UCSF Helen Diller Family Comprehensive Cancer Center

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Nivolumab in Combination with Chemoradiation for Patients with Stage II-IVB Nasopharyngeal Carcinoma, A Phase II Study with Correlative Biomarkers

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Protocol Signature Page

Protocol No.: CC# 162010

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

SUE S. YOM

_____
Printed Name

_____
Signature Date

Participating Site(s)

Principal Investigator	**Site**
_____ Printed Name	_____
_____ Signature	_____ Date

Abstract

Title	Nivolumab in Combination with Chemoradiation for Patients with Stage II-IVB Nasopharyngeal Carcinoma, A Phase II Study with Correlative Biomarkers
Patient population	Patients with stage II-IVB endemic-type nasopharyngeal carcinoma (NPC), who are scheduled for definitive-intent chemoradiation therapy.
Rationale for Study	The current platform of chemoradiation followed by adjuvant chemotherapy is the standard means of treating NPC around the world. However, the sustained use of cisplatin-based chemotherapy throughout this treatment plan is difficult for patients to complete and the additional chemotherapy delivered in the adjuvant phase may not provide optimal efficacy against the emergence of metastasis. Immune checkpoint inhibitors have shown efficacy against multiple tumor types including nasopharyngeal carcinoma and are efficacious in combination with platinum doublets or for post-platinum disease relapse. There is a need to investigate novel approaches for the locoregionally advanced NPC population that will reduce the severe and life-altering toxicities of the current standard of care and improve the therapeutic ratio. This study has been designed to determine if nivolumab can be integrated into the current paradigm of combined chemoradiation and adjuvant chemotherapy, with improved feasibility of treatment completion over the current standard of care.
Primary Objective	To establish the feasibility of a combined chemoradiation-nivolumab regimen followed by adjuvant nivolumab. The primary endpoint will be the rate of completion of all adjuvant immunotherapy, in comparison to the rate of completion of a standard adjuvant cisplatin-based platform (historical control).
Secondary Objectives	• To determine the clinical response as judged by the investigator; • To determine the overall response rate at 1 year from end of treatment, as determined by RECIST 1.1 criteria; • To determine the locoregional control rate at 1 year post-treatment; • To determine the distant metastasis rate at 1 year post-treatment; • To determine the overall survival rate at 1 year post-treatment; • To determine the rate of EBV DNA clearance at end of chemoradiation and at 1 year from end of treatment; • To determine the acute and late toxicity rates according to CTCAE v5.0, including immune-related adverse events (AEs); • To assess patients' quality of life from baseline through 1 year from end of treatment;

Exploratory Objectives	• To determine whether PDL1-positive immunohistochemistry and novel quantitative assays correlate to clinical outcome; • To determine if the density of infiltrating CD3+ T cells/μm2 correlates to clinical outcome; • To monitor immune changes by flow cytometry in the circulating T cell response to EBV antigens; • To compare the change in the circulating T-cell repertoire by TCR sequencing and single-cell T-cell profiling; • To quantify treatment-induced changes over time in the circulating T cell immune response to EBV using TCR sequencing and enzyme-linked immunospot (ELISPOT) assays
Study Design	• This is a phase II multi-institution, single-arm, open label clinical trial of concurrent and adjuvant nivolumab in Stage II-IVB endemic-type nasopharyngeal carcinoma patients who plan to undergo chemoradiation therapy for treatment of their cancer. • A run-in phase will precede expansion, to establish basic feasibility of the nivolumab schedule. The run-in cohorts will include 6 patients at each dose schedule, with 2 planned changes to the dose schedule if >33% toxicity or other dose limiting toxicity (DLT) is observed. A minimum of 6 patients and maximum of 18 patients may be enrolled in the run-in phase. • A total maximum of 40 evaluable patients will be enrolled for the primary endpoint. This design yields a type I error rate of 0.05 and power of 80% if the true rate of completion of adjuvant therapy is 0.7. • At the starting dose schedule, patients will receive nivolumab for 1 cycle prior to initiation of chemoradiation (approximately 14 days). Patients will subsequently continue with nivolumab every 14 days until completion of chemoradiation. If a dose schedule shows >33% toxicity or other DLT, then subsequently enrolled patients will be treated at the next dose schedule. In dose schedule 2, patients will start nivolumab concurrent with start of chemoradiation. In dose schedule 3, patients will start nivolumab after completion of chemoradiation (adjuvant nivolumab only). All patients will receive the same dose of nivolumab (240mg). • DLT criteria are grade ≥3 immune-related adverse events, need to hold nivolumab for >28 days due to toxicity, and for patients receiving concurrent nivolumab with chemoradiation, inability to complete chemoradiation or need to hold chemoradiation for >3 days due to immune-related toxicity. • Adjuvant therapy with nivolumab for 6 cycles will start at 4 weeks following completion of chemoradiation, or when immune-related toxicities are at grade 1 or lower, whichever comes later. • Patients will be followed for overall response rate, locoregional control and distant metastasis rates, and overall survival rate for 1 year after end of treatment.
Number of patients	A maximum of 40 evaluable patients will be enrolled in the study using a Simon's two-stage design for the primary endpoint. Non-evaluable patients will be replaced per the replacement policy.

Duration of Therapy	Patients will receive 23 weeks of an anticipated total therapy course, although the duration for an individual patient may be extended to as long as 33 weeks to allow for resolution of toxicities.
Duration of Follow-up	Follow-up visits will occur at **1, 3, 6, 9, and 12 months** for up to 12 months after end of treatment. Survival follow-up information may be collected via telephone calls or medical records review for **an additional 4 years**. Survival and disease status will be collected during this 5-year period until participant death, withdrawal, or if the participant is lost to follow-up.
Duration of study	The study will reach completion in 6 years from the time the study opens to accrual.
Study Drugs	Nivolumab will be administered intravenously, at a dose of 240 mg every 14 days. Nivolumab may be held for toxicity but there are no dose reductions.
Safety Assessments	Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v5.0 for reporting of non-hematologic adverse events and modified criteria for immune related adverse events. Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to nivolumab, all events of death, and any study specific issue of concern. The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and study treatment is initiated and ends 12 months following the last administration of study treatment or study discontinuation/termination, whichever is earlier.
Efficacy Assessments	The primary measure of feasibility will be the rate of completion of all adjuvant therapy. This will be determined based on ability to complete all 6 cycles of adjuvant nivolumab without discontinuation for disease progression or toxicity. Secondary measures of efficacy will be clinical response as judged by the investigator; ORR by RECIST 1.1; locoregional control rate, distant metastasis rate, overall survival rate determined by standard physical examination and radiologic imaging; the rate of EBV DNA clearance at end-chemoradiation and at 1 year post-treatment as determined by PCR assay; toxicity assessments graded by CTCAE v5.0 and modified immune related criteria; and quality of life by FACT-NP, FACT-Taxane, HHIE-S, and EuroQOL EQ-5D-3L. Exploratory assessments are self-explanatory.
Unique Aspects of this Study	This is the first study to evaluate the feasibility of nivolumab integrated with cisplatin in the concurrent and adjuvant treatment of nasopharyngeal carcinoma.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CHR	Committee on Human Research (UCSF IRB)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	hepatitis B virus
HCT	Hematocrit
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	Hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IND	investigational new drug application

