THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

Nivolumab plus Weekly Carboplatin and Paclitaxel as Induction in Resectable Locally Advanced Head and Neck Cancer

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IND/IDE Holder:	Jennifer Johnson, MD, PhD
IND/IDE Number:	136803
Study Product:	Nivolumab
Protocol IDs:	CA209-9FT JeffTrial # 11182 PRC # 2017-100 IRB Control # 17P.513

Version Number:	**Version Date:**
2.0	2017-05-02
2.1	2017-11-03
3.0	2017-11-16
3.1	2018-06-29
3.2	2018-10-26
3.3	2019-03-15

4.0	2019-04-09
5.0	2019-11-05

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name:

Title:

Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Thomas Jefferson University research policies

List of Abbreviations

AE	Adverse Event/Adverse Experience
BOR	Best Overall Response
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
CTOC	Clinical Trials Oversight Committee
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRC	Imaging Response Criteria
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCI	National Cancer Institute
NIH	National Institutes of Health
OAR	Organ At Risk

OHRP	Office for Human Research Protections
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PR	Partial Response
PRC	Protocol Review Committee
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SDS	Safety Data Sheet (formerly MSDS; Material Safety Data Sheet)
SKCC	Sidney Kimmel Cancer Center
SOP	Standard Operating Procedure
TJU	Thomas Jefferson University
UAP	Unanticipated Problem
ULN	Upper Limit of Normal

Study Summary

Title: Nivolumab plus Weekly Carboplatin and Paclitaxel as Induction in Resectable Locally Advanced Head and Neck Cancer

Précis: Patients with locally advanced squamous cell carcinoma of the head and neck who are candidates for curative intent surgery will be treated with a combination of induction weekly carboplatin and paclitaxel plus nivolumab, to assess the rate of pCR at the primary tumor over historical control with induction chemotherapy alone.

Objectives:

Primary:
The primary objective of the study is to estimate pathologic complete response (pCR) at the primary site in patients with newly diagnosed and untreated Stage III-IVA SCCHN of the Oral Cavity, Oropharynx, Larynx, and Hypopharynx treated with Nivolumab, paclitaxel, and carboplatin in addition to standard chemotherapy.

Secondary:
- Safety
- Complete Pathologic Response at all sites of disease
- Major pathologic response rate at primary site
- Overall Clinical Response Rate
- Clinical Complete Response Rate
- 1 year PFS.
- Overall survival.

Exploratory:
- To explore whether PDL1 expression is associated with treatment response
- To explore whether there is a net change in the Th1/Th2 ratio (IFN- γ , IL-4, IL10, etc.) or cell subset frequencies (M2 monocytes, myeloid-derived suppressor cells, etc.) within a patient's peripheral blood either at baseline or in response to treatment is associated with treatment response
- To explore whether exosomes or other immune related serum biomarkers change after combination therapy.
- To explore the predictive value of serial cell free DNA levels and response

Population: Patients with newly diagnosed and untreated stage III-IVA SCCHN of the: Oral cavity, Oropharynx, Larynx, and Hypopharynx.

Phase: II

Number of Sites:
- 3: Thomas Jefferson University, USA (lead site), Fox Chase Cancer Center,

-
- Abington Memorial Hospital

Statistics: An optimal Simon two-stage design will be used. The null hypothesis is that the true pathologic complete response rate at the primary tumor site is ≤ 0.20 and will be tested against the alternative that it is >0.20. After testing the regimen on 17 patients in the first stage, the trial will be terminated if 3 or fewer respond. If the trial goes on to the second stage, a total of 37 patients will be studied. If the total number responding is less than or equal to 10, the regimen is rejected. This design yields a type I error rate of 9.5% and power of 90% when the true response rate is 0.40. It has a 55% probability of stopping early. The pathologic complete response rate and its associated score 95% confidence interval will be estimated using the methods of Tsai et al (2008).[20]

Description of Intervention: This is a phase II trial looking at the combination of weekly carboplatin plus paclitaxel to which nivolumab is added as induction therapy prior to planned surgery for the definitive management of locally advanced squamous cell carcinomas of the head and neck.

Treatment Plan:
Induction Nivolumab + Carboplatin + Paclitaxel:

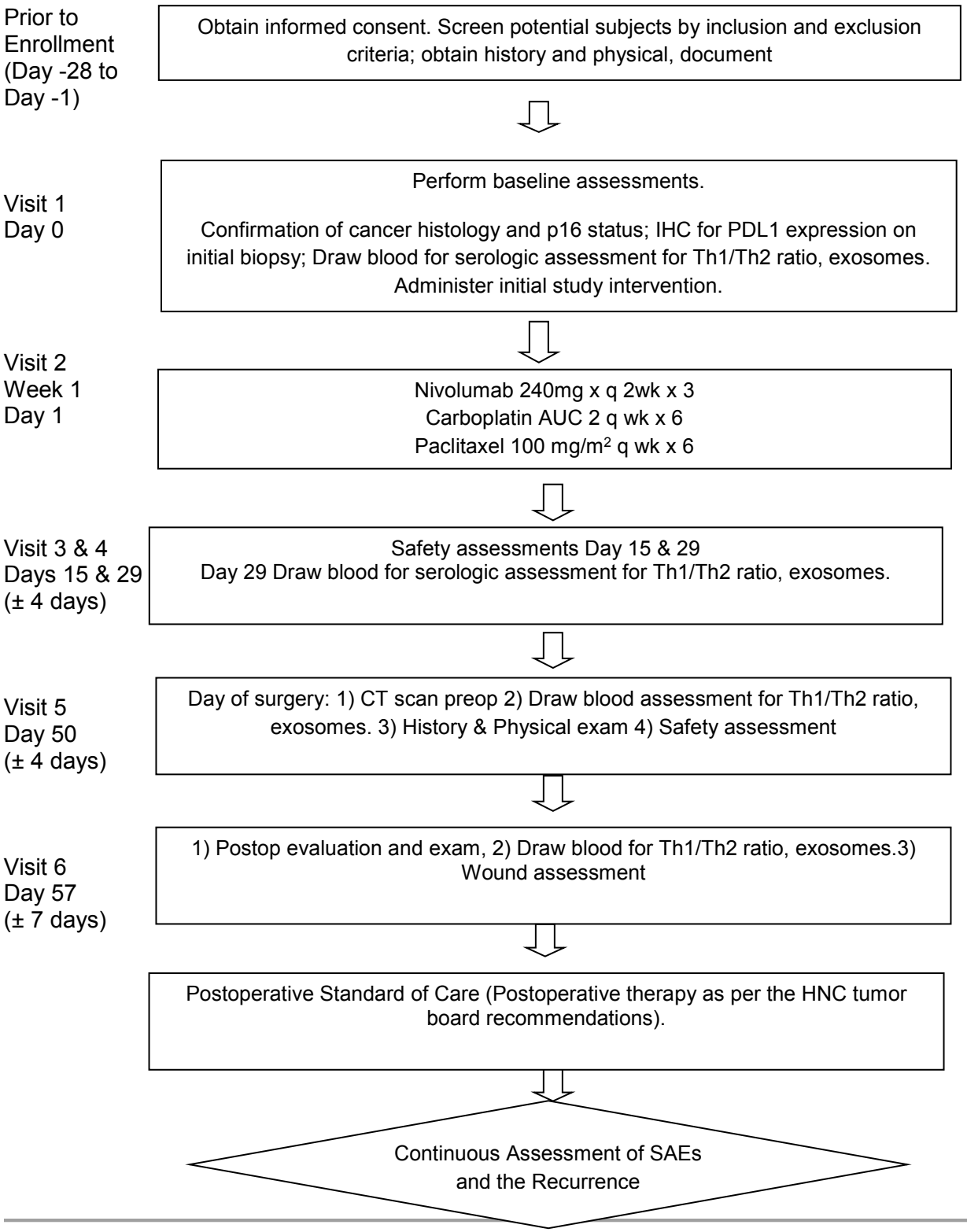
- Nivolumab 240mg every 2 weeks x 3 doses (last dose at least 3 weeks before surgery)
- Carboplatin AUC 2 weekly x 6 doses (last dose at least 2 weeks before surgery)
- Paclitaxel 100 mg/m^2 x 6 doses (last dose at least 2 weeks before surgery)

Study Duration: 38 months

Participant Participation Duration: 8 months

Estimated Time to Complete Enrollment: 30 months

Schematic of Study Design:



1 Introduction

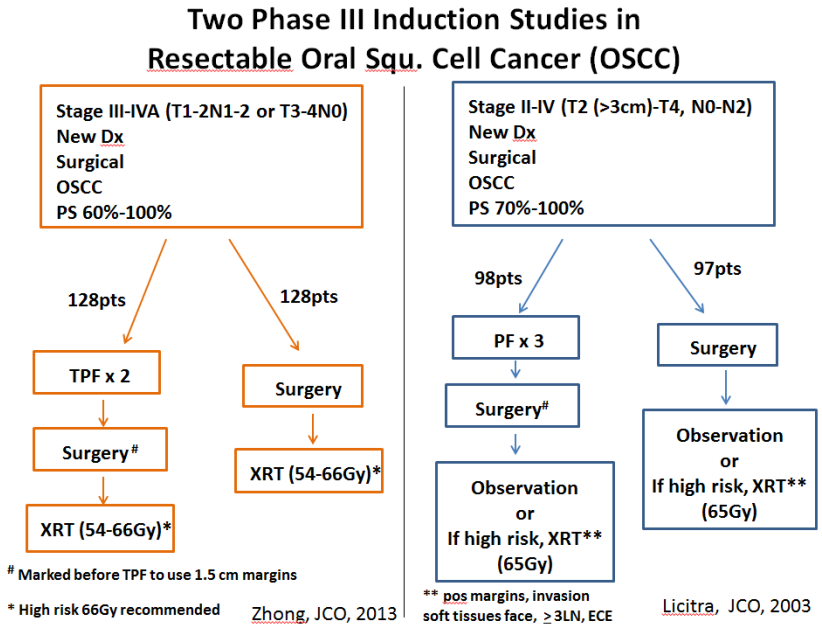
1.1 Background Information

Over 58,000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed leading to more than 1300 deaths each year in the United States[1]. Oropharyngeal cancer remains one of the few cancers that is on the rise in our population with an exceptional rate of increase per year[1]. The prognosis of head and neck cancer is highly variable based on subsite location and stage with an overall survival of 63% and with advanced stage disease with survival rates of 38-62%.[1] Earlier stage cancers are often treated with single modality therapy of either surgery or radiation, with advanced stages needing multimodality therapy including platinum based chemoradiotherapy regardless of surgery. Moreover, for early stage tumors and for those with local involvement of lymph nodes, resection is the cornerstone of therapy. Approximately 50% of head and neck cancer patients have primary surgery. More locally advanced cancers that are resected will also often require either adjuvant radiation therapy or chemoradiation to decrease local and regional recurrence rates. Surgical resections can cause considerable morbidity in the more locally advanced cases including a loss of swallowing and larynx function. Post-operative radiation can add further long term morbidity. In advanced local disease, after surgery and postoperative therapy, the current standard, 5 year survival rates are on the order of 50%. Patients with resectable locally advanced squamous cell carcinoma of the head and neck (SCCHN) remain at high risk for loco-regional and distant recurrence despite the standard approach of surgery followed by radiation or chemoradiation depending on the presence of intermediate/high risk features.[2] About half of patients with advanced local oral cavity cancer will die of either loco-regional and/or distant metastases or a second primary cancer. [3]

For locally advanced resectable disease, the standard remains surgery followed by observation, radiation or chemo-radiation depending on operative findings, the patient's condition and assessed level of risk of recurrence. However, given the substantial risk of recurrence and death after these interventions and the frequent sustained morbidity of the definitive procedures, presurgical induction therapy has been investigated.

Results from two phase III trials comparing induction chemotherapy followed by radical surgery versus upfront radical surgery in patients diagnosed with resectable oral squamous cell carcinoma have been reported (figure 1). [4,5]

Figure 1.



In the conducted by Zhong et al., patients with clinical stage III-IVA OSCC were randomized to immediate surgery or 2 cycles of TPF followed by postoperative single modality radiation in all patients in both arms. [4] In the PF induction study by Licitra et al., patients with clinical stage II-IV (T2(>3cm)-T4, N0-N2) OSCC were randomized to induction 3 cycles of PF or immediate surgery. [5] Postoperative radiation was given to patients in either arm only in high risk patients.

In the study by Zhong et al., patients had clinical stage III-IVA OSCC of whom 43% had clinical stage N0 stage with all patients having at least T1 (figure 2). In the study by Lictra et al, resectable clinical stages II-IV were eligible with a requirement that primary lesions be T2 > 3cm. About 57% had no clinical evidence of lymph node involvement at baseline (figure 3)

The percent of patients assigned each arm across the 2 studies who received the planned surgery and reasons for not getting the surgery are summarized here. A total of 256 patients were randomized in the TPF study of whom 124/128 in the induction arm received presurgical TPF and 118/124 (95%) of these had surgery compared to 127/128 (99%) randomized to surgery without induction. Of the 6/124 in the TPF arm who did not have surgery, 3/124 (2.4%) died during induction not felt to be from the TPF and 3 refused surgery (2 received radiation and 1 refused both surgery and radiation). Toxicities were modest with 6.6% having grade 3 hematologic toxicity and 0.8% and 1.6% having grade 3 diarrhea or febrile neutropenia respectively.

In the PF study, a total of 198 patients were randomized of whom 98/99 in the PF arm were evaluable and 96/99 completed follow-up. Of the evaluable patients on the PF arm, 92/98 (94%) received surgery compared to the 99 patients randomized to the control arm in which 97/99 were evaluable (2 lost after randomization) and 97/97 evaluable patients had surgery. Of the 6/98 (6%) on PF who did not have surgery, 3 died from toxicity, another 1 had an MI, one developed distant metastases and 1 refused. Two other patients had surgery on their primary but no planned lymph

node dissection but receiving radiation to the neck. Toxicities were more pronounced on this study compared to the TPF study with 25.5% and 11.2% of patients having at least on grade 3 or 4 toxicity respectively though only 1% of patients had a non-hematologic toxicity of grade 4, mucositis (and 3 patients had grade 5 toxicity).

Figure 2

Induction TPF - Surgery vs. Surgery III-IVA OSCC
Baseline clinical stage and pathologic stage

Baseline Clinical Stage

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	Total (N = 256) No.	%	Control Arm (n = 128) No.	%	Experimental Arm (n = 128) No.	%	P
Sex							.683
Male	179	69.9	88	68.8	91	71.1	
Female	77	30.1	40	31.2	37	28.9	
Age, years							.792
Median	55		56		55		
Range	26-75		26-75		29-74		
< 60	168	65.6	85	66.4	83	64.8	
≥ 60	88	34.4	43	33.6	45	35.2	
Site							.509
Tongue	113	44.1	60	46.9	53	41.4	
Buccal	45	17.6	20	15.6	25	19.5	
Gingiva	40	15.6	19	14.8	21	16.4	
Floor of mouth	30	11.7	18	14.1	12	9.4	
Palate	18	7.0	6	4.7	12	9.4	
Retromolar trigone	10	3.9	5	3.9	5	3.9	
T stage							.299
T1	9	3.5	6	4.7	3	2.3	
T2	57	22.3	27	21.1	30	23.4	
T3	149	58.2	79	61.7	70	54.7	
T4	41	16.0	16	12.5	25	19.5	
N stage							.294
N0	110	43.0	61	47.7	49	38.3	
N1	94	36.7	42	32.8	52	40.6	
N2	52	20.3	25	19.5	27	21.1	
Disease stage							.223
III	177	69.1	93	72.7	84	65.6	
IVA	79	30.9	35	27.3	44	34.4	
Pathologic differentiation							.802
Well	80	31.2	38	29.7	42	32.8	
Moderate	165	64.5	85	66.4	80	62.5	
Poor	11	4.3	5	3.9	6	4.7	

Pathologic Stage

Table 2. Description of Pathologic Characteristics of Tumors at Surgical Resection

Characteristic	Control Arm (n = 127) No.	%	Experimental Arm (n = 121) No.	%
Pathologic T stage				
pT0	0	0	15	12.4
pT1	7	5.5	28	22.0
pT2	29	22.8	42	34.7
pT3	64	50.4	26	20.5
pT4	27	21.3	10	8.3
Pathologic margins of resection				
Negative	127	100	121	100
Positive	0	0	0	0
Pathologic N stage				
pN0	48	37.8	55	45.5
pN1	24	18.9	17	14.0
pN2	55	43.3	49	40.5
pN2a	3	2.4	3	2.5
pN2b	42	30.1	35	28.9
pN2c	10	7.9	11	9.1
No. of positive lymph nodes				
0	48	37.8	55	45.5
1	27	21.3	20	16.5
2 to 5	43	33.9	38	31.4
6 to 10	8	6.3	7	5.8
> 10	1	0.8	1	0.8
Extracapsular spread				
No lymph node involvement	48	37.8	55	45.5
Yes	21	16.5	16	13.2
No	58	45.7	50	41.3

Zhong, JCO, 2013

Figure 3

Induction PF then surgery vs. up front surgery in T2 (>3cm) -T4 N0-2 Oral squamous CA Clinical Stage at Baseline (Licitra, JCO, 2003)

Table 1. Patients and Tumor Characteristics by Treatment Arm

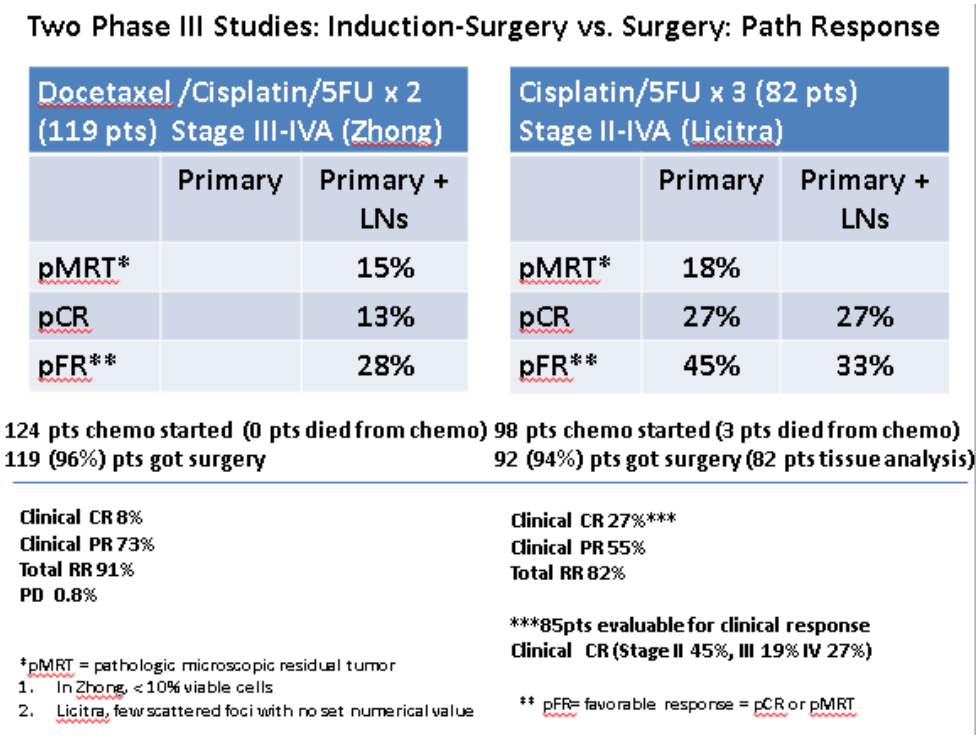
	Chemotherapy Arm (98 Patients)		Control Arm (97 Patients)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	85	86.7	78	80.4
Female	13	13.3	19	19.6
Mean age	55 years		55 years	
Tumor subsite				
Tongue	42	42.9	42	43.3
Floor of the mouth	30	30.6	26	26.8
Alveolar gingiva/cheek mucosa	11	11.2	15	15.5
Retromolar trigone/ant. pillar	15	15.3	14	14.4
UICC '87 cT category				
T2	42	42.8	38	39.2
T3	40	40.8	37	38.1
T4	16	16.3	22	22.7
UICC '87 cN category				
N0	56	57.1	55	56.7
N1	26	26.5	26	26.8
N2a	5	5.1	5	5.1
N2b	9	9.2	9	9.3
N2c	2	2.0	2	2.1
UICC '87 stage grouping				
Stage II	25	25.5	24	24.7
Stage III	46	46.9	40	41.2
Stage IV	27	27.6	33	34.0

Clinical responses to induction were seen in a high percentage of patients in both studies (figure 4). In the TPF induction study by (Zhong et al.), 122/124 (98.4%) patients received both cycles (2/124) just 1 cycle with a RR of 100 /124 (81%) of whom 10/124 (8%) were CRs with only 1 patient (0.8%) with PD. In the PF study (Licitra et al.), 85/98 (87%) received at least 2 of the 3 planned courses. The authors reported the responses on these 85 with RR of 70/85 (82%) of whom 28/85 (33%) were CRs at all sites of disease with PD not reported though 1 of these patients did have development of distant metastases and as noted above, all but 6 patients received the planned post induction surgery.

