu J, Schulten J, Ang KK, Bonner JA,, *Impact of p16 status on the results of the phase III cetuximab (cet)/radiotherapy (RT). .* J Clin Oncol, 2014. **32:5s, 2014 (suppl; abstr 6001).**
20. Snyder A, et al., *Genetic basis for clinical response to CTLA-4 blockade in melanoma.* N Engl J Med., 2014 **Dec 4;371(23):2189-99**.

21. Rizvi NA, et al., *Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.* Science 2015. **Apr 3;348(6230):124-8.**
22. J, H., *PASS 12. NCSS, LLC.* Kaysville: Utah, USA, 2013.
23. Marcus C, Ciarallo A, Tahari AK, Mena E, Koch W, Wahl RL, Kiess AP, Kang H, Subramaniam RM. *Head and neck PET/CT: therapy response interpretation criteria (Hopkins Criteria)-interreader reliability, accuracy, and survival outcomes.* J Nucl Med. **2014 Sep;55(9):1411-6**. doi: 10.2967/jnumed.113.136796. Epub 2014 Jun 19. PMID: 24947059.
24. Wray R, Sheikhbahaei S, Marcus C, Zan E, Ferraro R, Rahmim A, Subramaniam RM. *Therapy Response Assessment and Patient Outcomes in Head and Neck Squamous Cell Carcinoma: FDG PET Hopkins Criteria Versus Residual Neck Node Size and Morphologic Features.* AJR Am J Roentgenol. **2016 Sep;207(3):641-7**. doi: 10.2214/AJR.15.15730. Epub 2016 Jun 24. PMID:27341273.
25. Kendi AT, Brandon D, Switchenko J, Wadsworth JT, El-Deiry MW, Saba NF, Schuster DM, Subramaniam RM. *Head and neck PET/CT therapy response interpretation criteria (Hopkins criteria) - external validation study.* Am J Nucl Med Mol Imaging. **2017 Sep 1;7(4):174-180**. eCollection 2017. PMID: 28913156.
26. Sun M. Ahn, Jason Y. K. Chan, Zhe Zhang, et al. *Saliva and Plasma Quantitative Polymerase Chain Reaction–Based Detection and Surveillance of Human Papillomavirus–Related Head and Neck Cancer*. JAMA Otolaryngol Head Neck Surg. **Sept 2014;140(9):846-854**. doi:10.1001/jamaoto.2014.1338.
27. O'Sullivan, B., et al.. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol, 2013. 31(5): p. 543-50.
28. Maxwell, J.H., et al., Tobacco use in human papillomavirus-positive advanced oropharynx cancer patients related to increased risk of distant metastases and tumor recurrence. Clin Cancer Res, 2010. 16(4): p. 1226-35.
29. Weller, M.A., et al., Predictors of distant metastasis in human papillomavirus-associated oropharyngeal cancer. Head Neck, 2017. 39(5): p. 940-946.
30. Sheikhbahaei S, Mena E, Marcus C, Wray R, Taghipour M, Subramaniam RM. 18F-FDG PET/CT: Therapy Response Assessment Interpretation (Hopkins Criteria) and Survival Outcomes in Lung Cancer Patients. J Nucl Med. 2016 Jun;57(6):855-60. doi: 10.2967/jnumed.115.165480. Epub 2016 Feb 2. PMID: 26837337
31. Van den Wyngaert T, Helsen N, Carp L, Hakim S, Martens MJ, Hutsebaut I, et al; ECLYPS investigators. Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography After Concurrent Chemoradiotherapy in Locally Advanced Head-and-Neck Squamous Cell Cancer: The ECLYPSStudy. J Clin Oncol. 2017 Oct 20;35(30):3458-3464. doi: 10.1200/JCO.2017.73.5845. Epub 2017 Aug 30.
32. Ferris et al, N Engl J Med 2016; 375:1856-1867
33. FreePatentsOnline.com. November 21, 2013: http://www.freepatentsonline.com/20130309250.pdf

A Phase III Randomized study of Maintenance nivolumab versus observation in Patients with Locally Advanced, Intermediate Risk HPV Positive OPSCC

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF):

- Institutional Surgical Pathology Report
- Pathology materials
- ECOG-ACRIN Sample Tracking System (STS)-Generated Shipping Manifest

Instructions:

1. Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, will expedite any required communications with the institution (including site pathologists).
2. Pathology materials required for research, per patient consent:
   - FFPE Pre-Trial Diagnostic, Mandatory
   - FFPE from progression, if available, for patients that consented to "I agree to provide additional specimens for research."