List of Abbreviations

IP	investigational product
IRB	Institutional Review Board
IV	Intravenous
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PD	disease progression
PK	Pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
QOL	Quality of Life
RBC	red blood cell (count)
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal
WBC	white blood cell (count)

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1 Introduction

1.1 Background on Indication

1.1.1 Nasopharyngeal Carcinoma:

Nasopharyngeal carcinoma (NPC) is the predominant cancer type arising from the mucosal tissues of the nasopharynx. It has an incidence of 0.5-2 per 100,000 in Europe and the U.S., but it is an endemic disease in Southern China where the annual age-standardized incidence rates are as high as 20-30 cases per 100,000. NPC is also a common disease throughout the rest of Southeast Asia, the Mediterranean and the Artic. Among NPC patients in areas dominated by the endemic type, over 95% are classified as the undifferentiated type (type 2b) according to World Health Organization criteria, while in North America, 25% are classified as keratinizing (type 1) and 12% are classified as nonkeratizing (type 2a). The endemic-type NPC (type 2a and 2b) are near-universally associated with Epstein-Barr Virus (EBV), a strong etiologic factor that interacts with genetic predisposition and dietary intake of chemically preserved foods, while the keratizing cancers are associated with the traditional risk factors for head and neck cancer such as alcohol and tobacco consumption[1].

NPC is staged according to the AJCC/UICC staging system. Presentation with stage I disease is relatively uncommon, at approximately 7% of new incidence, whereas 66% of patients present with stage II or III disease and the rest present with stage IV disease. The 5-year survival for stage I and II cancer approaches 85-90% but for non-metastatic stage III-IV disease it is around 60%.

1.1.2 Concomitant Chemoradiation for Locoregionally Advanced Nasopharyngeal Carcinoma:

The current standard of care for stage I NPC is radiation monotherapy, but for newly diagnosed stage II-IVB NPC patients, treatment consists of a definitive upfront combination of approximately 7 weeks of fractionated radiation therapy (RT) with concurrent cisplatin chemotherapy that is often followed by 3 cycles of adjuvant cisplatin-5FU. This framework was established in the landmark Intergroup 0099 study, for which accrual terminated early due to a statistically significant survival advantage in the chemoradiotherapy arm as compared to radiotherapy alone[2].

Since that time, at least 8 randomized studies have confirmed the survival benefit of adding concurrent platinum-based chemotherapy to RT in patients with non-metastatic stage II to IVB NPC. Two meta-analyses have reported an 18% reduction in the risk of death and an absolute survival benefit of 4% to 6% at 5 years with the use of chemotherapy in addition to radiation. The largest effect was found for concomitant chemotherapy, with a pooled HR of 0.48 (95% CI, 0.32 to 0.72), which corresponds to an absolute survival benefit of 20% after 3 years, from approximately 65% to 85%[3,4].

However, despite the classic status of the Intergroup 0099 study regimen and its widespread reproduction and clinical use across the U.S. and Asia, there are numerous issues with this current standard of care, including a relatively low efficacy of this regimen of systemic chemotherapy in preventing distant metastases, difficulties with tolerability of the overall platinum burden particularly as prescribed in the concurrent plus adjuvant regimens, and a lack of recognized and efficacious alternatives to cisplatin for patients who cannot tolerate full courses of therapy.

In particular, the feasibility of adjuvant CDDP and 5-FU is problematic as only 50-60% of the patients enrolled in past trials were able to complete the prescribed regimen. For instance, in the Intergroup study, 63% of patients completed all 3 cycles of concurrent cisplatin (100 mg/m2 given every 3 weeks) and only 55% of patients completed all 3 cycles of adjuvant chemotherapy afterwards[2] . This is considered unfortunate as the adjuvant phase is intended to provide systemic therapy for a patient population at high risk of distant metastasis.

Justification for omission of adjuvant CDDP/5FU:

The very pressing question of whether there is any oncologic benefit to be accrued from the use of adjuvant chemotherapy in locoregionally advanced NPC was studied in a recent randomized trial from China[5]. This phase III study compared RT with weekly CDDP followed either by 3 cycles of CDDP/5-FU or no adjuvant treatment. In 508 patients, the study found no statistically significant improvement in either progression-free or overall survival from the addition of adjuvant cytotoxic chemotherapy. Of note, in this study, 82% of patients assigned to the arm receiving weekly cisplatin plus adjuvant cisplatin-5FU started adjuvant chemotherapy, but only 63% were able to complete all 3 adjuvant cycles (52% therefore started and completed all adjuvant therapy)[5]. During adjuvant chemotherapy, 42% of patients experienced grade 3-4 toxic effects; 49% had dose reductions and 69% experienced delays in treatment. This is notable given that there was no apparent increase in rates of completion or better tolerance compared to results from the earlier era.

This Chinese randomized study specifically tested the exact additional contribution of the adjuvant phase as opposed to the Intergroup study which tested the addition of concurrent-adjuvant chemotherapy but did not examine whether the concurrent or the adjuvant phase produced the observed benefits. Therefore, many consider the Chinese study to be more relevant in speaking to the issue of whether adjuvant chemotherapy should be included in the standard of care. At this point, given the high toxicity and lack of established additional benefit of adjuvant chemotherapy, the U.S.-based National Comprehensive Cancer Network guidelines no longer consider the adjuvant phase to be supported at the highest level of evidence and have downgraded the adjuvant phase of chemotherapy to a Category 2B recommendation. The category 2B designation indicates that the evidence supporting adjuvant-phase chemotherapy is of a low grade based on historical practice and that there is not uniform consensus on the NCCN panel that it is required. In keeping with this, many major centers in the U.S. and Asia no longer consider adjuvant therapy to be necessary to the standard of care and no longer administer it. In fact, several major standard-defining nasopharynx clinical trials in Asia did not administer adjuvant chemotherapy and produced major survival benefits comparable to those that did. Lastly, from a practical standpoint, up to half of patients cannot complete adjuvant chemotherapy anyway. Thus omission of adjuvant chemotherapy is entirely within the contemporary standard of care and experimental testing of improvements to the adjuvant phase of therapy is justifiable and desperately needed.