Pathologic responses were evaluated as pPD, pSD, pPR, pMRT (microscopic residual tumor) and CR variously at the primary site and LN and the primary site alone (figure 4). pMRT was described as scattered foci of a few tumor cells in the paper by Licitra et al. and more specifically as <10% viable tumor cells in the TPF induction study (Zhong et al.). The latter more precise definition underlay their later analyses of overall survival (OS) in those patients who had at least a pMRT. Of 124 patients who received induction TPF, a favorable pathologic response defined

as patients who had either pMRT or pCR, was seen in 27% for both primary and nodal disease with 13% of these having a pCR. In the study by Licitra et al., patients who received induction PF had a 33% pFR of whom 27% had a pCR. They also reported pFR of 45% at the primary site of whom 27% were pCR.

Figure 4.



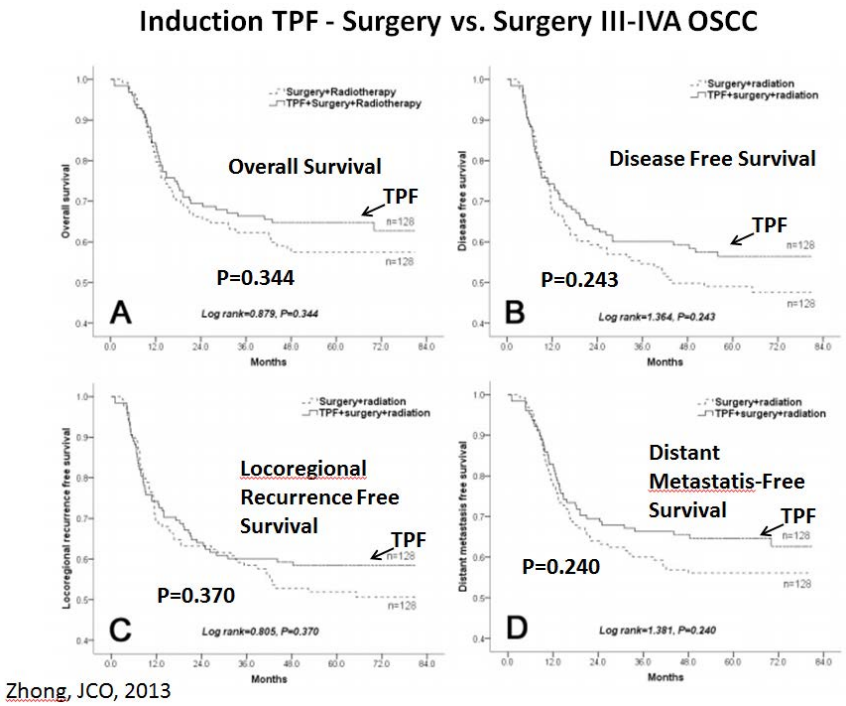
The induction arm did not yield increased OS in either study (figure 5, 6) though the authors of the TPF induction study conclude that failure to achieve a statistical improvement in OS may represent a type II error from a potentially underpowered study. They also observed that only 2 cycles rather than 3 or 4 cycles of induction were offered in contrast to other studies and this could have limited the level of efficacy (Zhong, JCO, 2013). However, when evaluating OS among patients who had a pFR in the TPF induction study, there was statistical improved OS compared to patients whose tumors did not have a pFR and compared to the patients who had no induction therapy (figure 7). Interestingly, though the patients who did not have a pFR did not have a superior survival, they had a numerically comparable OS compared to the patients who had no induction TPF. In the paper by Licitra et al., the subset of patients who achieved a pCR had a statistically improved DFS (p=0004).

The authors of the TPF study did not observe increased postoperative morbidity including flap failure (2 in each arm), postoperative hematoma (1 in each arm), and a chylous fistula after neck dissection in on patient in the experimental arm. Likewise, radiation toxicities were similar between the arms. In the PF induction study, there were statistically fewer mandibulectomies in the experimental arm (31% vs. 52% with a 21% difference (95% CI 7-34%)). There were also

fewer patients in the experimental arm who received radiation given decrease in stage and risk factors with 33% vs. 46% with a 13% difference (95% CI 0-27%). This would be expected to reduce long term morbidity.

Thus, in summary, the two phase III induction studies in stage II-IVA surgical OSCA were generally well tolerated, did not prevent surgery from toxicity or progression, did not lead to excess post-operative complications, and showed hints of decreased post-operative and post radiation morbidity compared to the control arm. In addition, there were some intriguing survival signals seen in the TPF induction study by Zhong et al. In both studies, pFR or pCR predicted improved OS compared to the non-induction immediate surgery controls.

Figure 5



Zhong, JCO, 2013

Figure 6

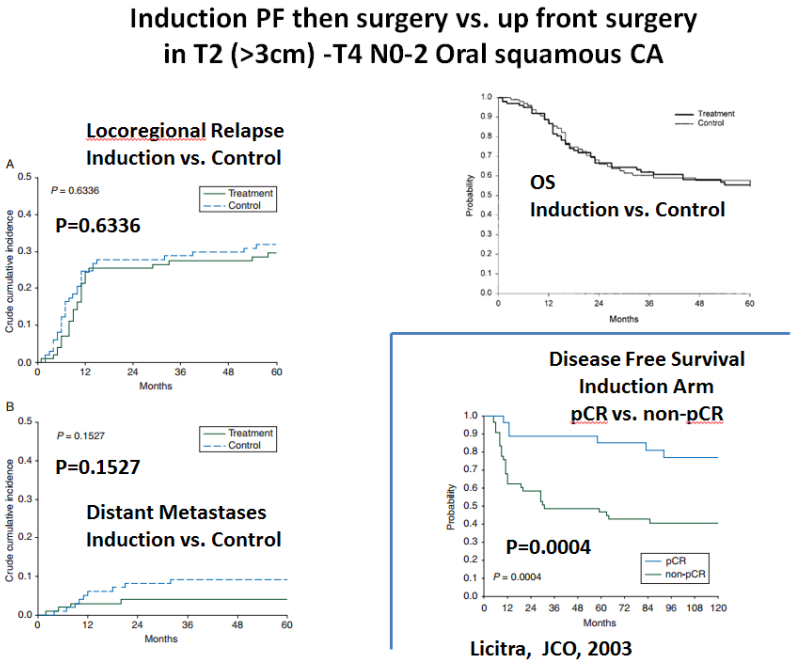


Figure 7

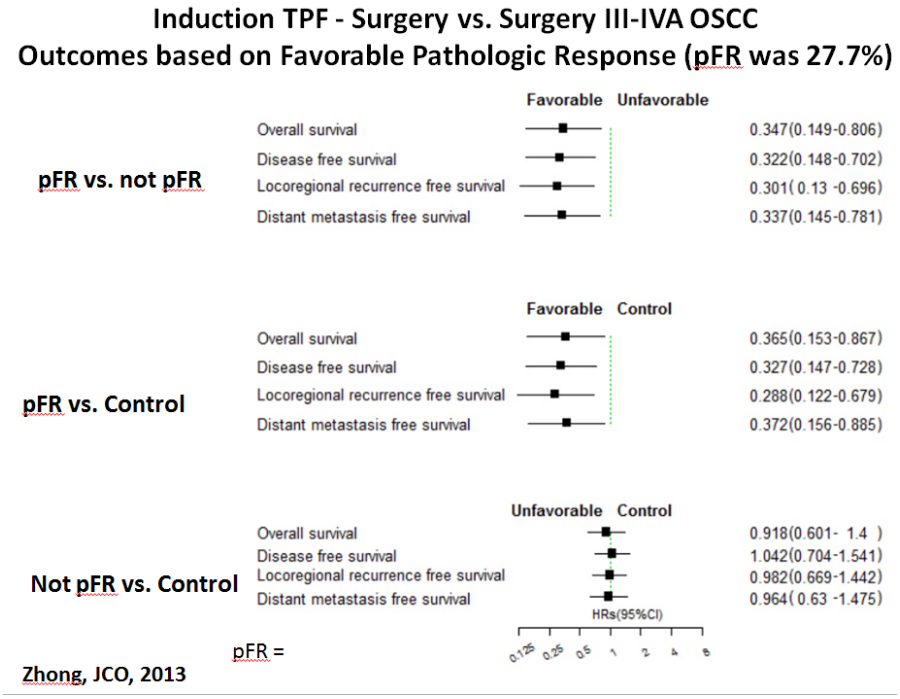


Figure 8

Table 2. Type of Surgical Techniques Adopted by Treatment Arm

Type of Resection	Chemotherapy Arm (98 Patients)		Control Arm (97 Patients)	
	No. of Patients	%	No. of Patients	%
Transoral resection	7	7.1	5	5.2
Pull-through resection (+/− marginal mandibulectomy)	40	40.8	29	29.9
Resection with swing mandibulotomy	13	13.3	10	10.3
Resection with segmental mandibulectomy	30	30.6	50	51.5
Other techniques	2	2.0	3	3.1
No surgery	6	6.1	—	—

Immune Therapy

Immunotherapy with checkpoint inhibitors has demonstrated clinical efficacy in several solid tumors types, including melanoma, renal cell carcinoma and non-small cell lung cancer. Early success was achieved with the CTLA4 antagonist ipilimumab in the treatment of advanced melanoma.[7] Further work with single agent pembrolizumab demonstrated 20-25% effectiveness with low rate of grade 3 or 4 toxicity in patients with recurrent/metastatic HNSCC. Since that time additional checkpoint inhibitors have been approved i.e. pembrolizumab for melanoma and nivolumab for non-small lung cancer and renal cancer.

Recently immunotherapy has become a promising new treatment option for recurrent head and neck squamous cell carcinomas.[8] Updated results on nivolumab in HNSCC can be seen in the CheckMate-141 phase III clinical trial. This study is the first randomized trial to show improved overall survival for platinum-refractory recurrent or metastatic HN-SCC patients using nivolumab compared to single-agent chemotherapy of the investigator's choice.[8,9] Usually these patients with recurrent HN-SCCs, who are unresponsive to platinum-based chemotherapy, have a poor prognosis and average survival less than 6 months. After failing platinum-based therapy for recurrent HNSCC within 6 months, patients were randomized 2:1 to receive nivolumab (a PD-1 inhibitor) or a single-agent chemotherapeutic or biological agent of the investigator's choice, which included methotrexate, docetaxel, or cetuximab. At interim analysis, there was already a 30% reduction in risk of death with nivolumab versus standard therapy. Regardless of PD-L1 status or HPV p16 status, median overall survival was 7.5 months for the nivolumab cohort versus 5.1 months for the investigator's choice of therapy. Further, HPV+ patients and patients with PD-L1 ≥1% had an even greater benefit and significantly longer overall survival with nivolumab. These patients also experienced an improvement in their quality of life across multiple measures.

The impressive results of T cell-directed immunotherapies are contrasted by the fact that only a subset of patients enjoys long-lasting remissions after single modality immune checkpoint therapy. This circumstance has reinvigorated interest in understanding how systemic and local factors may interfere with the function of T cells and other effector immune cells critical to tumor

control. It is now widely accepted that immunosuppressive cells and factors in the tumor microenvironment (TME) contribute to suboptimal responses to immune checkpoint therapeutics. Thus, there is interest in testing combinatorial approaches to “boost” the responses seen with nivolumab monotherapy.

Nivolumab

Nivolumab (Opdivo) is in clinical development for the treatment of subjects with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck carcinoma and other tumors (e.g., gastric cancer, glioblastoma multiforme, hodgkins lymphoma, small cell lung cancer). Opdivo as monotherapy has been approved in the US in multiple indications, including, unresectable or metastatic melanoma and disease progression following ipilimumab and a BRAF inhibitor, if BRAF V600 mutation positive; previously untreated patients with BRAF wild-type unresectable or metastatic melanoma; NSCLC with progression on or after platinum-based chemotherapy; and advanced renal cell carcinoma who have received prior anti-angiogenic therapy. The combination of nivolumab and ipilimumab has also been approved in the US for the treatment of previously untreated metastatic melanoma. Patients with recurrent or metastatic SCCHN have poor prognosis and experience limited survival benefit with standard of care therapies. In patients with recurrent or metastatic SCCHN who progress with platinum chemotherapy, nivolumab demonstrated prolonged survival benefit over standard of care in the Checkmate 141 study and is now the standard of care in this population. To further improve clinical outcomes in patients with recurrent or metastatic SCCHN in the first line treatment setting, nivolumab in combination with ipilimumab is being explored in the CA209651 clinical study.

Mechanism of action

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD 1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes33. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. 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. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

1.2 Rationale for the Proposed Study

Patients with resectable locally advanced squamous cell carcinoma of the head and neck (SCCHN) remain at high risk for loco-regional and distant recurrence despite the standard approach of surgery followed by radiation or chemoradiation depending on the presence of intermediate/high risk features.[2] About half of patients with advanced local oral cavity cancer will die of either locoregional and/or distant metastases or a second primary cancer.[3] Results from phase III trials comparing induction chemotherapy followed by radical surgery and postoperative radiotherapy versus upfront radical surgery and post-operative radiotherapy in patients did not

show improved overall survival using TPF, and PF respectively.[4] However, there were high response rates and patients with pathological complete response (pCR) had better PFS and OS.[4] Induction chemotherapy may result in major tumor responses that reduce surgical morbidity and decrease the likelihood of positive surgical margins and potentially reduce postoperative radiation therapy.[6] Thus, induction with TPF or PF did not reduce efficacy but showed evidence of reducing morbidity and afforded the chance to identify at surgery a subset of patients with pCR who had excellent prognosis.

Use of weekly carboplatin/paclitaxel may be an alternative to TPF and offers an active backbone regimen to incorporate novel therapies.[10] The addition of cetuximab to this backbone has been explored as induction prior to radiation therapy and may offer marginal further improvements in efficacy at the risk of increased toxicity.[11] The advent of immune checkpoint inhibitors offers the potential to not only improve response, but also long term disease control with minimal risk of additional toxicity thus presenting a fresh opportunity to explore the potential of presurgical induction therapy.

PD-1 checkpoint inhibitors are established in head and neck as second line therapy in advanced disease. Pembrolizumab was approved for use as second line therapy in advanced head and neck cancer in August 28th 2016 based on high and very sustained response rates in a single arm expansion cohort on a phase Ib study, KEYNOTE-12 trial.[12] Nivolumab resulted in longer overall survival than standard treatment in advanced platinum-refractory head and neck cancer with minimal increased toxicity.[9]

There is preclinical evidence supporting the addition of nivolumab to standard cytotoxic agents.[13] In a recently published randomized phase II in first-line advanced non-squamous NSCLC, patients randomized to carboplatin plus pemetrexed plus pembrolizumab showed improved response and time to progression compared to chemotherapy alone.[14] Encouraging safety and efficacy were observed in a multi-arm study 10mg/kg nivolumab with three doublet cisplatin/ gemcitabine, cisplatin/pemetrexed or carboplatin/paclitaxel or nivolumab 5mg/kg combined with one doublet, carboplatin/paclitaxel in first line advanced NSLCC. Though the number of patients in each arm was small, special promise observed in the nivolumab 5mg/kg plus carboplatin paclitaxel arm with 2 year survivals of 62%.[15] These NSCLC data support the safety of efficacy of standard chemotherapy combined with PD-1 inhibitors.

Given the single agent efficacy of nivolumab in SCCHN and the promising data with platinum-based doublets and immune checkpoint inhibitors in NSCLC we propose to study weekly carboplatin and paclitaxel plus nivolumab as an induction regimen in resectable SCCHN. It is tenable that the addition of nivolumab to carboplatin and paclitaxel will be both well tolerated and improve efficacy including response, pathological complete response and long term disease control. The induction setting is especially appealing to study nivolumab added to weekly carboplatin paclitaxel in resectable SCCHN given the chance to rapidly assess response, and the capacity to both determine the established predictive outcome of pathological complete response. Moreover, it affords the opportunity to obtain repeat tissue sampling for pharmacodynamics endpoint evaluation.

Hypothesis:

The addition of nivolumab to induction weekly carboplatin paclitaxel will increase the rate of pCR at the primary site over historical control with induction chemotherapy alone.

Immunotherapy in SCCHN

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma, hormone-refractory renal cell carcinoma and non-small cell lung cancer. Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. In SCCHN, down-regulation of T-cell function is thought to be mediated by multiple mechanisms: i.) Reduced expression of co-stimulating molecules of the B7-CD28 family71; ii.) Increased expression of PD-L1 in tumor cells and tumor associated fibroblasts; and, iii.) Loss of HLA-class I and selective down-regulation of HLA-A,B,C locus expression resulting in defective antigen presentation16,17,18. In a subset of HPV-infected SCCHN, data shows that antigen-processing machinery components are downregulated compared to the adjacent normal squamous epithelium with incomplete activation of tumor specific T cells or suboptimal target recognition enabling tumor progression19. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation.PD-1 engagement on T-cells by PD-L1-positive APC or PD-L1-positive tumor cells in the tumor microenvironment may limit effective immune responses. Conversely, PD-L1 expression may be a positive prognostic factor as it may indicate infiltration of tumor-specific T cells that secrete IFN-γ, which upregulates PD-L1 expression. Consistent with this hypothesis is the co-localization of lymphoid cell infiltrates and PD-L1 staining observed in human melanoma lesions26. PD-L1 expression in SCCHN has been reported, preliminary results from a phase 1 trial in patients with 27 recurrent or metastatic disease observed that 77.9% of patients tested (N=104) expressed PD-L1, defined as ≥ 1% of stained cells in the tumor microenvironment.