Rev. Add1

   Pre-trial diagnostic specimens are to be submitted within 4 weeks following registration to the trial. Progression samples are to be submitted within 4 weeks of collection.

   NOTE: If blocks are not available for submission, the following alternative is to be submitted: 1 H&E (from the source block), 20 unstained slides (5 microns thick) and 1-2 core punches (4 mm minimum). Slides, including the H&E, are to be numbered consecutively in the order cut.

   NOTE: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.
3. Copies of the pathology, cytology and procedure reports associated with the submitted tissue must be submitted. Double-check that ALL required forms, reports and pathology samples are included in the package.
4. A copy of the ECOG-ACRIN STS Sample Tracking System manifest or relevant sample submission documents should be kept for your records.
5. Double-check that ALL required forms, reports and pathology samples are included in the package**.**
6. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
   1515 Holcombe Blvd
   Houston, TX 77030
   Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
   Fax: 713-563-6506
   Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility.

Peter O'Dwyer, MD, and Mitchell D Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for EA3161: A Phase III Randomized study of Maintenance nivolumab versus observation in Patients with Locally Advanced, Intermediate Risk HPV Positive OPCA

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for laboratory studies.

Keep a copy of the submission for your records and return any relevant completed forms, the surgical pathology report(s), the slides and/or blocks and any other required material to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

Pathology materials submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies per patient consent. Paraffin blocks will be returned upon request for purposes of patient management.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

This review will be retrospective and will not impact patient participation in EA3161.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 1-844-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

A Phase III Randomized study of Maintenance nivolumab versus observation in Patients with Locally Advanced, Intermediate Risk HPV Positive OPSCC

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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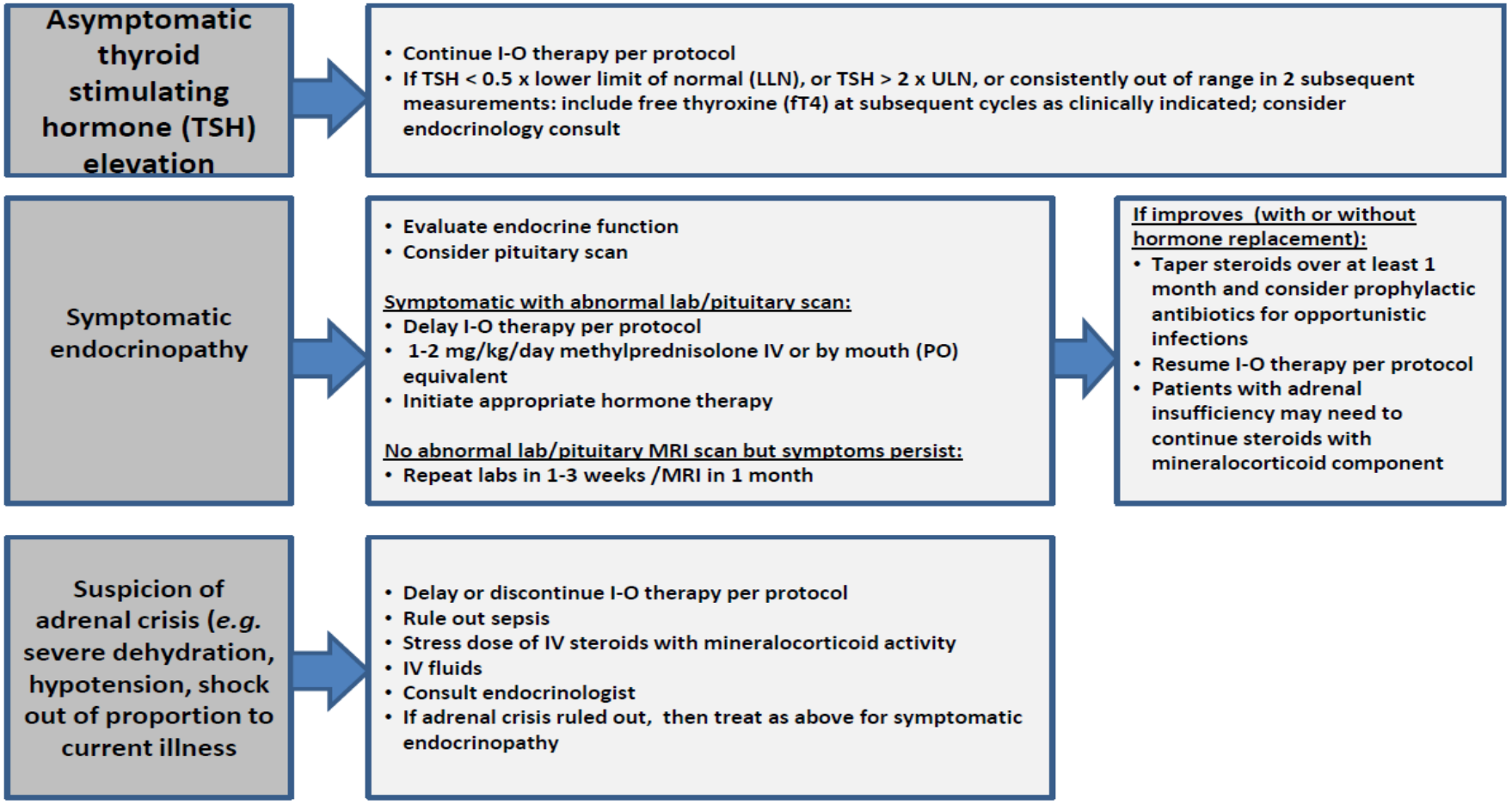
Appendix III