Overall justification for study concept:

Within this context, this phase II study is designed to establish the feasibility of nivolumab integrated into the chemoradiation backbone and establish the superior tolerability and feasibility of treatment completion of this strategy as an adjuvant regimen as compared to stand of care adjuvant chemotherapy. Our study is intended to establish the role of nivolumab in the locoregionally advanced disease setting and furthermore, to provide a scientific rationale for future study based on the extent of immunomodulation achieved by nivolumab initiated as a priming

dose, given concurrently with chemoradiation and continued into the adjuvant phase. The point is that if adjuvant CDDP/5FU is being increasingly abandoned due to toxicity, adjuvant nivolumab may offer greater benefit without the excessive toxicities of traditional adjuvant cytotoxic therapy.

The study will include an initial run-in over three cohorts with planned alterations in administration of concurrent or adjuvant nivolumab if unacceptable toxicity is observed. After completion of the run-in phase, an expansion cohort will be enrolled which is designed to test formally for the feasibility of completion of adjuvant therapy as compared to the standard of care adjuvant chemotherapy.

1.2 Background on Nivolumab

1.2.1 Overview

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. Nivolumab 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 provided in the Table below.

Physical and Chemical Properties	
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

PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes[6]. 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 has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family[7,8].

Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro[9-11]. Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1. In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-α release[12].

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.

1.2.2 Pharmacokinetics and Drug Metabolism (Safety)

1.2.2.1 Safety studies in cynomolgus monkeys

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab

was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. Five weekly IV doses of nivolumab were administered to cynomolgus monkeys at dose levels of 1, 10, and 50 mg/kg. The apparent elimination half-life (T-HALF) estimates were long (124 to 148 hours after 1 mg/kg doses, 223 to 267 hours after 10 or 50 mg/kg doses), and serum clearance was low[13-15].

Systemic exposure to nivolumab increased in an approximately dose-proportional manner. The low volume of distribution in cynomolgus monkeys (0.046 L/kg to 0.071 L/kg) indicates that there is little extravascular distribution of nivolumab.

Nivolumab at all doses was well tolerated. There were no clinical signs of toxicity or effects on body weight, food consumption, blood pressure, heart rate, respiration rate, ophthalmic and electrocardiographic parameters, or clinical or anatomic pathology related to the administration of nivolumab. Nivolumab was immunogenic in this study; anti-nivolumab antibodies were detected in 6 of 30 animals and, in general, correlated with reduced nivolumab exposures and PD-1 receptor occupancy. Despite the presence of anti-nivolumab antibodies, the majority of the animals tested at the end of the 4-week recovery phase (9 of 12) demonstrated PD-1 receptor occupancy and circulating levels of nivolumab. Thus, the presence of antibodies did not significantly impact the objective of the study to evaluate the potential toxicity of nivolumab. The results of this study showed that nivolumab was well tolerated when administered by weekly IV injections for 5 weeks at doses up to 50 mg/kg (5× the clinical dose of 10 mg/kg), with no adverse effects on any of the evaluated parameters.

In a 3-month toxicity study, twice weekly IV doses of nivolumab were administered to 6 animals per sex at doses of 0, 10, and 50 mg/kg and were well tolerated; no clinical signs of toxicity or drug-related body weight, cardiovascular, neurologic, respiratory, urinalysis, hematologic, organ weights, or macroscopic or histologic pathology findings were observed. Serum chemistry changes were limited to a reversible 28% decrease in T3 at Week 13 in females treated with 50 mg/kg. T4 and TSH levels were not affected, and in males treated with 50 mg/kg, no changes in T3, T4, or TSH levels were observed. Although anti-nivolumab antibodies were only detected in 1 of 24 animals, it is possible that high nivolumab concentrations interfered with the assay. The results of this study showed that nivolumab was well tolerated when administered by IV injections twice weekly for 3 months at doses up to 50 mg/kg (5x the clinical dose of 10 mg/kg), with no adverse effects on any of the evaluated parameters. In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted[16].

Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at 10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000 ug•h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice[17].

No mass balance or metabolism studies with nivolumab have been conducted in animals. The expected in vivo degradation of monoclonal antibodies is to small peptides and

amino acids via biochemical pathways that are independent of drug metabolism enzymes. Nivolumab is not expected to have any effect on cytochrome P450 or other drug metabolizing enzymes in terms of inhibition or induction, and is, therefore, not expected to induce these types of PK-based drug interactions.

1.2.2.2 Safety studies in humans

Single-dose PK of nivolumab was studied in 39 subjects with cancer[18].The single-dose PK of nivolumab was linear and dose-proportional in the range of 0.3 mg/kg to 10 mg/kg[7].

The mean terminal T-HALF of nivolumab ranged between 17 and 25 days across the dose range of 0.3 mg/kg to 10 mg/kg. Geometric mean total clearance varied from 0.13 mL/h/kg to 0.19 mL/h/kg, while mean volume of distribution varied between 83 mL/kg and 113 mL/kg across doses. The clearance and half-life of nivolumab are consistent with that of IgG4.

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Based on a population pharmacokinetic (PPK) analysis using data from subjects with various tumor types, including melanoma and NSCLC, the geometric mean (% CV%) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) is 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) is 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (23 to 87 years), gender, race, baseline LDH, PD-L1, tumour type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful.

1.2.3 Clinical Experience with Nivolumab

1.2.3.1 Clinical Efficacy of Nivolumab

In the U.S., nivolumab has been approved for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It has also been approved for use in patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, renal cell carcinoma, and some lymphomas. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC and in subjects with unresectable or metastatic melanoma.