The role of the PD-1 blockade in squamous cell carcinoma of the lung primary has been established in CA209017 study where nivolumab monotherapy in the 2nd line treatment setting demonstrated clinically meaningful survival benefit regardless of PD-L1 expression compared to standard of care docetaxel.[16] In squamous cell carcinoma of the head and neck, CheckMate CA209141 study, is a randomized, open-label, phase 3 trial that compared nivolumab, a fully human anti-programmed death 1 (PD-1) monoclonal antibody, to investigator's choice (IC) of systemic therapy in patients with recurrent or metastatic SCCHN who progressed from a platinum containing therapy.[17] At a preplanned interim analysis, the median OS was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) with nivolumab versus 5.1 months (95% CI, 4.0 to 6.0) with IC. There is a 30% reduction in the risk of death for patients on the nivolumab arm (hazard ratio 0.70; 97.73% CI, 0.51 to 0.96; P=0.0101) over standard of care. The overall response rate (ORR) was 12.1% with nivolumab versus 7.4% with IC. In addition, the overall safety profile of nivolumab was favorable compared to standard of care. Clinical benefit seen in this chemotherapy pre-treated SCCHN suggests the potential clinical activity of nivolumab in earlier treatment setting.

Combination of Nivolumab and chemotherapy

The interaction of a tumor with the immune system is complex. Tumors and the tumor microenvironment are known to express a variety of factors that impede a robust immune response from eliminating the tumor. Soluble and membrane-bound factors have been shown to inhibit the cytolytic activity of tumor infiltrating T-cells (e.g., PD-L1 expression; TGF-beta). In addition, some tumor-derived factors are able to enhance immune system counter-regulatory systems (e.g., increased T-regulatory cells). Finally, suboptimal tumor antigen delivery and presentation has been postulated as another mechanism by which tumors can successfully evade immune system recognition.

Cancer therapeutics such as chemotherapy may modulate tumor/immune-system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells.

Clinical insights into the toxicity and efficacy of combination nivolumab chemotherapy can be gleaned from a trial in NSCLC. Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive subjects with advanced NSCLC in study CA209012.[18] Nivolumab 10 mg/kg was combined with gemcitabine + cisplatin (12 patients), pemetrexed + cisplatin (15 patients) and Nivolumab 10 mg/kg, and 5 mg/kg, was combined with paclitaxel and carboplatin (15 and 14 patients respectively).

The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines (Table 1.1.5-1). The frequency of most immune-related select AEs was higher than what has been observed for nivolumab monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths.

Table 1.1.5-1: Treatment-related AEs Reported in ≥ 10% of all NSCLC Subjects Treated with Nivolumab plus Platinum-based Chemotherapy

	Total (n=56)	
Treatment-related AE, n (%)	All Grades	Grade 3/4
Patients with any AE	53 (95)	25 (45)
Fatigue	40 (71)	3 (5)
Nausea	26 (46)	1 (2)
Decreased appetite	20 (36)	1 (2)
Alopecia	17 (30)	0
Anemia	15 (27)	2 (4)
Rash	14 (25)	2 (4)
Diarrhea	12 (21)	1 (2)
Arthralgia	12 (21)	0
Constipation	11 (20)	0
Peripheral neuropathy	11 (20)	0
Dysgeusia	8 (14)	0
Hypersensitivity	8 (14)	1 (2)
Vomiting	8 (14)	0
Mucosal inflammation	7 (12)	0
Myalgia	7 (12)	0
Pneumonitis	7 (12)	4 (7)
Infusion-related reaction	6 (11)	0
Leukopenia	6 (11)	0
Lymphopenia	6 (11)	0

Activity was also evaluated by PD-L1 expression and was observed in subjects with both PD-L1 expressing and non-expressing tumors (Table 1.1.4-3). Overall, 79% (44/56) of subjects had evaluable tumor samples. At the 1% expression level, the response rate was 48% and 43% for expressers and non-expressers, respectively. The 1-year overall survival was 70% and 76% for expressers and non-expressers, respectively.

Table 1.1.4-3: Efficacy in Nivolumab + Chemotherapy by PD-L1 Expression Level

	≥ 1% expression (n=23)	< 1% expression (n=21)
ORR, n (%)	11 (48)	9 (43)
Median duration of response (95% CI)	27.3 (12.3, 85.4)	25.4 (13.1, 56.7)
PFS rate at 24 wks (95% CI)	59 (34,77)	44 (22, 64)
Median PFS, wks	25.9	22.6
1-year OS rate, % (95% CI)	70 (47, 84)	76 (52, 89)

Table 1.1.4-3: Efficacy in Nivolumab + Chemotherapy by PD-L1 Expression Level

	≥ 1% expression (n=23)	< 1% expression (n=21)
18-mo OS rate, % (95% CI)	57 (34, 74)	51 (28, 70)
Median OS, wks	88 (47, 118)	83 (53, 103)

Given the small number of patients in the study, conclusions are tentative. However, the data are consistent with the conclusion that the predictive value for PD-L1 expression may be attenuated in the nivolumab + chemotherapy setting, compared to what has been observed in the nivolumab monotherapy and nivolumab + ipilimumab settings in NSCLC. In NSCLC, there was no detectable diminution in activity for patients with PD-L1 non-expressing tumors, and response rates appear to be greater than in patients with PD-L1 non-expressing tumors treated with nivolumab, or nivolumab + ipilimumab. In patients with PD-L1 expressing tumors, nivolumab + chemotherapy showed a similar response rate compared to the N3 nivolumab + ipilimumab cohorts, but with higher toxicity. In patients with PD-L1 non-expressing tumors, nivolumab + chemotherapy showed a higher response rate compared to any of the nivolumab + ipilimumab cohorts.

1.3 Correlative Studies

PDL1 expression

Immune inhibitory receptors are expressed by tumor cells, tumor-infiltrating macrophages, and peripheral blood monocytes. Nivolumab has the capacity to alter expression of PDL1 in these cells. Therefore, we plan to monitor changes in PDL1 expression in these different cell subsets by immunohistochemistry and flow cytometry at various stages of treatment and look for association with clinical outcome.

Analysis of peripheral blood mononuclear cells and cytokines

We have documented extensive immune bias in peripheral blood of astrocytoma patients. We have performed preliminary studies on blood samples from patients with HNSCC and observed similar results. In this HNSCC patient cohort, we have found that immune bias begins in tumor draining lymph nodes and extends to the peripheral blood. We have developed a novel in vitro assay where we co-culture normal human monocytes with various patient samples to investigate polarization capacity. Using this assay, we have shown that astrocytoma-derived exosomes and soluble factors can bias normal monocytes towards M2. HNSCC patient sera can also bias monocytes towards M2 in this assay.

Evidence collected in other tumor models suggests that PDL1 is preferentially expressed on M2 monocytes and tumor-infiltrating macrophages with an M2 phenotype, thereby making them targets in nivolumab. To date, there have been no studies looking at the capacity of nivolumab to alter immune bias or macrophage polarization. Therefore, we plan to analyze peripheral blood mononuclear cells (PBMC) subsets before treatment to establish a baseline and at every blood draw thereafter to monitor changes in these compartments due to nivolumab therapy. We will stain PBMC with monoclonal antibodies specific for human CD3, CD4, CD8, CD11b, CD11c, CD14, CD33, CD163, CD204, and HLA-DR. Samples will be analyzed by flow cytometry. These phenotypic markers will enable us to monitor the effect of nivolumab therapy sizes of cell populations and activation status.

We routinely perform multiplex cytokine analyses on serum samples in our astrocytoma clinical trial. We plan to utilize magnetic Milliplex assays (HCYTOMAG-60K) to track changes in serum cytokines over the course of treatment.

Exosomes and nivolumab therapy

Exosomes are small membranous vesicles released by tumor cells which modulate the local microenvironment and communicate with distant cells. In order to accomplish these tasks, exosomes contain a variety of RNA species including miRNA, protein and specialized lipids. These attributes make exosomes attractive therapeutic targets, excellent biomarkers, and indicators of therapeutic responses. We have developed novel flow cytometric analyses where we utilize fluorescent dyes to track and quantify exosomes directly from patient sera. We plan to monitor exosomes levels in patient sera and look for changes in frequency or content following nivolumab therapy.

Patient Reported Outcomes (PRO):

There has been increasing recognition that Patient-Reported Outcome (PRO) measures—including, in particular, measures of health-related quality of life (HRQOL)—can convey essential supplementary information for assessing the overall burden of cancer and the effectiveness of interventions [21]. Hence, we will collect Functional Assessment of Cancer Therapy - General (FACT-G) and cancer specific FACT scales. The FACT questionnaires have been used by researchers previously and have shown to be optimal for use in oncology trials[22] .It has also been shown that depression is the most frequently found psychological symptom among individuals with cancer, up to 38% of cancer patients meeting criteria for a diagnosis of major depression [23]. Prevalence rates of depression in cancer patients differ extensively across studies [24, 25]. Previous studies have also shown that depression might

affect behavior and adherence to medical treatment [26].Hence, we will collect Patient Health Questionnaire (PHQ2&9). The PHQ-2 comprises the first two items of the PHQ-9. It is a screen for depression; patients who screen positive are further evaluated with the PHQ-9 which is used for making a criteria-based diagnosis of depression (based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for depression). The PHQ-2 has been validated in several studies [27]. The diagnostic validity of the PHQ was established in two large studies in primary care and obstetrics [28].

Additional Lab tests and waist to hip ratio:

C - reactive protein (CRP) is an acute phase reactant [29], which reflects tissue injury .It is also a well-established marker for inflammation[30]. However, in recent literature it has also been shown to be a predictive biomarker for immunotherapy[31], elevated CRP also predicted prognosis and treatment response[32]. The frequency of significant Immune Related adverse Events (irAE) in Immune Checkpoint Inhibitors (ICI) treated patients are about 10–20% and early recognition is critical to prevent serious morbidity and even mortality[33]. New onset autoimmune Diabetes Mellitus (DM) associated with immune checkpoint inhibitor treatment is extremely rare [33, 34]. Even though it is very rare possibility having Glycated Hemoglobin (HbA1c) levels will be beneficial to capture these rare events. Lipid metabolism is altered in proliferating cells and impact tumor progression[35, 36]. Therefore, tumor dependence towards lipids might hold potential for the treatment of the most intractable cancers.

Waist to hip ratio (WHR) has been associated with metabolic syndrome and higher mortality[37, 38]. Hence, WHR should be assessed in combination with BMI as part of risk assessment for obesity related premature mortality and risk of metabolic related conditions.

1.4 Potential Risks and Benefits

1.4.1 Potential Risks

The safety profile of nivolumab is well characterized from a large safety database at different dose and schedules as monotherapy or in combination. Consistent with the mechanism of action of nivolumab, the most frequently reported drug-related adverse events observed in clinical trials are those associated with activation of the immune system. The most common types of immune-mediated adverse events include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis and rash. In the combination regimen, the frequency and intensity of these events may vary and depend on the specific dose and schedule used.

- The safety of this drug combination with chemotherapy in Non-small cell lung cancer has shown the following. [18]

Table 3. Treatment-Related Select AEs Reported in Patients With Advanced NSCLC Treated With Nivolumab Plus PT-DC

	No. of Patients (%)									
	Nivolumab 10 mg/kg						Nivolumab 5 mg/kg			
	Gem-Cis (n = 12)		Pem-Cis (n = 15)		Pac-Carb (n = 15)		Pac-Carb (n = 14)		All Patients (N = 56)	
Select AE Category	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Skin	2 (17)	0	6 (40)	0	6 (40)	2 (13)	6 (43)	1 (7)	20 (36)	3 (5)
Rash	1 (8)	0	5 (33)	0	4 (27)	0	5 (36)	1 (7)	15 (27)	1 (2)
Pruritus	0	0	2 (13)	0	4 (27)	0	0	0	6 (11)	0
Rash maculopapular	1 (8)	0	0	0	2 (13)	2 (13)	0	0	3 (5)	2 (4)
Erythema	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Rash pruritic	0	0	0	0	0	0	1 (7)	0	1 (2)	0
GI	2 (17)	0	3 (20)	1 (7)	5 (33)	1 (7)	3 (21)	0	13 (23)	2 (4)
Diarrhea	2 (17)	0	2 (13)	0	5 (33)	1 (7)	3 (21)	0	12 (21)	1 (2)
Colitis	0	0	1 (7)	1 (7)	1 (7)	0	0	0	2 (4)	1 (2)
Hypersensitivity/infusion reaction	1 (8)	0	6 (40)	1 (7)	6 (40)	0	0	0	13 (23)	1 (2)
Hypersensitivity	1 (8)	0	3 (20)	1 (7)	4 (27)	0	0	0	8 (14)	1 (2)
Infusion-related reaction	0	0	4 (27	0	2 (13)	0	0	0	6 (11)	0
Renal	1 (8)	0	3 (20)	1 (7)	1 (7)	0	3 (21)	2 (14)	8 (14)	3 (5)
Blood creatinine increased	1 (8)	0	1 (7)	0	1 (7)	0	1 (7)	0	4 (7)	0
Acute renal failure	0	0	1 (7)	1 (7)	0	0	2 (14)	2 (14)	3 (5)	3 (5)
Allergic nephritis	0	0	1 (7)	1 (7)	0	0	1 (7)	1 (7)	2 (4)	2 (4)
Blood urea increased	0	0	0	0	0	0	1 (7)	0	1 (2)	0
Creatinine renal clearance decreased	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Renal failure	0	0	0	0	0	0	1 (7)	0	1 (2)	0
Tubulointerstitial nephritis	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Pulmonary	2 (17)	1 (8)	3 (20)	2 (13)	0	0	2 (14)	1 (7)	7 (13)	4 (7)
Pneumonitis	2 (17)	1 (8)	3 (20)	2 (13)	0	0	2 (14)	1 (7)	7 (13)	4 (7)
Endocrine	2 (17)	0	1 (7)	0	0	0	1 (7)	0	4 (7)	0
Hypothyroidism	1 (8)	0	0	0	0	0	1 (7)	0	2 (4)	0
Blood corticotropin decreased	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Blood TSH increased	1 (8)	0	0	0	0	0	0	0	1 (2)	0
Hyperthyroidism	1 (8)	0	0	0	0	0	0	0	1 (2)	0
Hepatic	0	0	1 (7)	0	0	0	0	0	1 (2)	0
ALT increased	0	0	1 (7)	0	0	0	0	0	1 (2)	0
AST increased	0	0	1 (7)	0	0	0	0	0	1 (2)	0

NOTE. Data are based on a September 2014 database lock. Table includes events reported between first dose date and 100 days after the last dose of study drug. No grade 5 events were reported. The causal relationship (related or not related) between study drug and AEs was determined by the investigator. Some patients had more than one AE.

Abbreviations; AE, adverse event; Carb, carboplatin; Cis, cisplatin; Gem, gemcitabine; NSCLC, non–small-cell lung cancer; Pac, paclitaxel; Pem, pemetrexed; PT-DC, platinum-based doublet chemotherapy; TSH, thyroid-stimulating hormone.

The safety of chemotherapy vs. chemotherapy plus pembrolizumab in NSCLC assists in making a judgement about the combination of nivolumab plus chemotherapy, and thus, the randomized chemotherapy plus/minus pembrolizumab data are instructive.[19] The incidence of grade 3 or worse toxicities were 39% and 26% with chemotherapy plus pembrolizumab vs. chemotherapy alone. There was 1 and 2 treatment related deaths in the pembrolizumab containing vs. control arm respectively. The authors concluded the triplet pembrolizumab containing regimen was tolerable.

	Pembrolizumab plus chemotherapy (N=59)				Chemotherapy (N=62)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Related to treatment*								
Any	32 (54%)	18 (31%)	4 (7%)	1 (2%)	40 (65%)	12 (19%)	2 (3%)	2 (3%)
Serious	2 (3%)	10 (17%)	3 (5%)	1 (2%)	1 (2%)	2 (3%)	1 (2%)	2 (3%)
Led to discontinuation	1 (2%)	4 (7%)	0	1 (2%)	5 (8%)	1 (2%)	0	2 (3%)
Led to death	0	0	0	1 (2%)	0	0	0	2 (3%)
Occurring in ≥10% of patients in either group or of grade 3, 4, or 5 severity†								
Fatigue	36 (61%)	2 (3%)	0	0	25 (40%)	0	0	0
Nausea	33 (56%)	1 (2%)	0	0	27 (44%)	0	0	0
Anaemia	12 (20%)	7 (12%)	0	0	24 (39%)	9 (15%)	0	0
Vomiting	15 (25%)	1 (2%)	0	0	11 (18%)	0	0	0
Rash	15 (25%)	1 (2%)	0	0	9 (15%)	0	0	0
Decreased appetite	11 (19%)	0	0	0	11 (18%)	0	0	0
Diarrhoea	12 (20%)	0	0	0	6 (10%)	1 (2%)	0	0
Increased aspartate aminotransferase	10 (17%)	1 (2%)	0	0	6 (10%)	1 (2%)	0	0
Decreased neutrophil count	7 (12%)	2 (3%)	1 (2%)	0	6 (10%)	2 (3%)	0	0
Increased alanine aminotransferase	9 (15%)	1 (2%)	0	0	6 (10%)	1 (2%)	0	0
Constipation	11 (19%)	0	0	0	6 (10%)	0	0	0
Dysgeusia	10 (17%)	0	0	0	6 (10%)	0	0	0
Increased lacrimation	7 (12%)	0	0	0	6 (10%)	0	0	0
Alopecia	8 (14%)	0	0	0	2 (3%)	0	0	0
Increased blood creatinine	6 (10%)	0	0	0	4 (6%)	0	0	0
Dizziness	6 (10%)	0	0	0	4 (6%)	0	0	0
Neutropenia	3 (5%)	2 (3%)	0	0	4 (6%)	1 (2%)	0	0
Decreased white blood cell count	4 (7%)	1 (2%)	0	0	4 (6%)	1 (2%)	0	0
Peripheral oedema	7 (12%)	0	0	0	2 (3%)	0	0	0
Decreased platelet count	1 (2%)	0	1 (2%)	0	6 (10%)	0	1 (2%)	0
Pruritus	7 (12%)	0	0	0	2 (3%)	0	0	0
Hypokalaemia	5 (8%)	1 (2%)	0	0	2 (3%)	0	0	0
Decreased lymphocyte count	3 (5%)	2 (3%)	0	0	2 (3%)	1 (2%)	0	0
Thrombocytopenia	1 (2%)	1 (2%)	1 (2%)	0	2 (3%)	0	2 (3%)	0
Stomatitis	3 (5%)	0	0	0	2 (3%)	1 (2%)	0	0
Dehydration	1 (2%)	1 (2%)	0	0	2 (3%)	1 (2%)	0	0
Acute kidney injury	0	2 (3%)	0	0	1 (2%)	0	0	0
Hypocalcaemia	2 (3%)	1 (2%)	0	0	0	0	0	0
Leukopenia	0	1 (2%)	0	0	2 (3%)	0	0	0
Sepsis	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Pancytopenia	0	0	0	0	0	1 (2%)	0	1 (2%)
Cellulitis	1 (2%)	1 (2%)	0	0	0	0	0	0
Anaphylactic reaction	0	0	1 (2%)	0	0	0	0	0
Febrile neutropenia	0	1 (2%)	0	0	0	0	0	0
Myocardial infarction	0	1 (2%)	0	0	0	0	0	0
Pneumonia	0	1 (2%)	0	0	0	0	0	0
Rash macular	0	0	0	0	0	1 (2%)	0	0
Increased transaminases	0	1 (2%)	0	0	0	0	0	0

(Table 3 continues on next page)

1.4.2 Benefits

Clinical activity of nivolumab monotherapy in patients with recurrent or metastatic SCCHN who progressed from a platinum containing therapy evaluated in CA209141 randomized phase 3 study, demonstrated prolonged survival benefit with nivolumab as compared to investigator's choice (IC) of chemotherapy. In this population, the safety profile of nivolumab was shown to be favorable as compared to standard of care chemotherapy. The addition of pembrolizumab to platinum doublets in NSCLC improved response and progression free survival compared to chemotherapy alone and of nivolimab plus platinum doublets compared to historical controls. Given the activity of both platinum doublets and nivolumab in head and neck cancer, these NSCLC data support the promise of improved pathologic response at the primary site of combination platinum doublet plus nivolumab in head and cancer.