Management Algorithms For Endocrinopathy, Gastrointestinal, Hepatic, Neurological, Pulmonary, Renal, And Skin Adverse Events

Endocrinopathy Management Algorithm

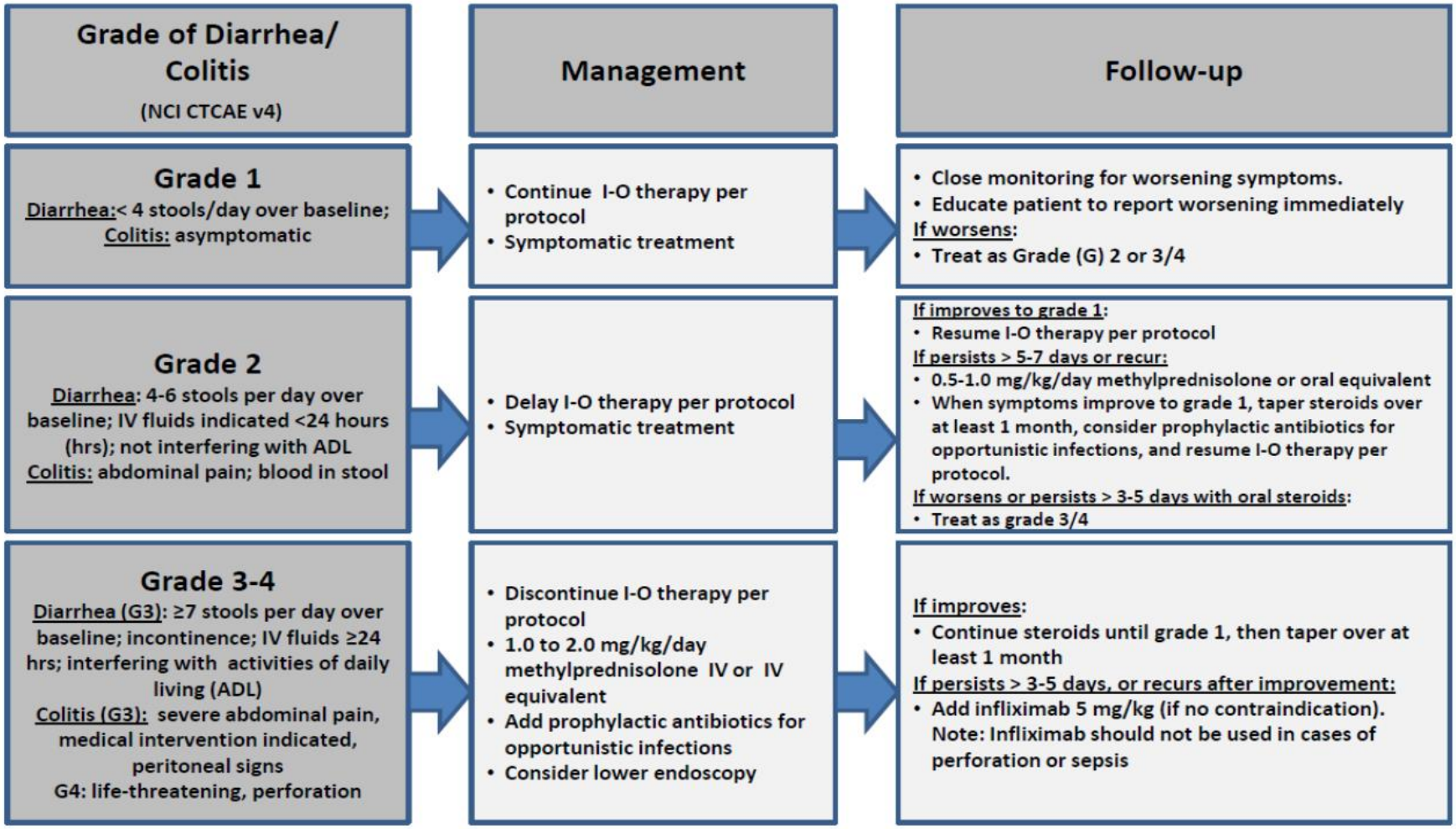
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