Nivolumab has demonstrated clinical activity in subjects with a variety of malignancies in the following indications and studies with available data:

Non small cell lung cancer:

- CA209057: completed Phase 3, randomized, open-label study of nivolumab vs. docetaxel in subjects with advanced NSQ NSCLC previously treated with platinum-based doublet chemotherapies
- CA209017: completed Phase 3, randomized, open-label study of nivolumab vs. docetaxel in subjects with advanced SQ NSCLC previously treated with platinum-based doublet chemotherapies
- CA209012: ongoing Phase 1 study with nivolumab monotherapy or in combination with ipilimumab, platinum-based chemotherapy or erlotinib in subjects with treatment-naiveStage IIIB/IV NSCLC
- ONO-4538-05: completed Phase 2, open-label study of nivolumab in Japanese subjects with Stage IIIB/IV or recurrent SQ NSCLC
- ONO-4538-06: completed Phase 2, open label study of nivolumab in Japanese subjects with Stage IIIB/IV or recurrent NSQ NSCLC

Melanoma:

- CA209069: completed Phase 2, randomized, double-blind study of nivolumab in combination with ipilimumab vs. ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma
- CA209066: completed Phase 3, randomized, double-blind study of nivolumab vs. dacarbazine in subjects with untreated, unresectable or metastatic melanoma who are BRAF-WT
- CA209067: ongoing Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab vs. ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma
- ONO-4538-02: completed Phase 2, open-label study of nivolumab in Japanese subjects with unresectable Stage III/IV or recurrent malignant melanoma

Renal cell carcinoma:

- MDX1106-03/CA20903: completed Phase 1 multidose escalation study with nivolumab monotherapy
- CA209010: completed Phase 2 dose-ranging monotherapy study in subjects with advanced or metastatic clear-cell RCC who received prior anti-angiogenic therapy
- CA209016: ongoing Phase 1 dose-escalation study of nivolumab in combination with VEGFR-TKIs or ipilimumab in subjects with metastatic RCC

Combined Malignant Tumors/Esophageal Cancer:

- ONO-4538-01: completed Phase 1, dose-escalation study of nivolumab monotherapy in subjects with advanced or recurrent malignant tumors
- ONO-4538-07: ongoing Phase 2 study of nivolumab monotherapy in subjects with esophageal cancer

<u>Rationale for nivolumab in nasopharyngeal carcinoma</u>

Programmed cell death ligand-1 (PD-L1) is highly expressed by cancer cells and tumor-infiltrating macrophages in virus-associated malignancies such as NPC[19]. There is emerging evidence that activation of the PD-1/PD-L1 pathway contributes to immune escape in NPC models[20,21]. PD-L1 is expressed in up to 90% of NPC tumors[19,20].

Nivolumab is being employed for recurrent/metastatic NPC (NCT02339558). Recently, results were reported from an ongoing multi-cohort, non-randomized Phase 1b trial (KEYNOTE-028) for patients with advanced unresectable and refractory NPC whose tumors expressed PD-L1 (≥1% of cells in tumor nests or PD-L1+ bands in stroma). Early findings from 27 heavily pre-treated patients with advanced NPC demonstrated an ORR of 22.2 percent (n=6/27) (per RECIST v1.1), including six partial responses (95% CI, 8.6-42.3). Additionally, 55.6 percent of patients had stable disease (n=15/27) (95% CI, 35.3-74.5), the disease control rate (DCR) was 77.8 percent (n=21/27) (95% CI, 57.7-91.4), and tumor shrinkage was achieved in 67 percent of patients. The 6-month progression-free survival (PFS) rate was 49.7 percent and the 12-month PFS rate was 28.9 percent. The median follow-up duration for evaluable patients was 12.9 months (range, 2.2-15.0) and the median response duration was 10.8 months (range, 4.8-10.8).

CheckMate-141 was a phase 3, open label, randomized study of nivolumab versus investigator's choice of therapy (2:1 randomization) in previously treated patients with squamous cell carcinoma of the head and neck who had tumor progression on or within 6 months of platinum therapy in the primary, recurrent, or metastatic setting. The trial randomized 361 patients and was stopped early when an assessment concluded that the study had met the primary endpoint of superior overall survival in the nivolumab arm. The median overall survival was 7.5 months in the nivolumab-treated patients versus 5.1 months for patients on chemotherapy, representing a 30% reduction in the survival hazard, and 36% of the nivolumab-treated patients were alive at 1 year compared to 16.6% of the patients receiving standard treatment. The incidence of adverse events (all grades) was 58.9% with nivolumab and 77.5% with investigator's-choice regimens. Grade 3/4 toxicity occurred in 13.1% versus 35.1% of the nivolumab and control groups. CheckMate-141 was the first study in head and neck cancer to demonstrate an improvement in survival with an immune checkpoint inhibitor as compared to standard chemotherapy. While the trial did not specifically investigate NPC, it lends further support to the rationale of potentially improved outcomes with nivolumab, at a lower rate of high-grade toxicity.

1.2.3.2 Clinical safety of nivolumab in humans

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8,600 subjects treated to date. For monotherapy, all available data suggest that nivolumab has a consistent AE profile across tumor types, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with non-small cell lung cancer, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most common adverse reaction (≥20%) in patients with melanoma is rash, and the most common adverse reactions (≥20%) in patients with advanced squamous non-small cell lung cancer are fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation. The most frequently reported treatment-related AE overall is fatigue, which is almost always of low grade.

There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose

level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

Across all studies conducted to date, the most common and impactful drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), hepatotoxicity, and hypersensitivity/infusion reaction. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) according to standardized management guidelines.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced immunotherapy combination under development is nivolumab + ipilimumab in subjects with non-small cell lung cancer, melanoma, and renal cell carcinoma. The combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases, with a greater frequency.

1.2.3.3 Adverse events associated with nivolumab

Adverse drug reactions (ADRs) that are considered to be causally related to nivolumab are classified by system organ class and frequency. The frequency of ADRs is defined using the following convention: very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); and very rare (< 1/10,000).

As of 04-July-2016, the following ADRs were reported in clinical studies **where nivolumab was given as monotherapy.** The reported overall frequency includes reported serious and non-serious ADRs.