2 Study Objectives

2.1 Objectives

2.1.1 Primary

The primary objective of the study is to estimate pathologic complete response (pCR) at the primary site in patients with newly diagnosed and untreated Stage III-IVA SCCHN of the oral cavity, Oropharynx, Larynx, and Hyopharynz with Nivolumab, paclitaxel and carboplatin in addition to standard chemotherapy.

2.1.2 Secondary

- Safety
- Complete Pathologic Response at all sites of disease
- Major pathologic response rate at primary site
- Overall Clinical Response Rate
- Clinical Complete Response Rate
- 1 year PFS.
- Overall survival.

2.1.3 Exploratory

- To explore whether PDL1 expression is associated with treatment response
- To explore whether there is a net change in the Th1/Th2 ratio (IFN-γ, IL-4, IL10, etc.) or cell subset frequencies (M2 monocytes, myeloid-derived suppressor cells, etc.) within a patient's peripheral blood either at baseline or in response to treatment is associated with treatment response
- To explore whether exosomes or other immune related serum biomarkers change after combination therapy.
- To explore the predictive value of serial cell free DNA levels and response

The aims for collecting PROs are to identify risks for poor physical and mental health outcomes; examine bio-behavioral factors associated with cancer treatment outcomes; and evaluate the physical and psychosocial needs of cancer survivors.

Patient Reported Outcomes Measures-: Depression: PHQ2, PHQ9; Quality of Life: FACT-G and FACT-HN

2.2 Endpoints/Outcome Measures

2.2.1 Primary

The primary objective of the study is to estimate the rate of pathologic complete response (pCR) at the primary site, defined as the absence of any residual invasive cancer on H&E evaluation of the resected specimen and all sampled ipsilateral lymph nodes, in patients with newly diagnosed and untreated Stage III-IVA SCCHN of the oral cavity, Oropharynx, Larynx, and Hypopharynx treated with standard neoadjuvant chemotherapy plus Nivolumab, paclitaxel, and carboplatin**.**

2.2.2 Secondary

Major pathologic response. This is defined as 10% or less residual viable tumor (Hellmann M, Lancet Oncol. 2014).

Safety will be continually assessed using the CTCAE version 5.0.

Overall Survival (OS) is defined as the time between the date of study entry and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

The proportion of subjects with each category of overall clinical response will be summarized by presence of baseline measurable disease (i.e., CR, PR, SD, PD, UE, ND). Beta(2,5) will be used as priors for combination regimens in calculating the posterior distribution of the pCR for each respective treatment group. Among subjects with measurable disease, a 95% credible region will be calculated for the odds ratio for each treatment combination relative to each other.

The association of biomarkers with pCR will be completed univariably by t-test for continuous measures and by chi-square test for categorical marker measures (for example positive versus negative expression). Longitudinal assessments of biomarkers will be assessed for association with pCR via linear mixed models of biomarker measures with pCR and treatment assignment and the interaction of pCR and treatment assignment as potential covariates. Additional exploratory analysis of longitudinal biomarkers may be completed using latent class models, with pCR and treatment assignment as potential covariates to inform latent class membership. The specific hypotheses indicated will be completed via contrasts from the linear mixed models, as appropriate.

2.2.3 Exploratory

Blood samples:

There will be 3 presurgical and 1 postsurgical blood draw. The first will be within 2 weeks of the initiation of the induction regimen, the second will just prior to the week 5 infusion, the third will be presurgical on the day of surgery and the last will be ≥ 1 < 4 weeks postsurgery. (see study schedule 6.0).

- **PDL1 expression**
  We plan to monitor changes in PDL1 expression on tumor cells, tumor-infiltrating macrophages, and circulating monocytes by immunohistochemistry and flow cytometry. We will look for correlations between PDL1 expression on these cell subsets and treatment-induced clinical responses.

- **Immune bias**
  We will monitor changes in immune bias during treatment using three assays.
  1) Changes in PBMC cell subset frequencies (M2 monocytes, myeloid-derived suppressor cells, etc.)
  2) Changes in patient serum cytokines (IL2, IL4, IL10, IL13, IFNg, etc.)
  3) Changes in the capacity to polarization normal human monocytes in vitro.

- **Exosomes**
  We will look for changes in exosome quantity and content following nivolumab and carboplatin plus paclitaxel.

Tumor specimen:

PD-L1 will also be assessed using IHC on the baseline tumor tissue and the surgical specimen. For this, the SP263 rabbit monoclonal antibody of Ventana will be used. Note for the baseline, an archived formalin fixed paraffin embedded sample can be used. Also, we anticipate that some patients will have a pCR. However, peri-cancerous tissue can also be PD-L1 assessed.

Baseline p16 status will also be obtained for all oropharyngeal cancer patients.

3 Study Design

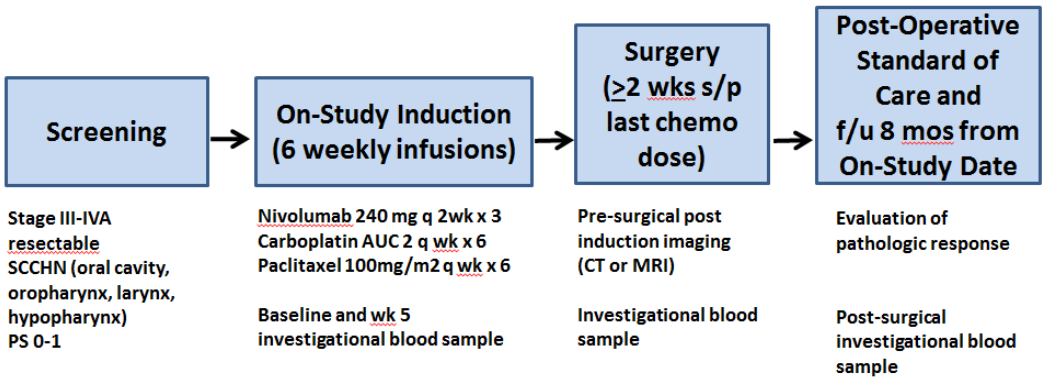
3.1 Characteristics

This is a phase II trial looking at the combination of weekly carboplatin plus paclitaxel to which nivolumab is added as induction therapy prior to planned surgery for the definitive management of locally advanced squamous cell carcinomas of the head and neck.

TREATMENT PLAN

Induction Nivolumab + carboplatin + paclitaxel

- Nivolumab 240mg every 2 weeks x 3 doses (last dose at least 3 weeks before surgery)
- Carboplatin AUC 2 weekly x 6 doses (last dose at least 2 weeks before surgery)
- Paclitaxel 100 mg/m^2 x 6 doses (last dose at least 2 weeks before surgery)



Evaluation of Response to Chemotherapy

Clinical response to chemotherapy will be measured by clinical exam by the medical and surgical oncologist throughout administration of chemotherapy. PET/CT or, if patients cannot have a PET/CT, a CT or MRI will be obtained during the initial staging work-up for all patients. If the treating medical oncologist determines that there is evidence that the patient is progressing while on treatment (i.e., tumor size if found to be increased during treatment), imaging with MRI, CT, or ultrasound will be obtained for evaluation. For patients who are determined to have progression during treatment by their medical oncologist, study treatment will be discontinued and the patient will be considered for immediate surgery, as determined by the discretion of their treating oncologist and surgeon. Finally, pathologic response will be assessed in the final tumor specimen, and attainment of pathologic complete response at primary site (defined as the absence of any residual invasive cancer on H&E evaluation of the resected primary cancer specimen) will be determined by pathologic review. Pathologic complete response of the entire tumor will also include all sampled lymph nodes.

Surgery

All patients will undergo surgery after completing the induction regimen. Surgery will be scheduled at least 2 weeks after the last dose of carboplatin and paclitaxel.

3.2 Number of Participants

37 participants. Enrollment will be competitive across all the sites.

3.3 Duration of Therapy

6 weeks

3.4 Duration of Follow Up

8 months after enrollment on trial

3.5 Study Timeline

3.5.1 Primary Completion

We anticipate accrual of 37 patients to the study over a 30 month time period. Patients will remain on study for 8 months total, 2 months of induction and then 6 months of follow-up after surgery whether or not patients receive post-operative radiation.

3.5.2 Study Completion

We anticipate completion of the study in 38 months.

4 Study Enrollment and Withdrawal

4.1 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to screening procedures being performed. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

1. Patients must be 18 years of age and older.
2. Pathologically confirmed SCCHN, not previously treated, with a plan to undergo surgery
3. Patients who have stage III-IV disease without distant metastases (M0) of 1) oral cavity, 2) larynx, 3) hypopharynx 4) oropharynx (HPV neg) using AJCC 8th edition
4. Patients who have oropharyngeal cancer that is HPV positive, Stage II-III disease without distant metastases (M0) using AJCC 8th edition
5. All patients with oropharyngeal SCCHN must be tested for HPV (by p16 and/or HPV ISH or PCR)
6. Patients must be evaluated by a head and neck surgeon and be deemed surgically resectable at baseline.
7. Tumor sample must be available for HPV p16 and PD-L1 testing and if oropharyngeal, must be tested for HPV p16
8. ECOG Performance status 0-1.

9. Adequate organ function:
    - While blood cells 2000/ul or more
    - Absolute neutrophil count 1500/ul or more;
    - Platelets 100,000/ul or more,
    - Hemoglobin 9 g/dl or more; (transfusion permitted)
    - Bilirubin less than or equal to 1.5 x the upper limit of normal (except subjects with Gilbert syndrome, who can have total bilirubin <3 mg/dl);
    - AST and ALT less than or equal to 3 x the upper limit of normal,
    - GFR greater than or equal to 40 ml/min using the Cockcroft-Gault formula or Serum creatinine less than or equal to 1.5 x ULN
10. Women of reproductive potential should have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 21 days of study enrollment.
11. Women of reproductive potential must use highly effective contraception methods to avoid pregnancy for 23 weeks after the last dose of study drugs. “Women of reproductive potential” is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.
12. Men of reproductive potential who are sexually active with women of reproductive potential must use any contraceptive method with a failure rate of less than 1% per year. Men who are receiving the study medications will be instructed to adhere to contraception for 31 weeks after the last dose of study drugs. Men who are azoospermic do not require contraception.
13. Informed Consent: All subjects must be able to comprehend and sign a written informed consent document.

4.1.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Primary nasopharyngeal carcinoma.
2. Patients who have participated in a study with an investigational agent or device within 2 weeks of initiation of treatment.
3. Any prior radiotherapy to the neck.
4. Any prior treatment for SCCHN.
5. Any prior therapy with anti-PD-1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways
6. Any history of a sever hypersensitivity reaction to any monoclonal antibody.
7. Any history of allergy to the study drug components.
8. Any concurrent malignancies- exceptions include- basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer or in situ cervical cancer that has undergone potentially curative therapy. Patients with a history of other prior

malignancy must have been treated with curative intent and must have remained disease-free for 3years post-diagnosis.

9. Any diagnosis of immunodeficiency or current immunosuppressive therapy including >10mg/day of prednisone within 14 days of enrollment is not permitted (excludes emergency transient steroid use at discretion of the treating physician).
10. Patients that have an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids (> 10 mg daily prednisone equivalents) or immunosuppressive agents. Subjects with vitiligo, type I diabetes mellitus, or resolved childhood asthma/atopy would be an exception to this rule. Inhaled or topical steroids, and adrenal replacement steroid doses ≤10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.
11. Patients with a known Human Immunodeficiency Virus infection (HIV 1/2 antibodies) or Acquired Immunodeficiency Syndrome (HIV/AIDS), active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
12. Patients with evidence of non-infectious pneumonitis or history of interstitial lung disease.
13. Patients who have received a live vaccine within 30 days prior initiation of the systemic regimen.
14. Patients must not be receiving any other investigational agents.
15. Patients with uncontrolled intercurrent illnesses including, but not limited to an active infection requiring systemic therapy or a known psychiatric or substance abuse disorder(s) that would interfere with cooperation with the requirements of the trial.
16. Women must not be pregnant (as above) or breastfeeding.

4.2 Gender/Minority/Pediatric Inclusion for Research

We will not exclude potential subjects from participating in this study based on ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients in this protocol and therefore address the study objectives in a patient population representative of the entire head and neck squamous cell cancer population treated at Thomas Jefferson University Hospital. There is nearly a 3:1 predominance of males to females in this diagnosis. We will review accruals to this trial quarterly in the Head and Neck MDG and review the number of males and females accrued. If this deviates from the expected ratio we will review our actual patient ratio for that time and determine a remediation plan within the MDG to ensure accrual of women.

4.3 Strategies for Recruitment and Retention

37 subjects will be recruited. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Surgical offices. Investigators will screen the patient's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study. Patients will be screened based on pathology,

image studies etc. 37 patients will be enrolled (see Statistical Analysis Plan) with replacement of patients who do not begin therapy.

4.4 Sub-Site Enrollment Procedure

When a potential patient is identified at the sub-site, the Thomas Jefferson University (TJU) study site contacted must be contacted within 1 business day via email or phone. Please see the Site Contact List for email and phone number for the TJU Study Site Contact. The sub-site will send the following to the TJU Study Site Contact:

1. Notify them of the pending patient registration
2. Email registration documents
3. Communicate the desired timeline of the registration.

The sub-site must include the eligibility checklist, signed informed consent, and any applicable documentation supporting eligibility.

Once eligibility has been confirmed locally, TJU study site contact or delegated personnel will email the Research Coordinator at the sub-site site to confirm eligibility. The participant will then be assigned a registration number. This number is unique to the participant on this trial and must be used moving forward. The TJU Research Nurse/Coordinator will enter patients enrolled at the sub-site into the protocol management system, JeffTrial.

A master study enrollment log will be maintained by the study team at Thomas Jefferson University. The sub-site site will also be asked to maintain an enrollment/screening log on-site, and email this information to the TJU Study Site Contact at least once a month.

Patients cannot be registered to this study on the weekends. If a patient is to be registered on a Friday, the sub-site will need to contact the TJU Study Site Contact by Friday at noon at the latest.

If a patient is enrolled at the sub-site without approval from the lead site, TJU will:

1) Temporarily suspend the sub-site

2) Complete mandatory re-training of staff at the sub-site on the enrollment process. This training will be fully documented.

If enrollment without approval occurs a second time, the sub- site will not be able to continue to participate in this study.

4.5 Participant Withdrawal

4.5.1 Reasons for Withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study participant's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

4.5.2 Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention

Patients who are discontinued from the study prior to initiation of study drug will not be considered as evaluable for this study and will be replaced.

4.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the Food and Drug Administration (FDA) and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

5 Study Intervention

5.1 Study Product

- Nivolumab
- Paciltaxel
- Carboplatin

5.2 Study Product Description

Nivolumab:

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. 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. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. OPDIVO (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

Carboplatin

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m2 of carboplatin. The initial plasma half-life (alpha) was found to be 1.1 to 2 hours (n=6), and the postdistribution plasma half-life (beta) was found to be 2.6 to 5.9 hours (n=6). The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/hour, 16 L and 3.5 hours, respectively. The Cmax values and areas under the plasma concentration vs time curves from 0 to infinity (AUC inf) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 - 500 mg/m2).

Carboplatin is not bound to plasma proteins. No significant quantities of proteinfree, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3 to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. PARAPLATIN Bristol-Myers Squibb Company Approved 1.0 Item 2 proposed.pdf Page 002 3 of 24 dosages should therefore be reduced in these patients

Paclitaxel

Paclitaxel is a natural product with antitumor activity. TAXOL (paclitaxel) is obtained via a semi-synthetic process from Taxus baccata. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Paclitaxel has the following structural formula: Paclitaxel is a white to off-white crystalline powder with the empirical formula C47H51NO14 and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216–217° C. CLINICAL PHARMACOLOGY Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

5.2.1 Acquisition

Nivolumab will be supplied by, Bristol-Myers Squibb. Nivolumab will be supplied directly to each participating site from Bristol-Myers Squibb.

Carboplatin is a standard of care medicine which will be supplied through the standard pharmacy. Each site will acquire this agent through their pharmacies.

Paclitaxel is a standard of care medicine which will be supplied through the standard pharmacy. Each site will acquire this agent through their pharmacies.

5.2.2 Formulation, Packaging, and Labeling

Nivolumab:

Nivolumab, also referred to as BMS-936558-01 or BMS-936558, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. The physical and chemical properties of nivolumab are:

BMS Number	*BMS-936558-01*
Other Names	Nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
Appearance	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present

Solution pH	5.5 to 6.5

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

Carboplatin

PARAPLATINÆ (carboplatin aqueous solution) INJECTION is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin. Carboplatin is a platinum coordination compound. The chemical name for carboplatin is platinum, diammine [1,1- cyclobutane-dicarboxylato(2-)-0,0í]-,(SP-4-2). Carboplatin is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 Bristol-Myers Squibb Company Approved 1.0 Item 2 proposed.pdf Page 001 2 of 24 mg/mL, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

Paclitaxel

TAXOL (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

5.2.3 Product Storage and Stability

Nivolumab:

Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

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

Carboplatin

Unopened vials of PARAPLATIN (carboplatin aqueous solution) INJECTION are stable to the date indicated on the package when stored at 25° C (77° F); excursions permitted from 15°-30° C (59°-86° F) [see USP Controlled Room Temperature]. Protect from light. PARAPLATIN (carboplatin aqueous solution) INJECTION multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25° C following multiple needle entries. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.

Paclitaxel

Stability

Unopened single-dose vials of TAXOL (paclitaxel) Injection for Dilution are stable until the date indicated on the package when stored in the original package below 25 degrees C. (Freezing does not adversely affect the product).

5.3 Dosage, Preparation, and Administration

Nivolumab:

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy manual, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Carboplatin

Per standard of care

Paclitaxel

Per standard of care

Dosage & Administration Time of Nivolumab

The dose of nivolumab is a flat dose 240mg administered intravenously over at least 30 minutes. Do not co-administer other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

Frequency of Treatment:

For the duration of the study, nivolumab is to be administered on a Q2 weeks and carboplatin and paclitaxel Q weekly. On the weeks of nivolumab administration, it will precede chemotherapy administration.