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.

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.

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.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

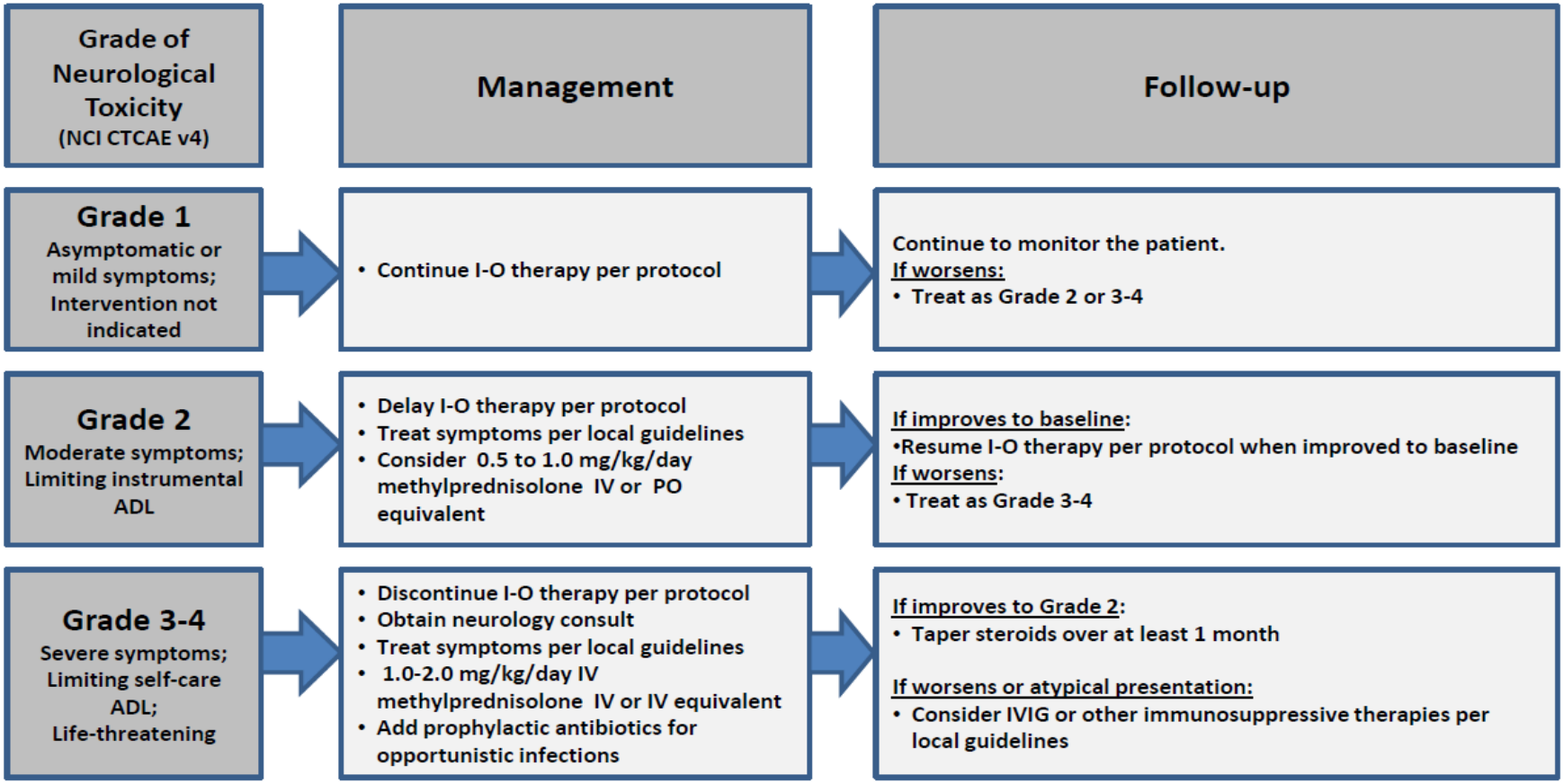
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