System Organ Class	Preferred Term	Overall Frequency[a]	Serious	Life Threatening	Fatal
Cardiac	Tachycardia	Uncommon			
	Arrhythmia	Uncommon	X		
Ear and Labyrinth Disorders	Vertigo	Uncommon			
Endocrine	Hypothyroidism	Common	X		
	Hyperthyroidism	Common	X		
	Hyperglycemia	Uncommon	X	X	
	Adrenal insufficiency	Uncommon	X	X	
	Thyroiditis	Uncommon	X		
	Hypophysitis	Uncommon	X		
	Diabetes mellitus	Uncommon	X		
	Hypopituitarism	Uncommon	X		
	Diabetic ketoacidosis	Rare	X	X	
Eye	Dry eye	Uncommon			
	Vision blurred	Uncommon			

	Uveitis (including iridocyclitis)	Uncommon	X		
Gastrointestinal	Diarrhea	Common	X		
	Nausea (Autoimmune)	Common	X		
	Vomiting	Common	X		
	Constipation	Common			
	Abdominal pain	Common	X		
	Stomatitis (including mucosal inflammation/ulceration, mouth ulceration)	Common	X		
	Dry mouth	Common			
	Colitis	Common	X		X
	Pancreatitis	Uncommon	X		
	Gastritis	Uncommon	X		
General	Fatigue (including asthenia)	Very common	X		
	Pyrexia	Common	X		
	Edema	Common	X		
	Chills	Common	X		
Hepatobiliary	Hepatitis (Autoimmune)	Uncommon	X	X	
Immune System	Infusion related reaction	Common	X	X	
	Hypersensitivity	Uncommon	X	X	
	Anaphylactic reaction	Rare	X	X	
	Sarcoidosis	Rare	X		
Infections and Infestations	Upper respiratory tract infection	Uncommon			
	Bronchitis	Uncommon			
Investigations	Alanine aminotransferase increased	Common	X		
	Aspartate aminotransferase increased	Common	X		
	Lipase increased	Common	X		
	Blood alkaline phosphatase increased	Common	X		
	Amylase increased	Common	X		
	Blood creatinine increased	Common	X		
	Blood thyroid stimulating hormone increased	Common			
	Blood bilirubin increased	Uncommon	X		
Metabolism and nutrition	Decreased appetite	Common	X		
	Hyponatremia	Common	X		
Musculoskeletal and connective tissue	Musculoskeletal pain	Common	X		
	Arthralgia (including arthritis, polyarthritis, and osteoarthritis)	Common	X		
	Myositis	Rare	X		
	Polymyalgia rheumatica	Rare	X		
	Rhabdomyolysis	Rare	X		
Nervous system	Headache	Common	X		

	Neuropathy	Common	X		
	Dizziness (including vertigo, vertigo positional)	Uncommon	X		
	Cranial nerve disorder	Uncommon	X		
	Myasthenia syndrome	Rare	X		
	Guillain-Barre syndrome	Rare	X		
	Demyelination syndrome	Rare	X		
	Encephalitis	Rare	X		
Renal and urinary	Renal failure (including acute kidney injury)	Uncommon	X		
	Nephritis	Uncommon	X		
Respiratory, thoracic, and mediastinal	Pneumonitis (including interstitial lung disease)	Common	X	X	X
	Dyspnea	Common	X	X	X
	Cough	Common	X		
	Respiratory failure	Uncommon	X	X	X
	Lung infiltration	Rare	X		
Skin and Subcutaneous	Rash	Very common	X		
	Pruritis	Common	X		
	Dry skin	Common			
	Vitiligo	Common			
	Erythema	Uncommon			
	Alopecia	Uncommon			
	Urticaria	Uncommon	X		
	Erythema multiforme	Rare	X		
	Rosacea	Rare			
	Stevens Johnson syndrome	Rare	X		
	Toxic epidermal necrolysis	Rare	X		X
Vascular	Hypotension	Uncommon	X		
	Hypertension	Uncommon			
	Vasculitis	Rare			

Laboratory abnormalities observed in monotherapy studies are as follows, graded by CTC version 4.0.

	Number (%) of subjects with worsening laboratory results from baseline					
	Nivolumab 3 mg/kg, unresectable or metastatic melanoma			**Nivolumab 3 mg/kg, squamous cell carcinoma of the lung**		
Test	**N**	**Grade 1-4**	**Grade 3-4**	**N**	**Grade 1-4**	**Grade 3-4**
Decreased hemoglobin	458	183 (40)	21 (4.6)	244	74 (30.3)	6 (2.5)
Decreased platelet count	464	53 (11.4)	1(0.2)	244	30(12.3)	1 (0.4)
Decreased absolute lymphocytes	456	188 (41.2)	32 (7.0)	243	113 (46.5)	32 (13.2)
Decreased absolute neutrophil count	457	43 (9.4)	4 (0.9)	244	17 (7.0)	4 (1.6)
Increased alkaline phosphatase	450	103 (22.9)	11 (2.4)	240	47 (19.6)	0

Increased AST	452	125 (27.7)	15 (3.3)	242	50 (20.7)	1 (0.4)
Increased ALT	455	98 (21.5)	11 (2.4)	242	36 (14.9)	0
Increased total bilirubin	452	52 (11.5)	7 (1.5)	242	10 (4.1)	2 (0.8)
Increased creatinine	457	68(14.9)	4 (0.9)	244	47(19.3)	0

Additional adverse drug reactions in subjects treated with nivolumab combined with ipilimumab were as follows.

			At least one with the outcome		
System Organ Class	**Preferred Term**	**Overall Frequency**	**Serious**	**Life Threatening**	**Fatal**
Eye	Diplopia	Uncommon	X		
	Dry eye	Uncommon	X		
	Vision blurred	Uncommon	X		
Gastrointestinal	Appendix disorder (enlarged appendix)	Uncommon	X		
	Colitis ulcerative	Uncommon	X		
	Enteritis	Uncommon	X		
	Enterocolitis	Uncommon	X	X	
	Gastritis	Uncommon	X		
	Ileus	Uncommon	X		
	Impaired gastric emptying	Uncommon	X		
General	Chills	Uncommon	X		
	Multi-organ failure	Uncommon	X		X
	Drug-induced liver injury	Uncommon	X		
	Hepatitis acute	Uncommon	X		
	Hyperbilirubinemia	Uncommon	X		
	Autoimmune disorder	Uncommon	X		
	Blood alkaline phosphatase increased	Uncommon	X		
	Hepatic enzyme increased	Uncommon	X		
	Transaminases increased	Uncommon	X		
	Blood creatinine increased	Uncommon	X		
	Dehydration	Uncommon	X		
	Meningitis (noninfective)	Uncommon	X		
	Myasthenia Gravis	Uncommon	X		X
	Miller Fisher Syndrome	Uncommon	X		
	Optic neuritis	Uncommon	X		
	Nephiritis allergic	Uncommon	X		
	Acute respiratory distress syndrome	Uncommon	X	X	X
	Respiratory distress	Uncommon	X		X
	Respiratory failure	Uncommon	X	X	X

As of 04-July-2016, there were no additional ADRs that have been reported in clinical studies in which the nivolumab was given as combination therapy with other agents and no additional ADRs were identified from ongoing blinded clinical studies with nivolumab. There have been no additional ADRs identified from postmarketing experience.