5.4 Dose Modifications and Dosing Delays

Nivolumab:

There will not be dose modifications

- Renal Impairment: The effect of renal impairment on the CL of nivolumab was evaluated in subjects with mild (GFR < 90 and ≥ 60 mL/min/1.73 m2; n=379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m 2; n=179), or severe (GFR <30 and ≥ 15 mL/min/1.73 m2; n=2) renal impairment compared to subjects with normal renal function (GFR ≥ 90 mL/min/1.73 m2; n=342) in the PPK analysis. No clinically important differences in the CL of nivolumab were found between subjects with mild or moderate renal impairment and subjects with normal renal function. Data from subjects with severe renal impairment are too limited to draw conclusions on this population. Thus, patients with severe renal impairment are excluded from the student presented here.

- Hepatic Impairment: The effect of hepatic impairment on the CL of nivolumab was evaluated in subjects with mild hepatic impairment (total bilirubin 1.0 to 1.5 times ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n=92) compared to subjects with normal hepatic function (total bilirubin and AST ≤ ULN; n=804) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between subjects with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in subjects with moderate (total bilirubin > 1.5 to 3 times ULN and any AST) or severe hepatic impairment (total bilirubin > 3 times ULN and any AST).

Dose Delays:

Dose delay criteria apply for all drug-related AEs.

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities

- Any Grade ≥ 3 skin *drug-related* AE

- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase
    - Grade 3 lymphopenia does not require a dose delay
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade 2 toxicity (Increase frequency of monitoring to every 3 days).
    - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The TJU PI should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Rescheduling:

- Nivolumab may be delayed until the next planned carboplatin plus paclitaxel dose if the next carboplatin plus paclitaxel doses are scheduled within the next 12 days. This will permit periodic carboplatin plus paclitaxel dosing to be synchronized with nivolumab dosing.
- It should be noted delay of nivolumab of a week could result in a dose of nivolumab on the last scheduled infusion of carboplatin plus paclitaxel just 2 weeks before scheduled surgery which is permitted.

Criteria to Resume Nivolumab Dosing:

- Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:
    - Subjects may resume treatment in the presence of Grade 2 fatigue.
    - Subjects who have not experienced a Grade 3 *drug-related* (non-radiation dermatitis) skin AE may resume treatment in the presence of Grade 2 skin toxicity.
    - Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
    - Drug-related pulmonary toxicity, neurologic toxicity, and hepatic toxicity must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the TJU PI.

- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤10 mg/day.

- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

- Subjects who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The TJU PI should be consulted prior to resuming nivolumab in such subjects.

Criteria to Discontinue Nivolumab

Treatment with nivolumab should be permanently discontinued for any of the following:

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

- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids

- Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration

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

    - Any Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.

    - Any Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation

    - Any Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.

- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm):
    - AST or ALT > 8x ULN
    - Total bilirubin > 5 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 *drug-related* adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset. The TJU PI should be consulted for Grade 4 amylase or lipase abnormalities
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the TJU PI.

- Dose delay of nivolumab which results in treatment interruption of > 2 weeks requires treatment discontinuation.

- Dosing delays lasting > 2 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the TJU PI.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Please see Appendix D for **Strategies to Treat Adverse Events**.

For subjects expected who require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider the following recommendations

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.

- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.

- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE 5.0 guidelines.

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

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

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

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

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

are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

Chemotherapy Dose Modifications:

Doses of carboplatin and paclitaxel may require reduction for hematologic or non-hematologic toxicities (see sections below). Dose adjustments should be made according to the organ system showing the greatest toxicity as graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE). Treatment may be delayed for up to two weeks. If a patient does not fulfill re-treatment criteria by that time, the responsible chemotherapy agent(s) should be discontinued. Table 5.A.5 summarizes the guidelines for paclitaxel and carboplatin doses to be used when modifications are required. If chemotherapy is discontinued, nivolumab therapy should also conclude and the patient will advance to surgery. The total induction treatment period should not exceed 8 weeks. If there are further toxicities warranting adjustments after the first dose reduction, the chemotherapy will be discontinued, nivolumab therapy should also conclude and the patient will advance to surgery.

Dose level reductions for paclitaxel and carboplatin

Dose Level	Paclitaxel (mg/m^2)	Carboplatin (target AUC)
Starting Dose	100	2.0
First Reduction	75	1.5

Hematologic Toxicity

In general, courses of paclitaxel and carboplatin should not be repeated until the neutrophil count is at least 1500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. The severity of neutropenia increases with dose. Table 5.A.5.a summarizes the guidelines for dose modifications based on hematologic toxicities. Mid-week use of filgrastim (suggest 5µg/kg SC days 3 and 4) will be included.

Table 5.A.5.a. Dose adjustments for paclitaxel and carboplatin for hematologic toxicity are based on weekly CBC results:

ANC		PLT	Dose Modification
500-1500/mm^3	or	75-100 000/mm^3	1 week delay
<500/mm^3	or	<75 000/ mm^3	1 week delay then reduce dose (see table 5.A.5)

Note:

- If blood counts have not recovered to ANC>1500/mm^3 and PLT>100,000/mm^{3}after a two week delay, then proceed to surgery.
- If febrile neutropenia occurs, discontinue chemotherapy and proceed to surgery, after recovery.
- Filgrastim 5mg/kg SC, at physician's discretion, may be administered on any 2 days inclusive days 2 -6 (preferred days 3 & 4) of each treatment week to reduce marrow suppression.

Peripheral Neuropathy

If grade 2 peripheral neuropathy occurs, the paclitaxel dose should be decreased by one dose level (see Table 5.A.5). If grade 3 or higher toxicity occurs, the chemotherapy should be discontinued.

Hypersensitivity Reactions to Paclitaxel

Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions attributed to paclitaxel such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not

be rechallenged with paclitaxel. The attending physician will make the ultimate determination of the advisability of continuing paclitaxel or not.

Hepatic Toxicity

Paclitaxel is not known to cause hepatic toxicity; however, its elimination may be delayed in patients with severe hepatic dysfunction. Therefore, the dose of paclitaxel in patients with hepatic dysfunction should be modified according to Table 5.A.5.d.

Table 5.A.5.d. Paclitaxel dose reductions for hepatic toxicity

NCI Liver function abnormalities	Paclitaxel dose modification
Grade 0-1	No change
Grade 2	Dose reduction (see table 5.A.5)

5.5 Study Product Accountability

Table 1 Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume) / Label Type	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing

Drug Destruction:

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

On-site disposal practices must not expose humans to risks from the drug.

On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

Written procedures for on-site disposal are available and followed. The procedures must be filed with the Sponsor SOPs and a copy provided to BMS upon request.

Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.

Accountability and disposal records are complete, up-to-date, and available for BMS to review throughout the clinical trial period as per the study agreement. A copy of the drug destruction certificate should be maintained for provision to BMS at the end of the study.

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

Paclitaxel

Paclitaxel must be obtained from commercial sources and will be provided and stored according to institutional guidelines. Paclitaxel 100 mg/m2 will be administered intravenously weekly on a 14-day cycle. Paclitaxel will be administered prior to carboplatin on the same schedule.

The following adverse events are expected with the administration of Paclitaxel. For complete information, see Package Insert.

Carboplatin

Carboplatin must be obtained from commercial sources and will be provided and stored according to institutional guidelines. Carboplatin AUC=2 will be administered weekly of a 14-day cycle. Carboplatin will be administered after paclitaxel.

The dose of carboplatin will be adjusted for renal dysfunction to achieve a calculated AUC as defined by the following Calvert Formula. The calculated GFR for the carboplatin dose will be based on the calculated creatinine clearance using the Cockroff-Gault formula.

Calvert Formula for carboplatin dose:

AUC Dose = 2.0 X (GFR + 25)

WHERE GFR (Cockroff-Gault):

GFR = (140 – Pt. Age in Yrs) (Weight in Kg) X 0.85 (females) or 1.0 (males)

Serum Creatinine X 72

The GFR dosing should not exceed 125 mL/min under any circumstance. If the calculated creatinine clearance is larger than 125 mL/min, a clearance of 125 mL/min should be used.

5.6 Assessing Participant Compliance with Study Product Administration

Patient records will be reviewed for compliance with chemotherapy and nivolumab treatments with all deviations and delays noted.

5.7 Concomitant Medications/Treatments

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

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

All concomitant medications received within 28 days before informed consent is signed and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered to treat SAEs and ECIs should be recorded as defined.

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

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids, with the following exceptions:
    - Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
    - Adrenal replacement steroid doses > 10 mg daily prednisone are permitted.
    - A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer.

- The use of amifostine is not permitted.
- The use of hematopoietic growth factors can be considered at the discretion of the treating physician
- All other medications are permitted except those that are contraindicated in the exclusion criteria (section 4.1.2).

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

Although monoclonal antibodies are not direct inhibitors/inducers of metabolizing enzymes, recent literature reports suggest that therapeutic proteins that are modulators of cytokines may indirectly affect expression of cytochrome (CYP) enzymes. The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes, at single and multiple doses of 0.3 to 10 mg/kg Q3W from CA209009. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment. 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. Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system). These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

All supportive measures consistent with optimal patient care will be given throughout the study. This includes the use of antiemetic therapy at the discretion of the treating physician, as well as pilocarpine and cevimeline. Use of these agents will be recorded on the data forms.

Aggressive oral and skin can is recommended, as are analgesics.

The prophylactic placement of a gastrostomy tube before treatment begins is at the discretion of the treating physician but it not encouraged. It is strongly recommended for patients with significant dysphagia and weight loss.

Salvage surgery may be performed after chemoradiotherapy is there is local and / or regional progression of disease.

5.8 Dietary Restrictions

There are no dietary restrictions

6 Study Schedule

6.1 Enrollment/Baseline (Visit 1, Day 0)

- Obtain and document consent from potential participant on protocol consent form.
- Review medical/dental history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Verify baseline tumor tissue specimen available. FFPE core/excisional specimen archived is highly encouraged preferably with at least 5 cores. Tissue for frozen and FFPE core or excisional biopsy will be obtained as feasible.
    - Tumor sample prior to therapy is mandatory to confirm the presence of squamous cell carcinoma, for HPV p16 testing in oropharyngeal carcinomas, and for PD-L1 testing for all patients. If a recent (obtained within 3 months of enrollment without interim therapy as dictated in the eligibility criteria) tumor sample is not available at screening, a fresh biopsy will be taken prior to enrollment.
- Perform medical examinations needed to determine eligibility, including complete head and neck examination including laryngoscopy. Standard of care oral and maxillofacial examinations. Dental examination will be done before surgery; ok to be done after initiating systemic therapy on study.
- Verify inclusion/exclusion criteria.
- Obtain demographic information, medical/dental history, medication history, alcohol, and tobacco use history.
- Record results of physical including ECOG Performance Status, Vital Signs, Complete Physical Exam (including BMI and waist to hip ratio [WHR]).
- Schedule study visits for individuals who are eligible and available for the initial treatments of the trial- carboplatin, paclitaxel, nivolumab.

The following procedures must be completed within 28 days of study enrollment unless otherwise indicated:

- PET/CT or, if a patient cannot have PET/CT, then a CT or MRI of the Head and/or Neck, and Chest, abdomen and pelvis with and without contrast must be completed within 28 days of initiation of therapy. If contraindicated in patient, scans will be done without contrast only.
- EKG

- Collect blood for baseline correlative studies (Luminex panel and exosomes), pre-treatment serum chemistries (Albumin, LDH, AST, ALT, ALK Phos, T.Bili, BUN, creatinine, Calcium, Mag, Phos, Na, Cl, Phos, Glucose, Amylase, Lipase, TSH, Free T4, Free T3, cortisol), PT/PTT, CBC with differential, viral studies (HepB surface antigen and hepatitis C antibody or hepatitis C RNA) within 14 days of initiation of study treatment.

- Serum or urine pregnancy test for women of childbearing potential must be done within 21 days of study enrollment.

The following procedures will only be performed for patients enrolled at Thomas Jefferson University:

- Complete PROs:
    - FACT-G
    - FACT-HN
    - PHQ2
    - PHQ9
- C-reactive protein (CRP), glycated hemoglobin (HbA1c), and lipid panel
- Body Mass Index (BMI) and Waist Hip Ratio (WHR)

6.2 Treatment Period

Visit 2, Week 1, Day 1- RUN-IN TREATMENT PHASE

- Targeted and complete physical examination
- Review entry labs, performed within 3 days of first administration of nivolumab and paclitaxel plus carboplatin. For WOCBP serum or urine pregnancy should be within 24 hours of the first study drug administration.
- Review concomitant medications.
- Administer the nivolumab (dose #1) and paclitaxel plus carboplatin (dose #1).
- Ensure that surgery dates and treatment planning are scheduled
- Record adverse events as reported by participant (PRO-CTCAE) or observed by investigator.

For patients who have agreed to collection and if determined feasible by the physician, an optional biopsy may be performed from and including days 14 and 23 of each cycle during the visit for weekly chemotherapy. Patients who have agreed to the collection and if determined feasible by the physician. The tissue collected will be sent for formalin fixed/paraffin embedded and a portion may also be frozen.

Visit 3 , Week 3, ± 4 days- (there will be no visit week 2. Visits are every other week during systemic therapy induction)

- Record adverse events as reported by participant (PRO-CTCAE) or observed by investigator.
- Targeted and complete physical examination.
- CBC with differential, CMP, Mag, Phos, Amylase, Lipase, LDH, TSH, cortisol, Free T4, and Free T3 prior to administration of the study drug; to be drawn within 3 days of administration. Serum or urine pregnancy test for women of childbearing potential within 24 hours of study drug administration
- Review concomitant medications.
- ECOG Performance Status
- Record adverse events reported by participant or observed by investigator

Administer the nivolumab (dose #2) and paclitaxel plus carboplatin (dose #3).**Visit 4, Week 5 ±4 days (there will be no visit week 4. Visits are every other week during systemic therapy induction)**

- Record adverse events as reported by participant (PRO-CTCAE) or observed by investigator.
- Targeted and complete physical examination.
- CBC with differential, CMP, Mag, Phos, Amylase, Lipase, LDH prior to administration of the study drug; to be drawn within 3 days of administration. TSH, Free T3, Free T4 cortisol. Serum or urine pregnancy test for women of childbearing potential within 24 hours of study drug administration
- Review concomitant medications.
- ECOG Performance Status
- Draw correlative laboratory studies

Administer the nivolumab (dose #3) and paclitaxel plus carboplatin (dose #5).**Visit 5, Week 8 ± 4 days (Surgery scheduled)**

- CT scan Preop (morning of surgery or day prior)
- Record adverse events as reported by participant (PRO-CTCAE) or observed by investigator.
- Targeted and complete physical examination.
- Correlative labs
- ECOG Performance Status
- CBC with differential, platelet count, CMP, Mag, Phos, amylase, lipase, LDH, PT/PTT, TSH, T4, T3, cortisol prior to surgery
- EKG
- Intraoperative specimens sent fresh on ice for correlative studies.

The following procedures will only be performed for patients enrolled at Thomas Jefferson University:

- Complete PROs:
  - FACT-G
  - FACT-HN
  - PHQ2
  - PHQ9
  - C-reactive protein (CRP), glycated hemoglobin (HbA1c), and lipid panel

Study Procedures-Administration of Paclitaxel and Carboplatin and Nivolumab and Surgery

Cycle 1-3 (Medical Oncologist): Each cycle is 2 weeks long. Full medical history, general physical exam, clinical tumor assessment and measurement by clinical exam, comprehensive metabolic panel (CMP), CBC, magnesium, phosphate, height, weight. Intravenous administration of paclitaxel 100 mg/m^2 and carboplatin AUC=2. ON Days 1 and 8 of each cycle, and Nivolumab 240 mg administered Day 1 of each cycle. On week 8, surgery.

Surgery will be performed approximately 2 weeks (Week 8) after the last dose of study treatment. Surgery is to be performed no later than 28 days after last chemotherapy dose (to allow patients to recover after chemotherapy)

6.3 Post-Surgical/Follow-Up

Visit 6, Week 9 ± 5 days Postop visit

- Postop evaluation and exam
- Whole blood Collection – Correlative labs
- Wound assessment
- Safety Assessment

The following procedures will only be performed for patients enrolled at Thomas Jefferson University:

- Complete PROs:
    - FACT-G
    - FACT-HN
    - PHQ2
    - PHQ9
- C-reactive protein (CRP), glycated hemoglobin (HbA1c), and lipid panel
- Body Mass Index (BMI) and Waist Hip Ratio (WHR)

Visit 7, 3 months ±2 weeks post-surgical completion*

- Focused physical assessment
- History
- Wound assessment
- Whole Blood collection for correlative labs
- PET scan at 3 months post treatment ± 2 weeks.
- Record adverse events as reported by participant (PRO-CTCAE) or observed by investigator

*If post-op xrt, then repeat PET scan will be delayed to 3 months ± 2 weeks after completion of radiation. If surgery is not done, the post-treatment date establishing mandatory follow-up visits will be 1-3 weeks after last chemo dose.

6.4 End of Treatment Study Procedures

Final Study Visit (Visit 8, 6 months ± 3 weeks post-surgical completion)

Record adverse events as reported by participant (PRO-CTCAE) or observed by investigator.

- Complete Physical Exam
- Review concomitant medications.
- Draw correlative laboratory studies (end of treatment time point).

6.5 Post-Treatment/Follow-Up

Patient's medical records will be reviewed every 3 months for the next 6 months to obtain information on survival and disease recurrence.

Follow Up Imaging is to be completed per the institutional standards.

6.6 Withdrawal Visit/Discontinuation of Therapy

At the time of withdrawal from the study, patients will be offered the opportunity to provide serum samples for correlative studies.

Adverse events will be collected and recorded as will the reason for discontinuation.

6.7 Surgery

The resection volume will be planned considering the tumor extension at the initial clinical evaluation, but the final surgical choice will be left to the judgment of the responsible surgeon, also on the basis of the actual extent at the time of surgery. A macroscopic safe margin of at least 1.5 cm is mandatory. Surgical procedures can include transoral or transcervical approaches with mandibulotomy or, marginal, or segmental mandibulectomy as necessary. In all cases, an ipsilateral neck dissection will be performed. Bilateral neck dissection will be performed when contralateral lymph nodes are present, when the tumor extends to within 1 cm of midline, or at the surgeon's discretion. Reconstruction will be performed as needed by means of local, regional, or free tissue flaps.

6.8 Radiation

After surgical resection, the decision for postoperative radiotherapy ± concurrent chemotherapy will be determined by the HNC tumor board. Radiation therapy will start 4 to 6 weeks after surgery, if not postoperative complications occur.

Treatment planning

The immobilization device should include head, neck and shoulder immobilization. The treatment planning CT scan should have a thickness of 0.3 cm or smaller slices through the region that contains the primary target volumes.

Volumes

The prescribed radiotherapy dose will be 60-66 Gy in 2 Gy once-daily fraction size (total of 30-33 fractions), based on the status of the surgical margins and the presence of nodal extra capsular extension. Radiotherapy should begin on a Monday, Tuesday or Wednesday. Megavoltage energy photon beam irradiation is required.

All plans must be normalized such of 95% of the volume of the PTVs are covered with the prescription dose. At 1 cc PTV volume, the dose should not be > 110% of the prescribed dose.