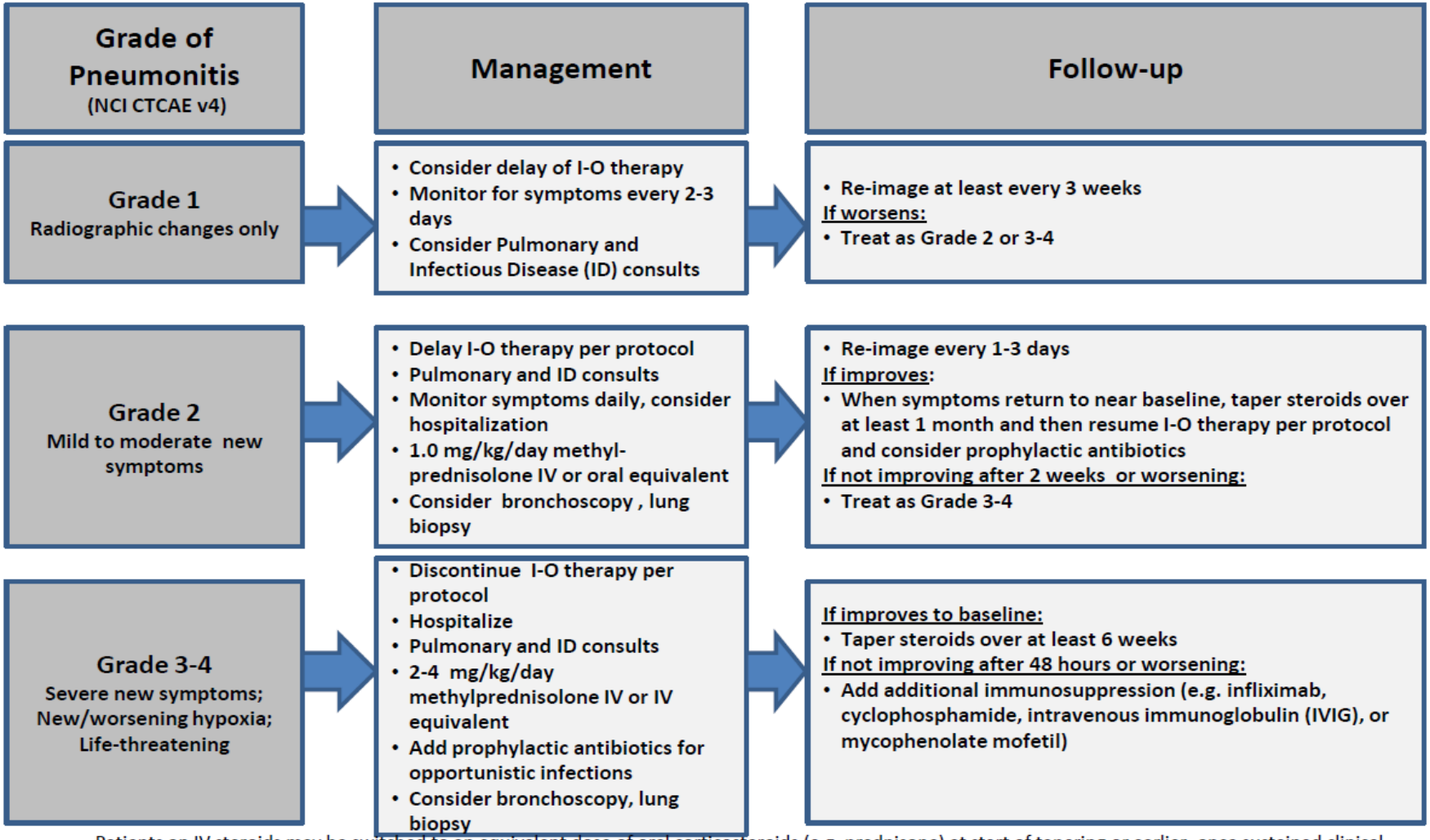
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Pulmonary Adverse Event Management Algorithm