1.2.3.4 General management strategy for nivolumab related ADRs

The approach to suspected nivolumab-related AEs is similar across any involved organ system. Standardized safety algorithms have been developed (see Appendix 7). Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE). The management of AEs considered related to any combination treatment is similar to the management of AEs caused by either agent alone and utilizes the same safety management algorithms.

It is rare for a patient receiving immunosuppression for nivolumab-related AEs to develop an opportunistic infection. Subjects with inflammatory events of any organ category expected to require more than 4 weeks of corticosteroid or other immunosuppressive agents to manage the AE should be considered for antimicrobial/antifungal prophylaxis, per institutional guidelines, to prevent opportunistic infections such as P. jiroveci (formerly P carinii) 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 addition, a concomitant opportunistic infection should be considered in the differential diagnosis if a patient develops recurrent AEs in the setting of ongoing or prior immunosuppressive use. Nivolumab should not be used in subjects with active autoimmune disease given the mechanism of action of the antibody.

Specific management algorithms are provided in Appendix 7.

1.3 Rationale for the Proposed Study

We hypothesize that standard concurrent chemoradiation in combination with priming, concurrent, and adjuvant nivolumab will improve the feasibility of treatment completion by allowing completion of a regimen that is highly effective but more tolerable than the current standard of care.

This study will begin with a run-in phase to establish the basic feasibility of the nivolumab schedule and determine the MTD (maximally tolerated dose) schedule. This will be followed by an expansion phase which will more rigorously test the feasibility of completion of all therapy as compared to the standard of care.

Furthermore, the design of this trial will allow us to perform immunologic analyses on tumor and peripheral blood specimens pre-treatment and after exposure to nivolumab, chemoradiation-nivolumab, and adjuvant nivolumab. This will allow us to investigate possible future patient specific selection criteria for this regimen and correlate mechanisms of incomplete response to immunologic predictors, which may allow for design of more advanced rational therapies for patients at high risk of distant metastasis.

1.4 Correlative Studies

1.4.1 PD-L1 immunohistochemistry

In a study of 119 patients with histological diagnosis of NPC from a cancer registry in Thailand, PD-1 and PD-L1 expression were characterized using immunohistochemistry staining on formalin-fixed, paraffin-embedded tumor samples. PD-L1 expression was defined by using a cut-off of ≥1% (≥1-9%=1+, 10-49%=2+, ≥50%=3+). PD-L1 was found to be positive in 72% (13% IHC 3+). PD1+ was observed in 11% of patients. Most patients in this study had EBER+ tumors (96%) indicating EBV-related etiology.

In another study from China, co-expression of PD-1 and PD-L1 was found to correlate to poor outcome in NPC treated with standard chemoradiation. Formalin-fixed, paraffin-embedded tissue biopsies from 139 patients treated with conventional chemoradiotherapy were studied. By immunohistochemistry, expressions of PD-1 on tumor-infiltrating lymphocyte and PD-L1 on tumor tissue were detected. The staining results were evaluated with H-score. 52 of these 139 tumors (37.4%) were PD-1+. PD-L1 expression was detected in 132 patients (95.0%) on tumor tissue. High expression of PD-L1 (median H-score >35) in tumor tissue significantly correlated with a poor prognosis of disease-free survival (P = 0.009). Co-expression of PD-1 and PD-L1 in NPC at diagnosis correlated with the poorest prognosis of disease-free survival (P = 0.038)[22].

The DAKO PD-L1 IHC 28-8 pharmDxTM test was recently FDA-approved as a complementary diagnostic test to help physicians determine which patients may benefit most with nivolumab. By using immunohistochemistry staining, expression of PD-L1 on tumor tissue will be detected. The staining results will be evaluated with H-score. The correlation between PD-L1 expression and clinical response will be analyzed. We hypothesize that upregulated PD-L1 expression that persists after two weeks of treatment with nivolumab will be predictive of poor clinical response, but patients who show lower PD-L1 expression at the time of rebiopsy will show an improved clinical response.

1.4.2 EBV DNA

Pre-treatment EBV DNA in plasma has been proven to correlate with cancer stage, clinical outcome, and prognosis in patients with endemic NPC[23-25]. However, post-radiation plasma EBV DNA has an even better correlation with prognosis and has been used to monitor recurrence after definitive therapy[26-29]. Rising post-treatment plasma EBV DNA has been shown to predate clinical recurrence by 3 to 7 months[30-32]. Undetectable levels of plasma EBV DNA are observed in patients who remained in remission.

In a large (n=170) NPC study in which most patients were treated uniformly with definitive RT (with only 15 patients also receiving weekly CDDP at 40mg/m^2 during RT), the levels of post-treatment plasma EBV DNA strongly predicted for progression-free survival (PFS) ($p<0.001$) and OS ($p<0.001$), and this post-treatment EBV DNA dominated the effect of pre-treatment EBV DNA. The 1-year PFS was 93% among patients with post-treatment EBV DNA ≤ 500 copies/mL, and 48% for those with > 500 copies/mL[33].

A quantitative plasma EBV DNA assay was developed as an international harmonization study to facilitate EBV biomarker trials. Post-harmonization, the intraclass correlations for each site compared to the index site were 0.83 (0.5-0.95), 0.95 (0.83-0.99) and 0.96 (0.86-0.99),

respectively[34]. The centers in this study will use an assay harmonized among the participating sites.

2 Objectives of the Study

2.1 Primary

- To establish the feasibility of treatment completion of a combined chemoradiation-nivolumab regimen followed by adjuvant nivolumab.