Definition of Target Volumes CTV60: This volume will receive 2 Gy per day. CTV60 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus region(s) of grossly involved lymphadenopathy. CTV56: This will include all other regions felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. For example, this would apply to the contralateral hemineck being irradiated electively for base of tongue cancer. This volume will receive approximately 1.85 Gy per day. CTV66: This would include a region or regions felt to be at especially high risk for recurrence (e.g., an area of positive margin of resection, or nodal extracapsular extension). This area will be receiving a daily fraction size of 2.0 Gy and will be delivered sequentially after the 60 Gy treatment will be finished.

Image Guidance for Image Guided Radiation Therapy (IGRT)

Daily image guidance of IMRT/VMAT will be achieved using linear-accelerator mounted kV or MV helical conebeam CT images. For those institutions that are using daily IGRT the minimum CTV-to-PTV expansion is 3.0 mm.

7 Study Procedures and Evaluations

7.1 Study Procedures/Evaluations

- Medical History including intercurrent illnesses and specific attention to autoimmune disorders, may be obtained from the medical record
- Concomitant meds: prescription medications taken for the 28 days prior to enrollment
- Physical exam: height, weight, obtained from the medical record
- ECOG performance status from the medical record

- Obtain histologic confirmation of disease, including p16 status for oropharyngeal primaries from the medical record
- Standard oral evaluation pre-radiation therapy by OMFS
- Vital Signs

The following procedures are only for patients enrolled at Thomas Jefferson University:

- PROs are self-administered
- Waist Hip Ratio: measurement to be taken per the NHLBI, NIH guideline to measure waist circumference. https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf
    - To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration.
    - Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor.
- Body Mass Index (BMI) to calculated as kg/m2

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

- Pregnancy Test: WOCBP prior to dosing nivolumab.
- A serum or urine pregnancy testing is required within 24 hrs of starting study treatment
- Laboratory testing prior to each dose of nivolumab: Within 72 hours prior to re-dosing- CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase. Within 72 hours prior to re-dosing- TSH (with reflexive Free T4 and Free T3)

7.2.2 Special Assays or Procedures

Please see accompanying laboratory manual

7.2.3 Specimen Preparation, Handling, and Storage

Two 10 ml purple top tubes will be collected for correlative studies. Samples can be held at room temperature and will be brought directly to the Harshyne Laboratory: 233 South 10th Street Rm 606, Philadelphia, PA 19107, USA.

Samples collected at the sub-site will be sent to the Harshyne Laboratory. Please see the accompanying laboratory manual additional information.

7.2.4 Specimen Shipment

Please see accompanying laboratory manual

8 Evaluation of Safety

8.1 Specification of Safety Parameters

8.1.1 Unanticipated Problems

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

8.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)

- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition.
- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is an SAE
- Although pregnancy, overdose, cancer and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs

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

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

Non-serious Adverse Event Collection and Reporting:

- The collection of nonserious AE information should begin at initiation of study drug. All treated related nonserious adverse events should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment. During this time, the clinical research staff will call the patient monthly.

8.2 Safety Assessment and Follow-Up

Adverse event reporting will begin after study treatment, unless AE/SAE is caused by a study specific screening procedure, and continue until 100 days (for non-serious AEs) or 100 days (for SAEs) after the last day of study participation. At each study visit, the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3 Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 8.2 Safety Assessment and Follow-Up.

8.3.1 Relationship to Study Intervention

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

8.3.2 Expectedness

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

8.3.3 Severity of Event

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

8.3.4 Intervention

Any intervention implemented to treat the adverse event must be documented for all adverse events.

8.4 Safety Reporting

8.4.1 Reporting to IRB

8.4.1.1 *Unanticipated Problems*

Thomas Jefferson University: All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 8.1.1 Unanticipated Problems require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the IRB on an OHR-20 form via the eazUP system within 5 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the IRB at the next continuing review.

Sub-Site: All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 8.1.1 Unanticipated Problems are to be reports to the sub-site IRB per institutional guidelines.

UAPs occurring at the sub-site must also be reported to Thomas Jefferson University using the Unaticipated Problems Form (see Appendix F). The TJU study site contact will submit the UAPs occurring at the sub-site to the TJU IRB.

8.4.1.2 *Adverse Events*

Grade 1 AEs will be reported to the IRB at continuing review.

Grade 2 AEs will be reported to the IRB at the time of continuing review.

8.4.1.3 *Serious Adverse Events*

Thomas Jefferson University:

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will be reported to the IRB within 5 working days.

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.

All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

Sub-Sites:

SAEs occurring at the sub-site are to be reported to the sub-site IRB per institutional guidelines. Section 8.4.2 provides information on reporting SAEs to TJU.

8.4.2 Sub-Site SAE Reporting

All SAEs occurring at the sub-site must be reported to the TJU Study Site Contact within 24 hours of notification. This initial notification can take place via email or phone, followed by the submission of a formal report.

SAEs should be reported to TJU using the Sub-Site Serious Adverse Event form (Appendix G) or the FDA Medwatch 3500A, and should comprise a full written summary, detailing relevant aspects of the adverse events in questions, including grading and attribution to study drug. Where applicable, information from relevant hospital case records and autopsy reports should be included.

SAE Reports should be signed by the sub-site PI, and then emailed to the Thomas Jefferson University Study Site Contact within 24 hours.

The TJU coordinator will notify the TJU PI and obtain the TJU PI signature, and report these events to the TJU Medical Monitor/IRB appropriately (within 5 working days if it deems an amendment, or in a spreadsheet at the time of annual review if no amendment is necessary).

Additional follow-up SAE reports should be submitted when available.

All reportable Adverse Events (AEs) should be reported to the TJU Research Coordinator within 48 hours using the FDA MedWatch 3500 form.

A reportable AE is any adverse event NOT identified in the IB or consent form as a risk.

Any non-reportable AE must be kept by the sub-site on an ongoing tracking log to be reviewed by TJU quarterly.

Unanticipated problems (UAPs) that pose risk to subjects or others, and that are not AEs/SAEs should be reported to TJU within 5 working days using form Unanticipated Problems Form (see Appendix F) and should be email to the Thomas Jefferson University study site contact within 5 days.

8.4.3 Reporting to SKCC DSMC

All AEs and SAEs, safety and toxicity data, and any corrective actions will be submitted to the DSMC per the frequency described in the SKCC DSMP. The report to the SKCC DSMC will also include any unanticipated problems that in the opinion of the PI should be reported to the DSMC.

The sub-site is required to provide copies of any Unanticipated Problems, protocol deviations, and AE logs to the TJU study site contact for submission to the SKCC DSMC.

For expedited reporting requirements, see table below:

DSMC AE/SAE Reporting Requirements

	Grade 1	Grade 2		Grade 3				Grades 4 and 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I - 48 Hours (Death: 24 Hours) Phase II - 5 working days
Possible Probably Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase I - 48 Hours Phase II - 5 working days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I and Phase II - 48 Hours (Death: 24 Hours)

8.4.4 Reporting to Funding Supporter

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

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

Site specific forms will be requested for review.

The sponsor/investigator will be required to reconcile SAEs reported in the clinical database with SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E); worldwide.safety@bms. BMS requests this to be done quarterly and prior to the database lock or final data summary.

A summary of the process for the sponsor/investigator:

- Sponsor/Investigator sends a request to BMS GPV&E for a “GPV&E reconciliation report”. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The request should provide the BMS protocol ID, study title and PI, and sponsor/investigator protocol ID.

- BMS will send a report back to the sponsor/investigator. The data elements listed on the GPV&E reconciliation report will contain information the investigator can use for individual case identification. Cases on the list from BMS GPV&E should be compared to the SAE cases in the clinical database.

- If the sponsor/investigator determines a SAE case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS

The sub-site will complete the Medwatch 3500 Form and provide this to the TJU study site contact via email.

8.4.5 Reporting to FDA

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible

and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

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

MedWatch SAE forms should be sent to the FDA at:

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

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

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

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

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

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

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

For any fatal or life-threatening adverse event that is unexpected and assessed by the investigator as possibly related to the use of nivolumab, the sub-site must submit a completed FDA Medwatch 3500A Form and email form to the TJU study site contact for submission to the FDA and BMS. The initial communication may take place via telephone but should be followed up with the completed form within 24 hours of first learning of the event.

8.4.6 Reporting of Pregnancy

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

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

- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 21 days prior to the start of nivolumab

- Women must not be breastfeeding

- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception

- Should a woman be found to be pregnant during the study further treatment will be immediately discontinued. Permission from the patient will be sought to continue to assess her for adverse events and for fetal outcomes.

8.5 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities must be captured as appropriate

- any laboratory test result that is clinically significant or meets the definition of an SAE

- any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted

- any laboratory test result that required the subject to receive specific corrective therapy

- It is expected that wherever possible the clinical rather than laboratory term would be used by the reporting investigator

8.6 Overdose

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

Any such events will be recorded on an SAE form and reported to BMS within 24 hours/1 business day.

Sub-site: If an overdose occurs, the sub-site must submit a completed FDA Medwatch 3500A Form and email form to the TJU study site contact for submission to BMS.

8.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

8.8 Halting Rules

Please see Section 11.3 for stopping rules.

9 Study Oversight

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC). The SKCC DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the NCI.

10 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of

participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SKCC DSMP.

11 Statistical Considerations

11.1 Study Hypotheses

Our hypothesis is that in patients with newly diagnosed, previously untreated squamous cell carcinoma of the head and neck, the administration of nivolumab in combination with weekly carboplatin and paclitaxel will increase the pathological complete response rate at the primary cancer compared to the historical control of carboplatin and paclitaxel alone.

11.2 Analysis Plans

Primary Endpoint Evaluation:

An optimal Simon two-stage design will be used. The null hypothesis is that the true pathologic complete response rate is ≤ 0.20 and will be tested against the alternative that it is >0.20. After testing the regimen on 17 patients in the first stage, the trial will be terminated if 3 or fewer have a pCR of the primary tumor. If the trial goes on to the second stage, a total of 37 patients will be studied. If the total number having a pCR of the primary tumor is less than or equal to 10, the regimen is rejected. This design yields a type I error rate of 9.5% and power of 90% when the true response rate is 0.40. It has a 55% probability of stopping early. The pathologic complete response rate and its associated score 95% confidence interval will be estimated using the methods of Tsai et al (2008). [20]

Secondary Endpoint Analyses:

Descriptive statistics, including means, standard deviations, medians, quartiles, frequency counts, and percentages will be computed for all study variables.

All secondary response rates (complete pathologic response at all sites of disease, major pathologic response at primary site, overall clinical response, clinical complete response) will be estimated.

Kaplan-Meier methods will be used to describe and display the survival experiences of the study patients and estimate their 1 year PFS and assess their overall survival at 1 year.

Exploratory Endpoint Analyses (CORRELATIVE STUDIES):

T cell subsets will be analyzed by flow cytometry before, at the 5th week, and on the day of surgery after carboplatin/paclitaxel/nivolumab to explore their potential as predictive and/or prognostic markers that are related to response or clinical benefit of this induction regimen. The T cell subtypes will be analyzed from peripheral mononuclear cells (PBMC) via flow cytometry. These data and other biomarkers, including cytokine and exosome variables, will be

explored by first categorizing the before and after carboplatin/paclitaxel/nivolumab T cell data as well as the change observed and then using these categories as strata for cross-tabulation with complete pathologic response and for Kaplan-Meier subgroup analyses of the survival endpoints.

Association of PDL1 expression and other baseline marker levels with response will be evaluated using logistic regression. Association of change in markers with response will be evaluated using two-sample tests (e.g., t-tests or Wilcoxon rank sum tests). When longitudinal marker measurements are available, responders will be compared to non-responders using mixed effects linear regression. In addition, potential correlations of these pharmacodynamics markers with the duration of treatment, safety, survival, and anti-tumor activity of the regimen will be explored by summary statistics, data plots, and regression modeling tools.

We plan to conduct descriptive statistics on all study variable, including PROs, lab data, demographics, and anthropometrics using standard statistics such as frequency tables, means, and standard deviations.

For the correlative studies on PROs and metabolic measures (e.g., CRP, HbA1c, and lipid panel), we plan to estimate Spearman's ranks-based correlations and explore multivariable relationships with ordinary least squares regression modeling. These variables will also be considered for their potential role in the planned Cox survival and logistic regression response modeling.

11.3 Interim Analyses and Stopping Rules

Stopping Rules:

The study will stop for futility if pathologic complete response at the primary tumor is not observed in more than 3 of the first 17 patients.

There are no formal stopping rules for safety, however, rates of grade 3-5 toxicities will be monitored continually. The selected doses of nivolumab were safe in previous studies. There is no dose escalation or de-escalation planned in this study. Individual patients can have dose modification during the study.

The study will stop if 3 of the first 17 patients experience excessive toxicity due to study treatment, leading to delays in definitive surgery greater than 56 days from enrollment.

11.3.1 Safety Review

See above.in stopping rules. We meet weekly as a group to review adverse events on all trial patients. A running tab is kept of the number of patients with serious adverse events and their grade, nature and attribution.

11.3.2 Efficacy Review

The principle endpoint of this study is pathologic complete response. The early stopping rule requires cessation of further accrual if there are 2 or fewer pathologic complete response among the first 17 patients. If there are 3 or more pCRs obvserved prior to the accrual of 17 patients, this minimal condition for continuing accrual will be met and there will be no need to halt the study on the basis of therapeutic futility. However, if it has not been met prior to the accrual of 17 patients, then, with the further accrual will be halted at the time the 17th potentially evaluable patient signs consent until all 17 evaluable patients have had their surgical specimens evaluable for pathologic response. Accrual can then restart only if there are 3 or more pCRs as per the stopping rules.

11.4 Sample Size Considerations

An optimal Simon two-stage design will be used. The null hypothesis is that the true pathologic complete response rate at the primary site is ≤ 0.20 and will be tested against the alternative that it is >0.20. After testing the regimen on 17 patients in the first stage, the trial will be terminated if 3 or fewer respond. If the trial goes on to the second stage, a total of 37 patients will be studied. If the total number responding is less than or equal to 10, the regimen is rejected. This design yields a type I error rate of 9.5% and power of 90% when the true response rate is 0.40. It has a 55% probability of stopping early.

11.4.1 Replacement Policy

Patients who do not have surgery will be replaced on the study.

11.4.2 Accrual Estimates

We hope to enroll 37 participants onto this trial and accrual is competitive across all sites.

11.5 Exploratory Analysis

Please see the attached laboratory manual

12 Source Documents and Access to Source Data/Documents

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

13 Quality Control and Quality Assurance

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given

access to all of the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

14 Ethics/Protection of Human Participants

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Pregnant and breastfeeding women are excluded from this trial due to the nature of the agents being used. Otherwise, we will attempt to accrue women and men equally on this study, representative of the epidemiologic distribution of the disease.

14.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

14.6 Future Use of Stored Specimens and Other Identifiable Data

No identifiable data will be retained.

15 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

15.2 Data Capture Methods

Data will be captured on paper case report forms and transferred to an electronic database which will be kept behind a password protected firewall- RedCap. Each site will enter data as described into the electronic database. The lead site (Thomas Jefferson University) will query the database at regular intervals.

15.3 Types of Data

Data that will be collected include patient history and physical examination data, safety, laboratory studies, patient reported outcomes, pathology staging studies, and immunohistochemistry as determined in the laboratory.

15.4 Study Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

15.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB and other regulatory bodies according to their requirements.

16 Study Finances

16.1 Funding Source

Bristol-Myers Squibb is providing the investigational products, Nivolumab, for this study.

16.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

16.3 Participant Stipends or Payments

Subjects will receive a payment of $50 at each study visit for participation in the study. Subjects will be paid via Clincard.

17 Publication and Data Sharing Policy

This study will comply with the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final

peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific *steps to ensure compliance* with NIH implementation of FDAAA.

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Appendices

Appendix A: Schedule of Events

Appendix B: ECOG Performance Status

Appendix C: AJCC 8th Edition Staging System

Appendix D: Management of Algorithms

Appendix E: NCI-PRO-CTCAE Items

Appendix F: Sub-Site Unanticipated Problems Form

Appendix G: Sub-Site Serious Adverse Event Form

APPENDIX A: SCHEDULE OF EVENTS

Study Period	**Visit 1, Day 0 (Baseline)**	**Treatment**							**Observation (d)**	
Week		**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**	
Treatment		**Paclitaxel+Carboplatin + Nivolumab**						**Surgery**	**Standard of care (d)**	
Nivolumab		X		X		X				
Paclitaxel		X	X	X	X	X	X			
Carboplatin		X	X	X	X	X	X			
Filgrastim (i)		X	X	X	X	X	X			
Consent form signed by patient	X									
Biopsy/Marking of primary site	X							X (f,g)		
History and physical exam (including vital signs, weight, BMI, height) (p)	X(s)	X		X		X		X(s)	X(s)	X
ECOG Performance Status (p)	X	X		X		X		X		X
Assessment of concurrent therapies (p)	X	X		X		X		X		
Tumor assessment by	X	X		X		X		X		X

physical exam with intent to be alert to signs of early failure of efficacy as per the judgement of treating physicians (p).										
PET/CT	X(r)									X (e)
CT or MRI	X(r)							X		
CBC, differential, platelet count (j)	X	X	X	X	X	X	X	X		X
CMP, (j)	X	X	X	X	X	X	X	X		X
magnesium, phosphate, Amylase, Lipase, LDH (k)	X	X		X		X		X		
PT/PTT (l)	X	X						X		
C-reactive protein (CRP), HbA1c, and lipid panel*	X							X	X	
Endocrine (TSH, Free T4, Free T3, cortisol) (m)	X	X		X		X		X		X
Pregnancy test (women of childbearing potential)(o)	X	X		X		X				

EKG (n)	X							X (h)		
Blood Draw for CTCs(q)	X					X		X (b)	X(c)	X(c)
Adverse Event Assessment + PRO-CTCAE		X	X	X	X	X	X	X		X
PROs*		X						X	X	
Tumor Biopsy (a)	X		X		X			X		

*These procedures are only to be performed for patients enrolled at Thomas Jefferson University

(a) Five cores or excisional specimen. Archival tissue within 3 months of study enrollment can be used. If recent tumor is unavailable, a fresh biopsy will be taken prior to enrollment (see section 6.1). Optional biopsies from and including days 14 to 23 will be done if patients agree to the collection and if feasible at the discretion of the physician.

(b) Prior to surgery

(c) At least a week after surgery and less than 4 weeks after surgery. If post-operative radiation therapy to be done, draw prior to this therapy. A fifth blood draw 2 months later. If radiation is given after surgery, then this last blood draw 2 months after

(d) Observation or further therapy (for example post-operative radiation) as per standard of care. Follow for adverse events at least until 8 months s/p day 1 of induction therapy.

(e) Timing of first post-operative repeat as per standard of care. For patients who will not have post-op xrt, the PET/CT will be 3 months ± 2 weeks post-op. For patients who do receive post-op xrt, the PET/CT will be 3 months ± 2 weeks after the completion of xrt. Further imaging (standard of care imaging will not be repeat PET/CT at this timepoint) will be another 3 months ±2 weeks after the follow-up PET/CT.

(f) Intraoperative specimens sent fresh on ice for correlative studies.