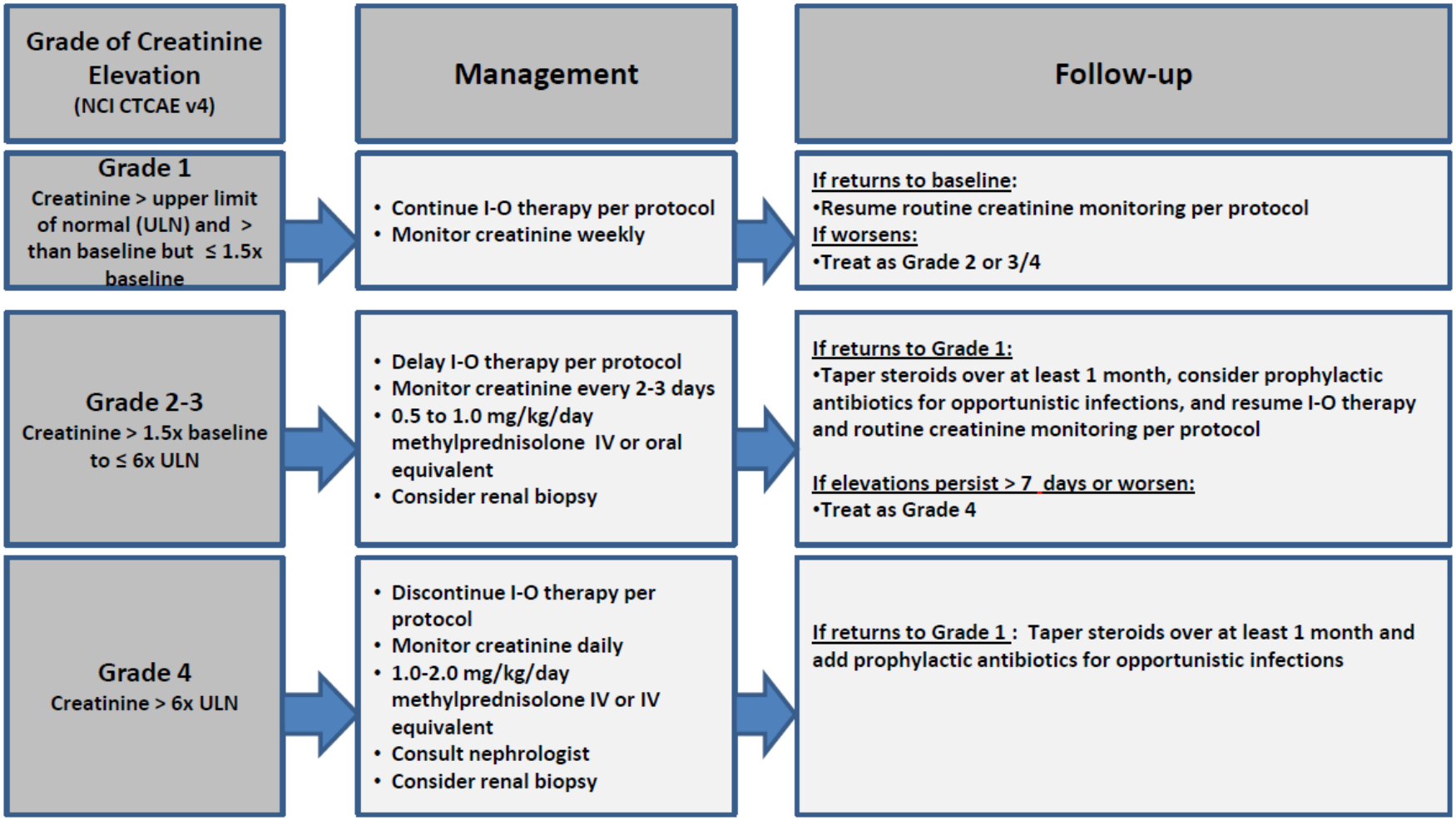
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