2.2 Secondary

- To determine the clinical response as judged by the investigator;
- To determine the overall response rate at 1 year from completion of therapy, as determined by RECIST 1.1 criteria;
- To determine the locoregional control rate at 1 year post-treatment;
- To determine the distant metastasis rate at 1 year post-treatment;
- ;
- To determine the rate of EBV DNA clearance at end of chemoradiation and at 1 year post-treatment;
- To determine the acute and late toxicity rates according to CTCAE v5.0, including immune-related adverse events (AEs);
- To assess patients' quality of life from baseline through 1 year post-treatment

2.3 Exploratory Objectives, Other Assessments

- To determine the overall survival rate at 5 year post-treatment
- To determine whether PDL1-positive immunohistochemistry and novel quantitative assays correlate to clinical outcome;
- To determine if the density of infiltrating CD3+ T cells/μm2 correlates to clinical outcome;
- To monitor immune changes by flow cytometry in the circulating T cell response to EBV antigens;
- To compare the change in the circulating T-cell repertoire by TCR sequencing and single-cell T-cell profiling;
- To quantify treatment-induced changes over time in the circulating T cell immune response to EBV using TCR sequencing and enzyme-linked immunospot (ELISPOT) assays**.**

2.4 Endpoints

2.4.1 Primary Endpoints

- The primary endpoint will be the rate of completion of adjuvant immunotherapy, in comparison to the rate of completion of a standard adjuvant cisplatin-based platform (historical control). This will be determined based on the ability to complete all prescribed concurrent and/or adjuvant nivolumab without discontinuation for disease progression or toxicity.

2.4.2 Secondary Endpoints

- ORR determined by investigator's assessment and RECIST 1.1 criteria;
- Locoregional control rate;
- Distant metastasis rate;
- Rate of EBV DNA clearance from plasma by standardized PCR assay;
- Treatment-emergent AEs and laboratory abnormalities as determined by National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0 and modified immune related criteria;
- Quality of life as assessed by patient reported outcomes (FACT-NP, FACT-Taxane, HHIE-S, and EuroQOL EQ-5D).

2.4.3 Exploratory Endpoints

- Overall survival rate;
- PDL1-positive immunohistochemistry and novel quantitative assays;
- Density of infiltrating CD3+ T cells/μm2;
- Changes by flow cytometry in the circulating T cell response to EBV antigens;
- Change in the circulating T-cell repertoire by TCR sequencing and single-cell T-cell profiling;
- Changes over time in the circulating T cell immune response to EBV using TCR sequencing and enzyme-linked immunospot (ELISPOT) assays**;**

3 Study Design

3.1 Characteristics

This is a Phase 2, single arm, open-label, multicenter study evaluating the feasibility of a treatment regimen comprised of nivolumab administered approximately every 2 weeks before and during chemoradiation and as an adjuvant therapy for 3 months to patients with stage II-IVB NPC who are planning to undergo chemoradiation treatment of their cancer.

A run-in phase will precede expansion, to establish basic feasibility of the nivolumab schedule. The run-in cohorts will include 6 patients at each dose schedule, with 2 planned changes in dose schedule if >33% toxicity or other DLT is observed. A minimum of 6 patients and maximum of 18 patients may be enrolled in the three run-in cohorts. The MTD schedule will be selected when 4/6 patients at a dose schedule complete therapy without grade 3-4 immune related toxicity. All patients will receive the same dose of nivolumab (240mg).

At the starting dose schedule, patients will receive nivolumab for 1 cycle prior to initiation of chemoradiation (approximately 14 days). Patients will subsequently continue with nivolumab every 14 days until completion of chemoradiation. In dose schedule 2, patients will start nivolumab concurrent with start of chemoradiation. In dose schedule 3, patients will start nivolumab after completion of chemoradiation (adjuvant nivolumab only).

DLT criteria are grade ≥3 immune-related adverse events, need to hold nivolumab for >28 days due to toxicity, and for patients receiving concurrent nivolumab with chemoradiation, inability to complete chemoradiation or need to hold chemoradiation for >3 days due to immune-related

toxicity.

The expansion phase will continue after the run-in phase has been used to establish the MTD schedule for nivolumab. The expansion phase will be powered to test the feasibility of completion of the program as compared to the current standard of care.

3.2 Study Schema

On-treatment schema (Dose Schedule 1):

													Adjuvant Phase										
Cycle #	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**		**12**
Week #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Cisplatin			C	C	C	C	C	C	C														
Radiation			X	X	X	X	X	X	X														
Nivolumab	N		N		N		N		N				N		N		N		N		N		N

Nivolumab schedule (starting dose schedule): Priming and concurrent nivolumab will be given in conjunction with chemoradiation. Patients will receive 1 cycle of priming nivolumab on C1D1, and 14 days later, start weekly cisplatin 40 mg/m^2, IV, concurrent with 33-35 fractions (6.5-7 weeks) of RT, with concurrent cycles 2-5 of nivolumab every 14 days. No nivolumab will be given on C6D1, to allow for recovery from toxicities. At C7D1, patients will initiate adjuvant nivolumab, every 14 days for cycles 7-12. Immune-related toxicities should be at grade 1 or lower prior to starting a patient on the adjuvant phase of therapy; if not, initiation of the adjuvant phase should be delayed until resolution of toxicities.

On-treatment schema (Dose Schedule 2):

											Adjuvant Phase										
Cycle #	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**
Week #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Cisplatin	C	C	C	C	C	C	C														
Radiation	X	X	X	X	X	X	X														
Nivolumab	N		N		N		N				N		N		N		N		N		N

Nivolumab schedule (Dose Schedule 2): Priming and concurrent nivolumab will be given in conjunction with chemoradiation. Patients will receive 1 cycle of nivolumab on C1D1 (no priming), and start weekly cisplatin 40 mg/m^2, IV, concurrent with 33-35 fractions (6.5-7 weeks) of RT, with concurrent cycles 2-5 of nivolumab every 14 days. No nivolumab will be given on C5D1, to allow for recovery from toxicities. At C6D1, patients will initiate adjuvant nivolumab, every 14 days for cycles 6-11. Immune-related toxicities should be at grade 1 or lower prior to starting a patient on the adjuvant phase of therapy; if not, initiation of the adjuvant phase should be delayed until resolution of toxicities.

On-treatment schema (Dose Schedule 3):

											Adjuvant Phase										
Cycle #	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**		**10**		**11**
Week #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Cisplatin	C	C	C	C	C	C	C														
Radiation	X	X	X	X	X	X	X														
Nivolumab											N		N		N		N		N		N

Nivolumab schedule (Dose Schedule 3): Nivolumab will be only given after chemoradiation. On C1D1, patients will start weekly cisplatin 40 mg/m^2, IV, concurrent with 33-35 fractions (6.5-7 weeks) of RT every 14 days. At C6D1, patients will initiate adjuvant nivolumab, every 14 days for cycles 6-11. Immune-related toxicities should be at grade 1 or lower prior to starting a patient on the adjuvant phase of therapy; if not, initiation of the adjuvant phase should be delayed until resolution of toxicities.