(g) Formal assessment and documentation of degree of pathologic response (as in appendix)

(h) EKG alone

(i) Filgrastim, at physician's discretion, any 2 consecutive days between days 2-6 (preferred days 3,4) of each treatment week

(j) CBC with differential, CMP, need to be done baseline (within 14 days of initiation of study treatment), within 3 days of first dose of chemotherapy, and no more than 1 days before each weekly chemotherapy administration. No more than 7 days before surgery.

(k) Magnesium, phosphate, amylase, lipase, and LDH baseline (within 4 weeks of screening), weeks 3 and 5. No more than 7 days before surgery.

(l) PT/PTT baseline (within 4 weeks of screening) No more than 7 days before surgery.

(m) Endocrine (TSH, Free T4, Free T3, cortisol, baseline (within 4 weeks of screening). Again at weeks 3 and 5. No more than 7 days before surgery. After surgery as per standard of care.

(n) EKG: baseline (within 4 weeks of study enrollment) and after last dose of chemo and before surgery.

(o) Pregnancy test at baseline must be within 21 days of study enrollment. Pregnancy test must be re-tested within 24 hours of start of study drug.
(p) Must be done within 4 weeks of study enrollment and then during visits 2, 3, 4, end of study visit
(q) Must be done within 2 weeks of study enrollment
(r) If patient cannot have PET/CT, then a CT or MRI of the Head and/or Neck, Chest, Abdomen, and Pelvis and a bone scan must be performed.
(s) For patients enrolled at Thomas Jefferson University only: Physical examination at baseline and end of treatment must include BMI and waist to hip ratio (WHR)

APPENDIX B: ECOG PERFORMANCE STATUS

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

APPENDIX C: AJCC 8TH EDITION STAGING SYSTEM

1. LIP AND ORAL CAVITY

DEFINITIONS

Primary Tumor (T)

TX Primary tumor cannot be assessed
Tis Carcinoma in situ
Tis Carcinoma *in situ*
T1 Tumor ≤2 cm ≤5 mm depth of invasion (DOI) (DOI is depth of invasion and not tumor thickness)
T2 Tumor ≤2 cm DOI >5 mm and ≤10 mm or tumor > 2cm but ≤4 cnm abd ≤10 mm DOI
T3 Tumor >4 cm or any tumor > 10 mm DOI
T4 Moderately advanced or very advanced local disease
T4a Moderately advanced local disease: (lip) tumor invades through corical bone orinvolves the inferior alveolar nearve, floor of mouth, or skin of face (ie, chin or nose); (oral cavidty) tumor invades adjacent structures only (eg, through corical bone of the mandible or maxilla, or involves the maxillary sinus or skin or the face); note that superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.
T4b Very advanced local disease: tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

Regional Lymph Nodes (N)

Lip and Oral Cavity Clinical

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE negative
N2 Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE negative3; or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative, or metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE negative
N2a Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE negative
N2b Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive
N3a Metastatis in a lymph node larger than 6 cem in greatest dimension and ENE-negative
N3b Metastasis in any node(s) and clinically overt ENE-positive

Lip and Oral Cavity Pathologic

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE negative
N2 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-positive; or more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greater dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, ENE-negative
N2a Metastasis in a single ipsilateral or contralateral lymph node 3 cm or less in greatest dimension and ENE-positive; or metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension an ENE-negative
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in a single ipsilateral lymph node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive
N3a Metastasis in a single ipsilateral node more than 6 cm in greatest dimension and ENE-negative
N3b Metastasis in a single ipsilateral node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive

Distant Metastasis (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
Biopsy of metastatic site performed
Source of pathologic metastatic specimen

Stage Grouping

0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0

	T3	N2	M0
	T4a	N2	M0
IVB	Any T	N3	M0
	T4b	Any N	M0
IVC	Any T	Any N	M1

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated

Residual Tumor (R)
RX: Presence of residual tumor cannot be assessed
R0: No residual tumor
R1: Microscopic residual tumor
R2: Macroscopic residual tumor

Additional Descriptors
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.
m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.
y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.
r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.
a prefix designates the stage determined at autopsy: aTNM.

2. PHARYNX (INCLUDING BASE OF TONGUE, SOFT PALATE, AND UVULA) DEFINITIONS

Oropharynx (HPV neg) Clinical and Pathologic
Tx Primary tumor cannot be assessed
Tis Carcinoma in situ
Tl Tumor 2 cm or smaller in greatest dimension
T2 Tumor more than 2 cm but not larger than 4 cm in greatest dimension
T3 Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderatley advanced or very advanced local disease
T4a Moderaly advanced local diseae; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible (Mucosal extension to lingual surface of epiglottis from

primary tumors of the base of the tongue and vallecular does not constitute invasion of the larynx).

T4b Very advanced local disease; tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Oropharynx (HPV pos) Clinical and Pathologic

T0 No primary identified
Tl Tumor 2 cm or smaller in greatest dimension
T2 Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3 Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced local disease: tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*

* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Regional Lymph Nodes (N)

Oropharynx (HPV neg) Clinical

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE negative
N2 Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE negative3; or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative, or metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE negative
N2a Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE negative
N2b Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive
N3a Metastatis in a lymph node larger than 6 cem in greatest dimension and ENE-negative
N3b Metastasis in any node(s) and clinically overt ENE-positive

Oropharynx (HPV neg) Pathologic

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE negative
N2 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-positive; or more than 3 cm but not more than 6 cm in greatest dimension and ENE-

negative; or metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greater dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, ENE-negative

N2a Metastasis in a single ipsilateral or contralateral lymph node 3 cm or less in greatest dimension and ENE-positive; or metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension an ENE-negative

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative

N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative

N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in a single ipsilateral lymph node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive

N3a Metastasis in a single ipsilateral node more than 6 cm in greatest dimension and ENE-negative

N3b Metastasis in a single ipsilateral node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive

Oropharynx(HPV pos) <u>Clinical</u>

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 One or more ipsilateral lymph nodes, none larger than 6cm
N2 Contralateral or bilateral lymph nodes, none larger than 6cm
N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
Biopsy of metastatic site performed
Source of pathologic metastatic specimen

Stage Grouping: Oropharynx (HPV neg)

0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0

	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Stage Grouping: Oropharynx (HPV pos) Clinical Stage 8th Edition Staging Manual

	N0	N1	N2	N3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

Any M1 is stage IV

Histologic Grade (G) (Oropharynx)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated

Residual Tumor (R)

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

Additional Descriptors

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy.

The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

3. HYPOPHARYNX

Hypopharynx

T 1 Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
T2 Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3 Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue(2)
T4b Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

Hypopharynx Clinical

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE negative
N2 Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE negative3; or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative, or metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE negative
N2a Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE negative
N2b Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive
N3a Metastatis in a lymph node larger than 6 cem in greatest dimension and ENE-negative
N3b Metastasis in any node(s) and clinically overt ENE-positive

Hyphopharynx Pathologic

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE negative
N2 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-positive; or more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greater dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, ENE-negative
N2a Metastasis in a single ipsilateral or contralateral lymph node 3 cm or less in greatest dimension and ENE-positive; or metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension an ENE-negative

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in a single ipsilateral lymph node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive
N3a Metastasis in a single ipsilateral node more than 6 cm in greatest dimension and ENE-negative
N3b Metastasis in a single ipsilateral node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
Biopsy of metastatic site performed
Source of pathologic metastatic specimen

Stage Grouping: Hypopharynx

0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Histologic Grade (G) (Hypopharynx)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated

Residual Tumor (R)

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

Additional Descriptors
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.
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The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.
r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.
a prefix designates the stage determined at autopsy: aTNM.

4. LARYNX

DEFINITIONS
Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis
T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility

T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis
T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation
T4a Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Regional Lymph Nodes (N)
Larynx Clinical
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE negative
N2 Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE negative3; or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative, or metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE negative
N2a Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE negative
N2b Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive
N3a Metastatis in a lymph node larger than 6 cem in greatest dimension and ENE-negative
N3b Metastasis in any node(s) and clinically overt ENE-positive

Larnynx Pathologic
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE negative
N2 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-positive; or more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greater dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, ENE-negative
N2a Metastasis in a single ipsilateral or contralateral lymph node 3 cm or less in greatest dimension and ENE-positive; or metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension an ENE-negative
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
N2c Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE negative
N3 Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in a single ipsilateral lymph node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive
N3a Metastasis in a single ipsilateral node more than 6 cm in greatest dimension and ENE-negative
N3b Metastasis in a single ipsilateral node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
Biopsy of metastatic site performed
Source of pathologic metastatic specimen

Stage Grouping

0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0

	Any T	N3	M0
IVC	Any T	Any N	M1

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated

Residual Tumor (R)

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

Additional Descriptors

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy.

The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: Atnm

APPENDIX D: MANAGEMENT ALGORITHMS

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

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

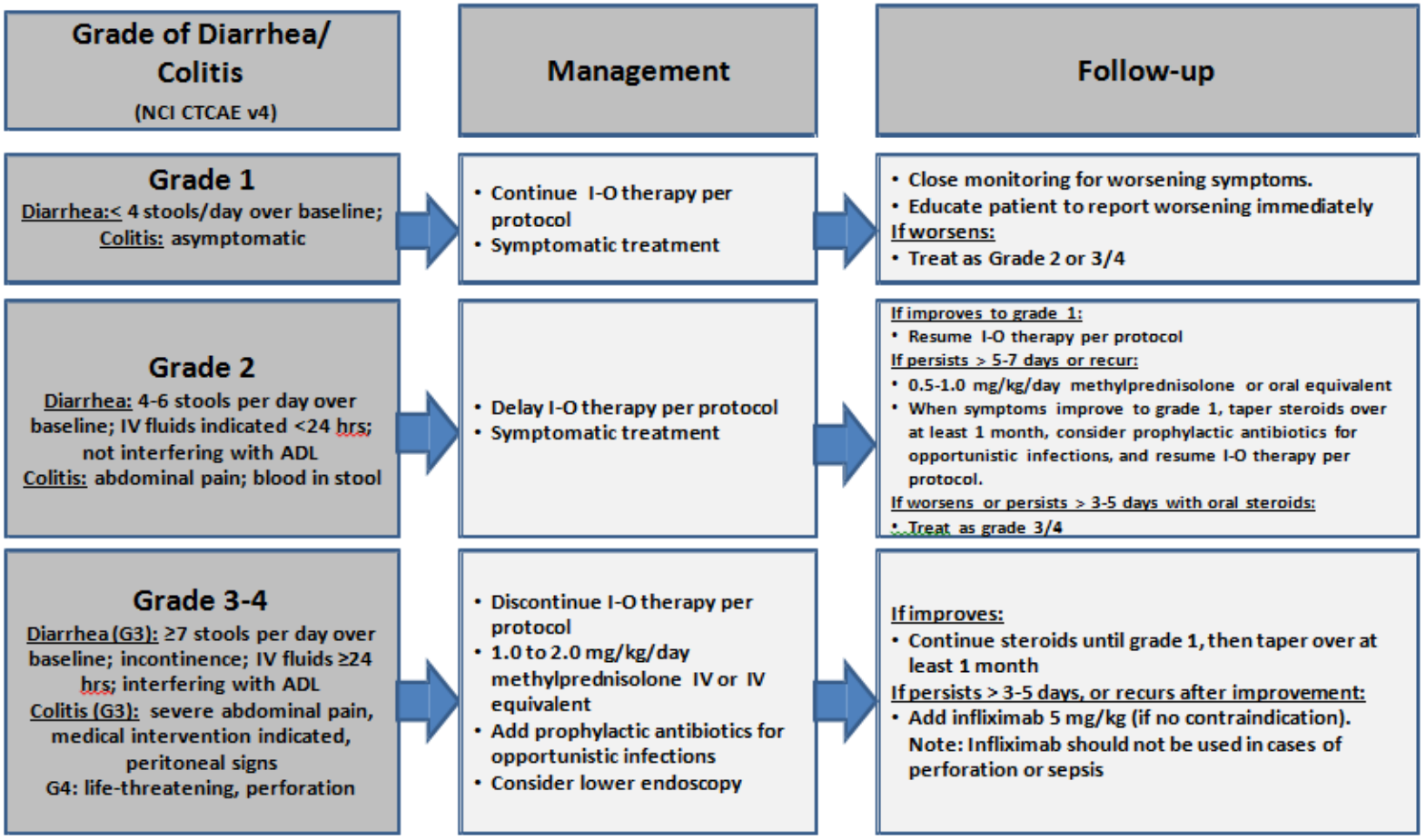
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

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

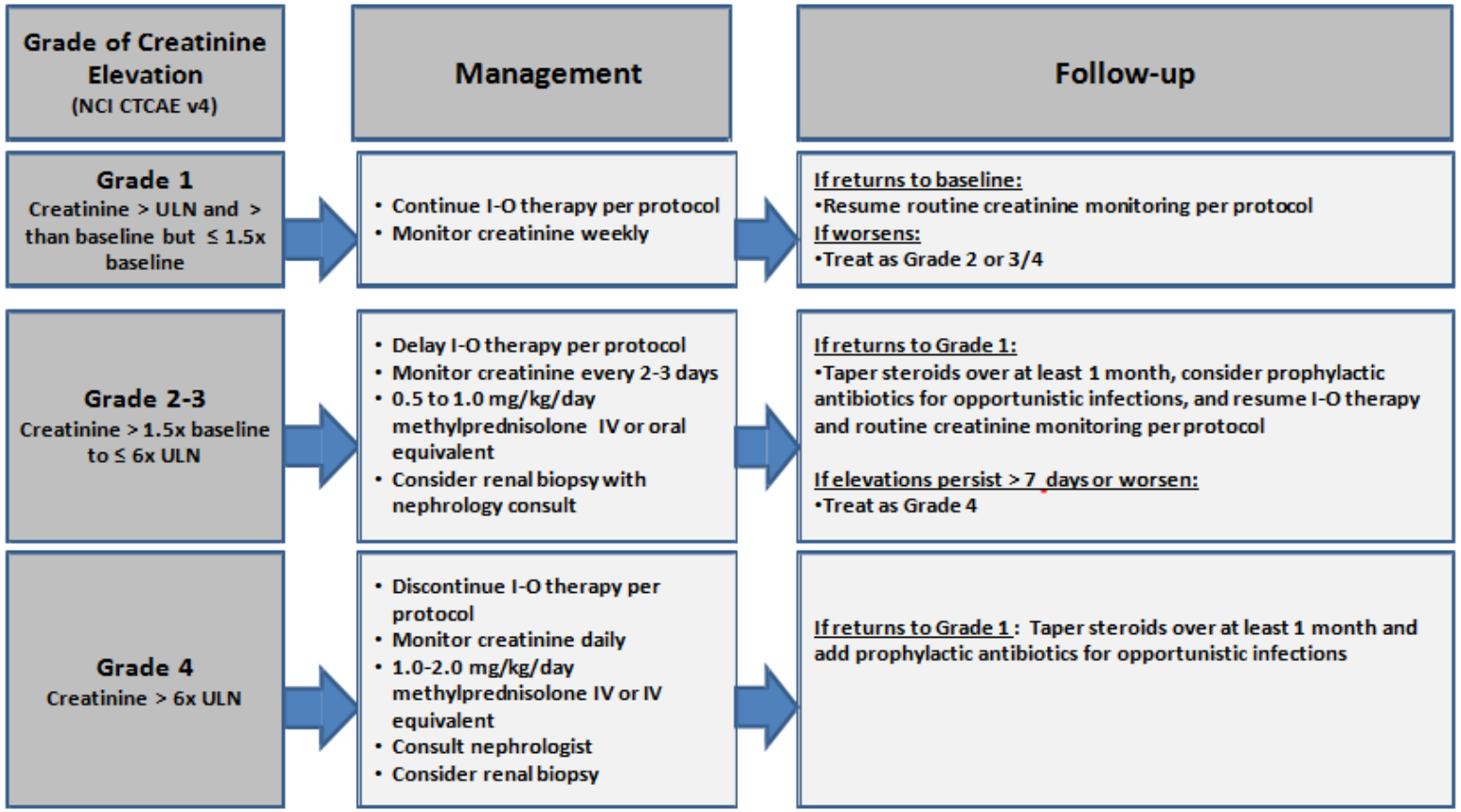


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

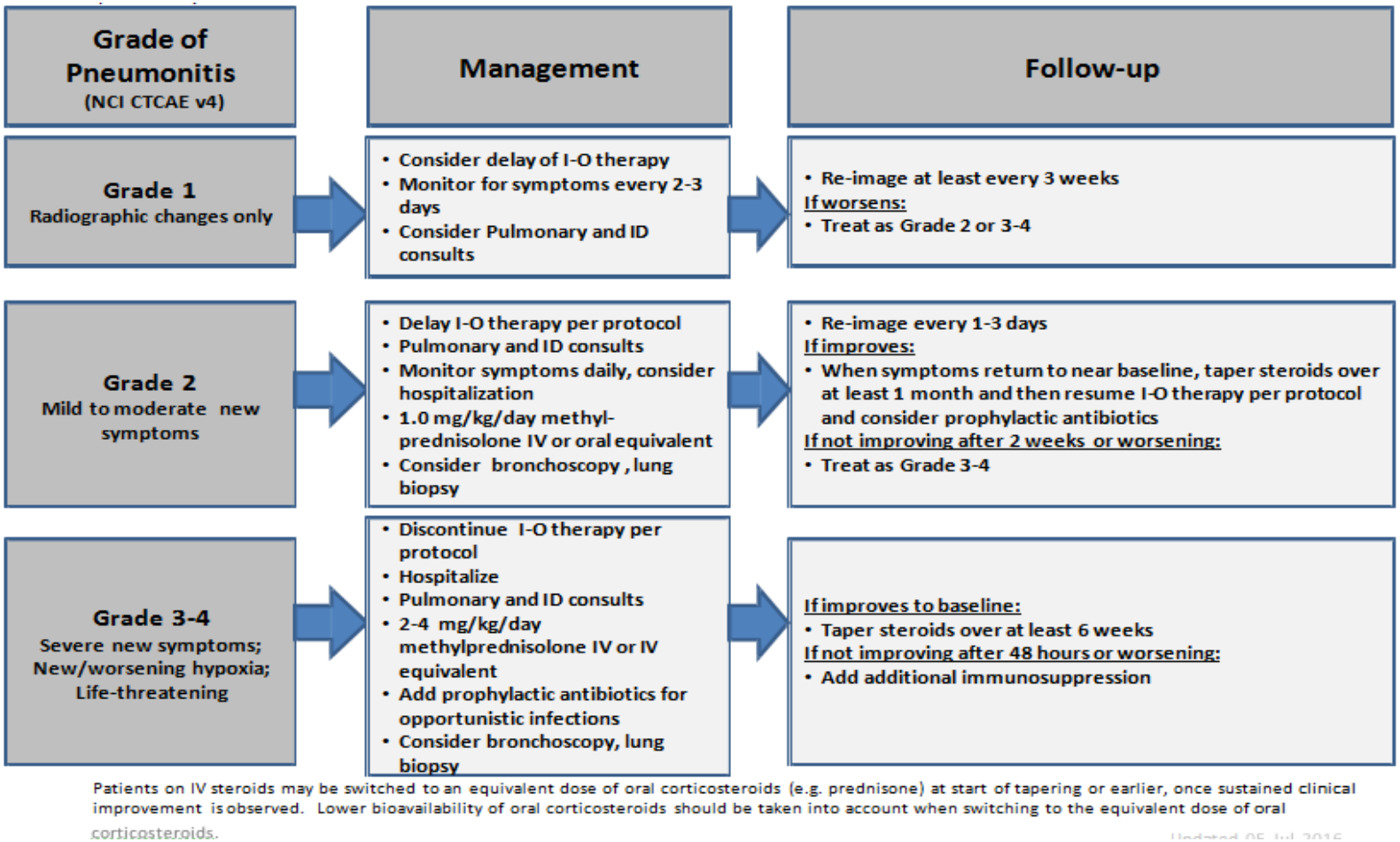
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy



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

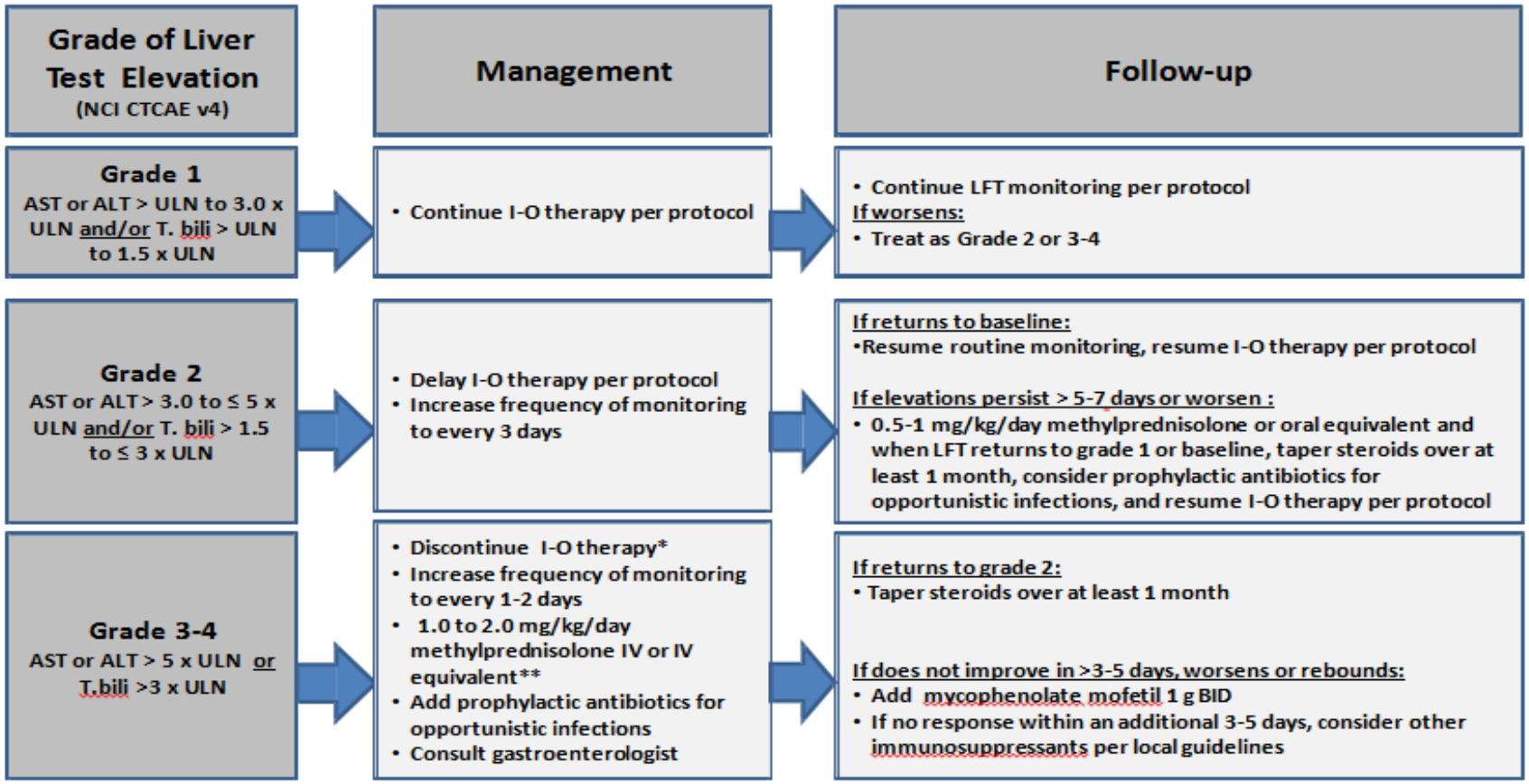
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

Hepatic Adverse Event Management Algorithm

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



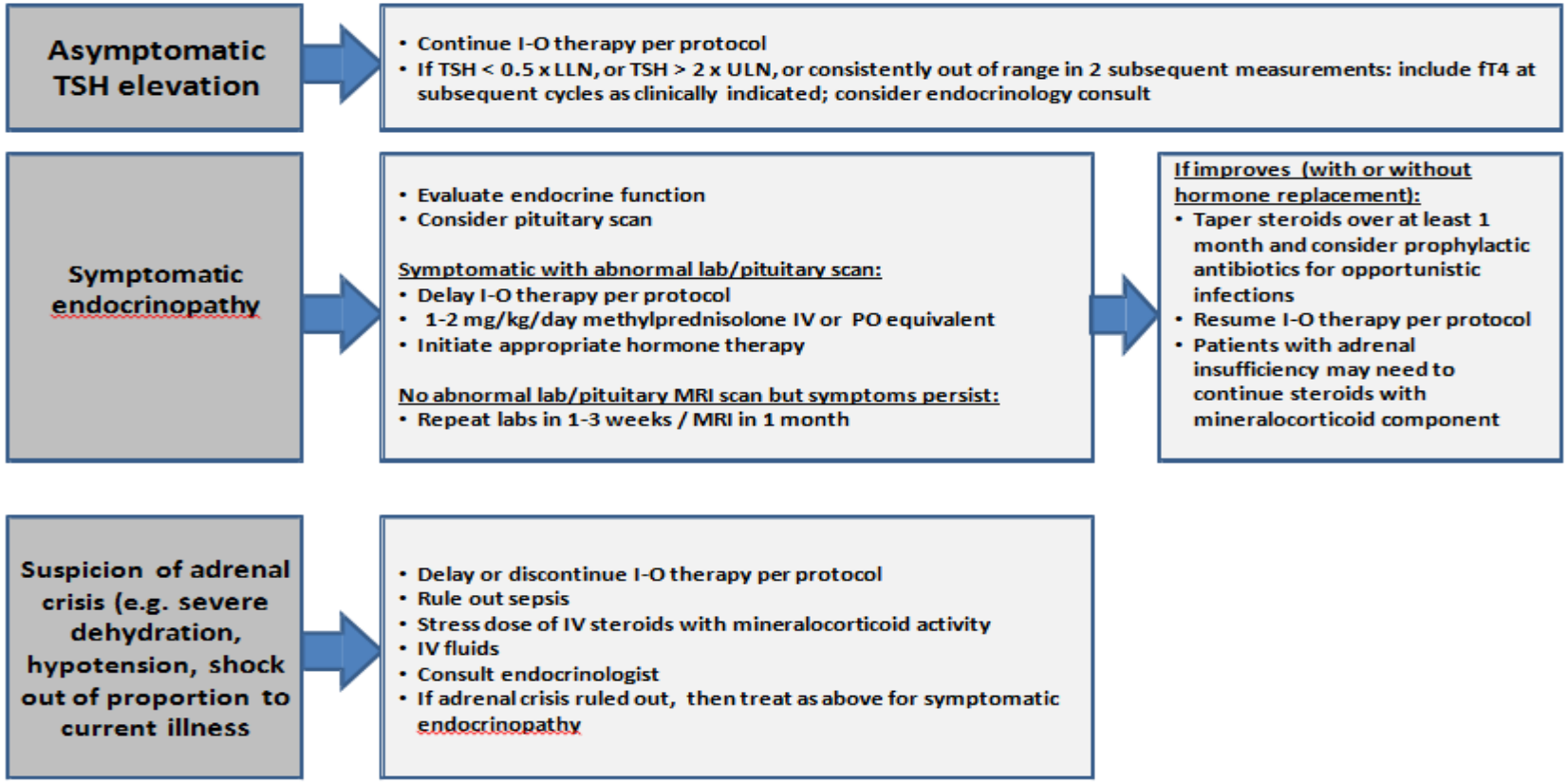
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

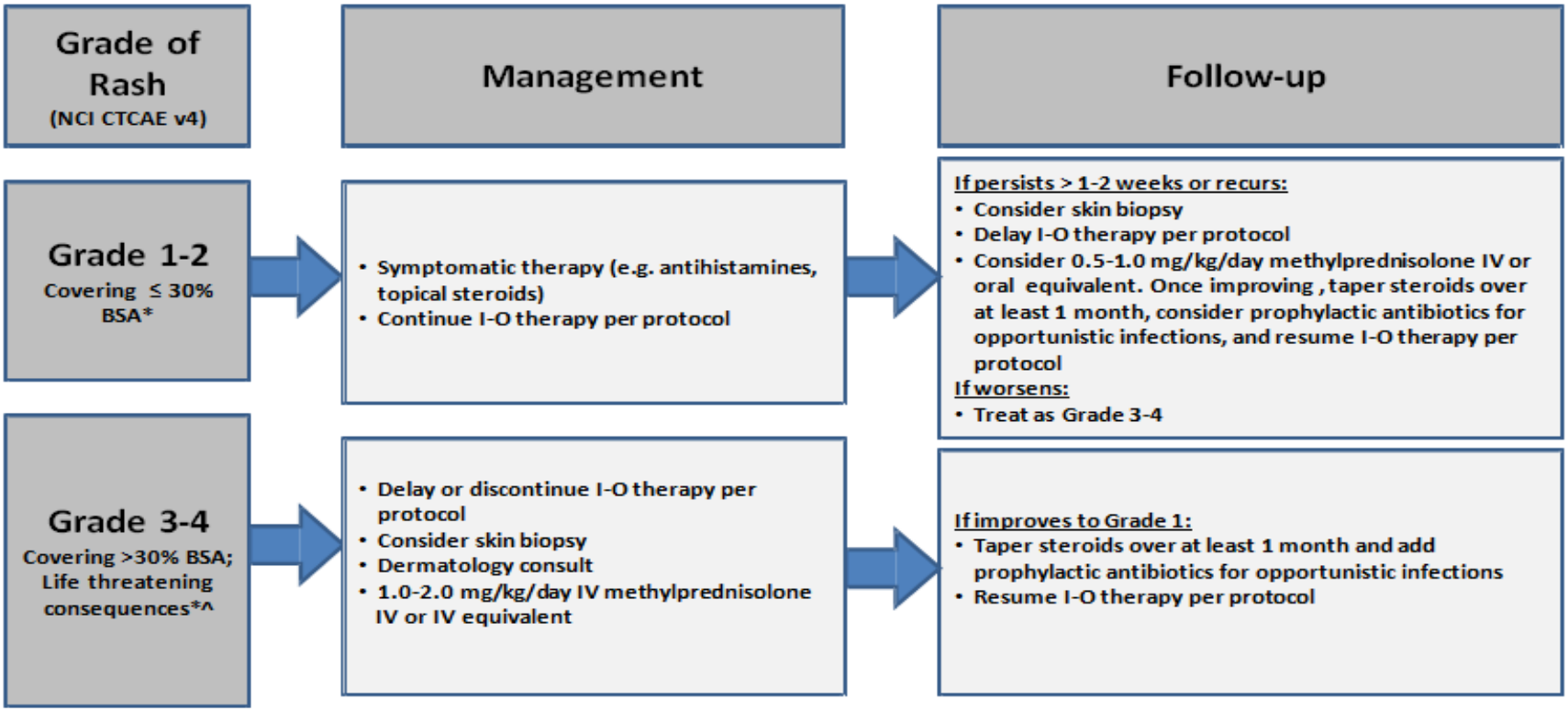
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



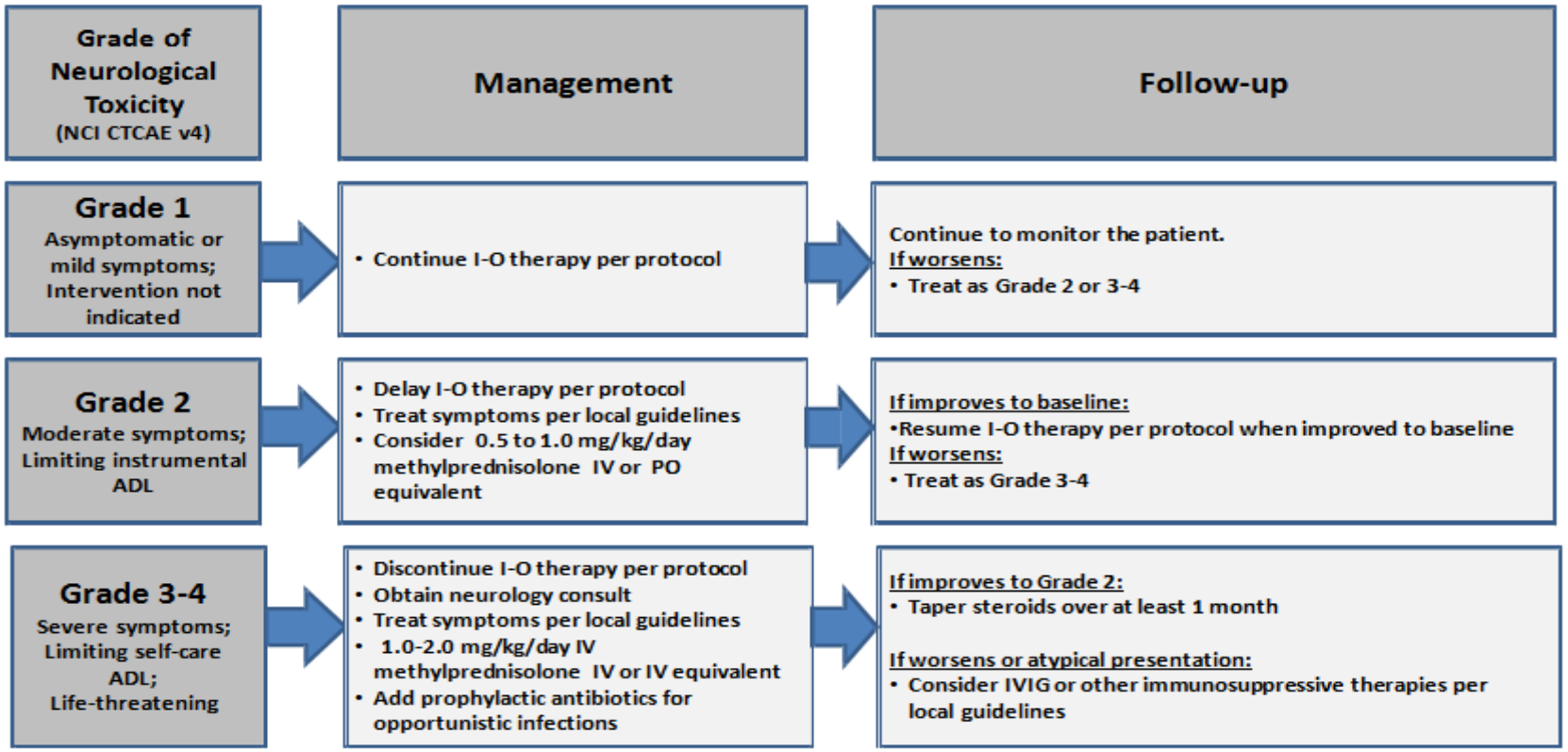
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

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.

APPENDIX E: NCI PRO-CTCAE ITEMS

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

4.	In the last 7 days, what was the SEVERITY of your HOARSE VOICE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

6.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

7.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

8.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

9.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	○ None	○ Mild	○ Mo[Copy]e	○ Severe	○ Very severe

10.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

11.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

12.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

13.	In the last 7 days, how OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

14.	In the last 7 days, did you have any RASH?				
	○ Yes	○ No			

15.	In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Copy

16.	In the last 7 days, did you have any HAIR LOSS?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

17.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

18.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

19.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

20.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH CONCENTRATION at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PROBLEMS WITH CONCENTRATION INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

21.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

22.	In the last 7 days, how OFTEN did you feel ANXIETY?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

23.	In the last 7 days, how OFTEN did you FEEL THAT NOTHING COULD CHEER YOU UP?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your FEELINGS THAT NOTHING COULD CHEER YOU UP at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FEELING THAT NOTHING COULD CHEER YOU UP INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

24.	In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

25.	In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

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Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Copy

APPENDIX F: SUB-SITE UNATICIPATED PROBLEM FORM

Sidney Kimmel Cancer Center at Thomas Jefferson University

UNANTICIPATED PROBLEM REPORT FORM
For Sub-Site Reporting

Thomas Jefferson University Principal Investigator: _____

Sub-Site Principal Investigator: _____

TJU IRB Control Number/Sub-Site Identifier: _____

Protocol Title: _____

_____

Subject ID: _____ Approx. Date of Problem: _____ Date Aware: ____

Description of Problem: _____

_____

Is this Unanticipated Problem a Protocol Deviation? Yes ☐ No ☐

Did the Unanticipated Problem pose risk to subjects or others? Yes ☐ No ☐

If no, have PI or Co-I sign the form. If YES, describe the risk below:

Describe the Corrective Action Plan: _____

_____

Has the problem been resolved? Yes ☐ No ☐

Does the consent or protocol require modification? Yes ☐ No ☐

_____

Signature of person preparing report Date Email/Phone number

_____

Sub-site PI signature Date Email/Phone number

Appendix G: SUB-SITE SERIOUS ADVERSE EVENT FORM

SAE REPORT FORM FOR SUBSITE REPORTING

Thomas Jefferson University Principal Investigator: _____

Sub-Site Principal Investigator: _____

TJU IRB Control Number/Sub-Site Identifier: _____

Protocol Title: _____

_____

Subject Initials and ID: _____

Event Date- Onset: _____ Terminated: ____ Ongoing?: ____ Date PI/TJU Aware: ____

Study Drug(s)/Device: _____

Description of adverse event: _____

Severity of adverse reaction: _____

Action Taken: _____

☐ Resulted in or prolonged inpatient hospitalization ☐ Resulted in permanent disability ☐ Subject died Autopsy

Cause of adverse reaction (if not related to research): ☐ Underlying disease ☐ concomitant medication ☐ Other

If other explain:

If List concomitant medications:

Is this: A new report? Yes ☐ No ☐ A Follow Up Report? Yes ☐ No ☐ Date of First Report

In your opinion, was the SAE caused by the therapy/procedures associated with this protocol?

Is the risk of this adverse reaction described in the consent form? Yes ☐ No ☐

If **Not Currently in consent form**, should this risk be described in the consent form: Yes ☐ No ☐

If No, please provide justification for not including this reaction as a risk in the consent form:

Has this adverse reaction been reported to the sponsor? Yes ☐ No ☐ To FDA? Yes ☐ No ☐

Should presently enrolled subjects be informed of event? Yes ☐ No ☐

_____
Signature of person preparing report Date Email/Phone number

_____
Sub-site PI signature Date Email/Phone number