Renal Adverse Event Management Algorithm

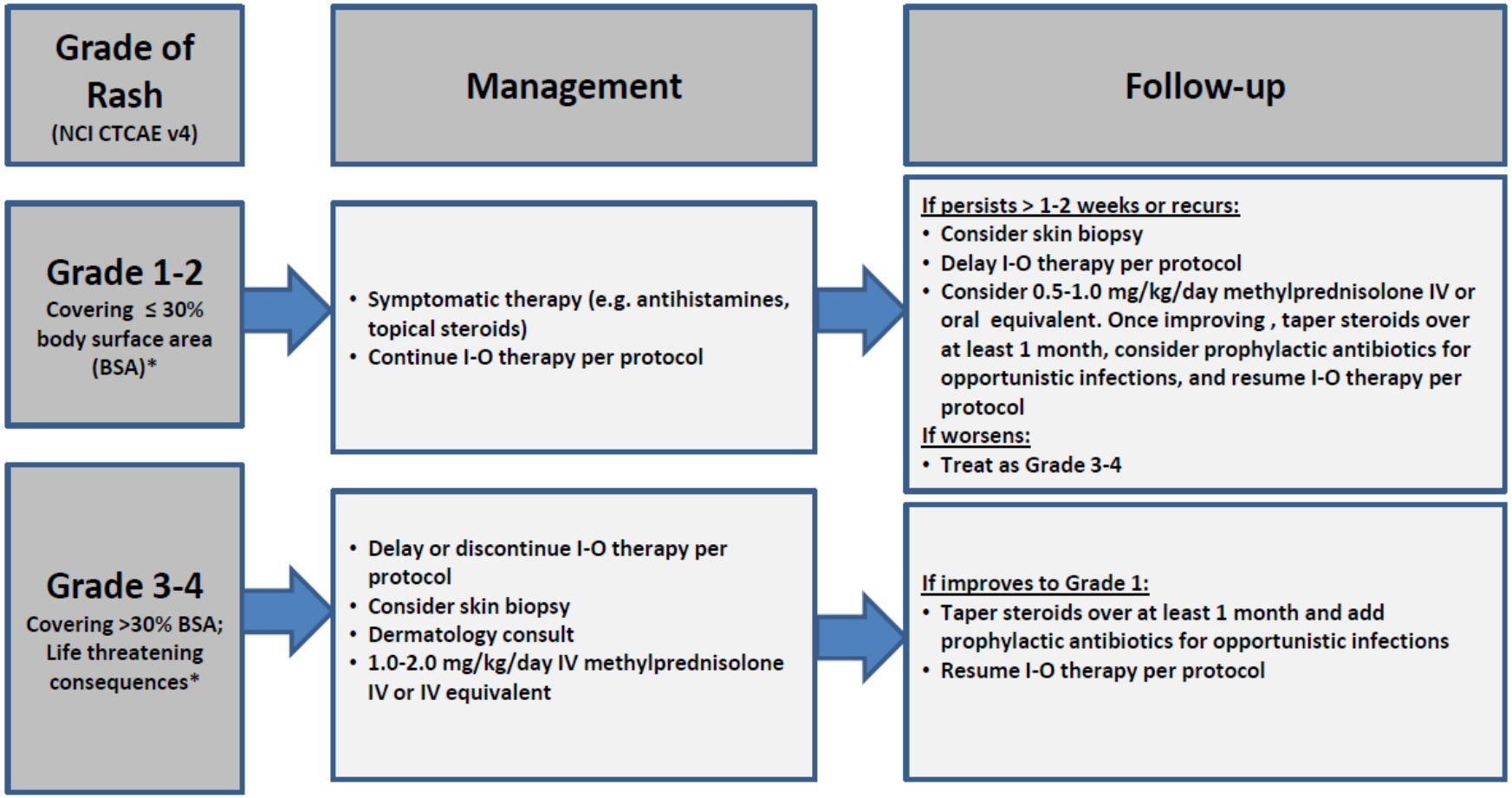
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

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.

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Appendix IV

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

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Appendix V

ECOG Performance Status

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

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Rev. Add4

Appendix VI

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on nivolumab or within 28 days of the female patient's last dose of nivolumab must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

For this study, a pregnancy, suspected pregnancy (including a positive or inconclusive pregnancy test) must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm the pregnancy requires reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status in CTEP-AERs accessed via Medidata Rave. Newborn infants should be followed until 30 days old.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.

- *It is recommended the female patient be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERs report should be initiated (via Medidata Rave) reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss

For this study, the pregnancy loss must initially be reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The pregnancy loss must be reported as a Grade 4 “Pregnancy Loss” under the System Organ Class (SOC) “Pregnancy, puerperium and perinatal conditions.”

A pregnancy loss should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient’s death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as “A death occurring during the first 28 days after birth” that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality AND any infant death after 28 days that is suspected of being related to the in utero exposure to Nivolumab must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the event is entered into Rave, the Rules engine on the Expedited Reporting Evaluation Form will confirm whether or not the event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The neonatal death must be reported as a Grade 4 “Death neonatal” under the System Organ Class (SOC) “General disorder and administration site conditions”.

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient’s death.

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any

additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix VII

EA3161 Collection and Shipping Kit Order Form

NOTE: Starter kits are not available.

It is preferred that baseline kit requests are made AFTER patient registration. At a minimum, the patient must have signed consent to participate in the trial and agree to the collection and submission of the research bloods. Kits for collection of samples for the *recurrence* time point are to be requested after recurrence is determined.

For the collection and submission of research bloods on EA3161, Specimen Collection/Shipping Kits are provided by CENETRON CENTRAL LABORATORIES and may be ordered ONLINE at www.cenetron.com

Please complete the online form completely, including the valid ECOG-ACRIN protocol number, ECOG-ACRIN patient case number, and complete shipping address. If information is missing the kit processing will be delayed.

Ordering process:

Proceed to www.cenetron.com. Click the “Order Kits” button at the top right.

Complete the online form as follows

- Sponsor (REQUIRED): ECOG-ACRIN
- Contact Name (REQUIRED): Name of the site’s kit contact. Should match the name of the individual provided in OPEN as the kit contact
- Protocol Number (REQUIRED): EA3161
- Phone Number (REQUIRED): Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller.
- Site Number (REQUIRED): Institution’s NCI site ID
- Fax Number: Fax number of the kit contact
- Investigator: Last name of the kit contact is adequate
- Email (REQUIRED): The email of the site’s kit contact. Must be entered twice to confirm.
- Date Supplies Needed (REQUIRED): Add 3 **business** days or more to order date. E.g. if ordering on 2/5/2016, indicate 2/10/2016 to accommodate the weekend. Reminder that holidays must also be considered in this timeline.
- Kit Name (REQUIRED): Complete with the appropriate kit
  - Prior to Start of Treatment
  - On Study (For timepoints: 12 weeks post cisplatin/RT, 9 months post cisplatin/RT)
- Quantity: 1
- Comments: Provide EA3161 Case ID and full shipping address
  - “Patient caseID =” #####
  - “Ship kit to” Name of the individual to whom the kit is shipped
  - Full street address, town, state and zip code
- Answer the security question

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron clinical trials group at 512-439-2000