3.3 Feasibility assessment in the run-in phase

A run-in phase will be conducted initially to determine feasibility. The main schema will be used as illustrated, but dosing of nivolumab will be subject to dose reduction if high grade immune related adverse events are observed.

Six patients will be enrolled for the initial run-in phase, starting with nivolumab dosing of 240 mg. Enrollment will cease until all 6 patients have completed concurrent chemoradiation and nivolumab. If 3/6 patients have experienced grade 3-4 immune related toxicity or other DLT during concurrent chemoradiation and nivolumab therapy, then the dose schedule will be changed to the next dose schedule and the run-in will restart at that schedule. In dose schedule 2, patients will start nivolumab concurrently with chemoradiation and there will be no priming dose prior to chemoradiation. Using these same procedures, there may be one further change to dose schedule 3. In dose schedule 3, patients will not have priming or concurrent nivolumab and will only start nivolumab in the adjuvant phase after chemoradiation is concluded. No dose reductions of nivolumab will be allowed. No dose escalation will be allowed.

The run-in will cease when 4/6 patients or more have completed their specified concurrent nivolumab therapy at the same nivolumab dose schedule without experiencing grade 3-4 toxicity or other DLT, or alternatively, if 3/6 patients have experienced grade 3-4 toxicity or other DLT during the adjuvant phase at dose schedule 3 (in which case the entire study will terminate). Therefore, a minimum of 6 patients and a maximum of 18 patients will be enrolled in the run-in phase.

DLT criteria are grade ≥3 immune-related adverse events, need to hold nivolumab for >28 days due to toxicity, and for patients receiving concurrent nivolumab with chemoradiation, inability to complete chemoradiation or need to hold chemoradiation for >3 days due to immune-related toxicity.

3.4 Number of Subjects

A maximum of 40 evaluable patients will be enrolled in the study using a Simon's two-stage design for the primary endpoint. Patients who are enrolled at the maximally tolerated dose of

nivolumab during the run-in phase will be included in the determination of the primary endpoint. Non-evaluable patients will be replaced per the replacement policy (see section 8.2.5). For the primary endpoint, this design yields a type I error rate of 0.05 and power of 80% if the true rate of completion of adjuvant therapy is 0.7.

3.5 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 enrollment. The following criteria apply to all patients and all eligibility criteria must be met prior to enrollment on the study unless otherwise specified.

3.5.1 Inclusion Criteria

1. Males and females ≥18 years of age.

2. Histologically or cytologically confirmed nasopharyngeal carcinoma, stage II-IV by AJCC 7th edition, endemic-type (defined as WHO type 2a and 2b nonkeratizing or undifferentiated subtypes, excluding WHO type I keratizing subtype) performed on a biopsy that occurred within 90 days of registration.

3. PET-CT (preferred) or a CT of chest, abdomen, and pelvis within 60 days of registration showing radiographic stage II to IVB nasopharyngeal cancer.

4. No distant metastasis as verified by one of the study investigators.

5. Documentation that the patient is a candidate for chemoradiation of their nasopharyngeal cancer by one of the study investigators.

6. Ability to tolerate radiation therapy (e.g. lie flat and hold position for treatment).

7. Measurable disease as defined by RECIST v1.1.

8. ECOG performance status of 0 to 1.

9. Lack of contraindications to systemic immunotherapy (see list of exclusions below).

10. Resolution of all acute toxic effects of any prior chemotherapy, radiotherapy or surgical procedures to NCI CTCAE Version 5.0 grade 1.

11. Adequate hepatic, hematologic, and renal indices permitting administration of cisplatin and nivolumab (within 14 days of registration):

    <u>Hepatic Function:</u>

    Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN);

Total bilirubin ≤ 1.5 × ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

Adequate bone marrow function:

WBC ≥ 2000/μL

Neutrophils ≥ 1500/μL

Platelet ≥ 100 x10^3/μL

Hemoglobin > 9.0 g/dL

Adequate renal function:

Serum creatinine	≤ 1.5 × upper limit of normal (ULN)
OR	
Creatinine clearance	> 40 mL/min (or ≥ 50 mL/min for Singapore sites only) (if using the Cockcroft-Gault formula below):

Female CrCl = (140 - age in years) x weight in kg x 0.85

72 x serum creatinine in mg/dL

Male CrCl = (140 - age in years) x weight in kg x 1.00

72 x serum creatinine in mg/dL

12. Women of childbearing potential must have a negative serum pregnancy test within 24 hours prior to the first dose of study treatment and agree to use appropriate highly effective methods of contraception, during the study and for 5 months following completion of study treatment;

    A “Woman 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 62 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

    Female Subjects:

    Women of child bearing potential are expected to use one of the highly effective methods of contraception listed below.

    Male Subjects:

    Male subjects must inform their female partners who are women of child bearing potential of the contraceptive requirements and are expected to adhere to using contraception with their partner. Female partners of male subjects, who are women of child bearing potential, are expected to use one of the highly effective

methods of contraception listed below. In addition, male subjects are expected to use a condom as noted in the list below.

Highly Effective	Progestogen only hormonal contraception associated with inhibition of ovulation
	Hormonal methods of contraception including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, implants and intrauterine devices (IUDs)
	Non-hormonal IUDs such as ParaGard®
	Bilateral tubal ligation
	Vasectomized Partner
	Intrauterine hormone-releasing system (IUS)
	Complete abstinence
Other Methods	Condom
Unacceptable Methods	Vaginal sponge
	Progestin only pills
	Cervical cap with spermicide
	Periodic abstinence (calendar, symptothermal, post-ovulation methods)
	Withdrawal (coitus interruptus)
	Spermicide only
	Lactation amenorrhea method (LAM)
	A male and a female condom must not be used together

13. Men with a female partner of childbearing potential must agree to use highly effective methods of contraception or any contraceptive method with a failure rate of less than 1% per year during the study and for 7 months following completion of study treatment.

14. Ability to sign informed consent.

3.5.2 Exclusion Criteria

Any of the following criteria will exclude patients from study participation:

1. Active second malignancy, i.e. patient known to have potentially fatal hematologic malignancy or another solid primary tumor present for which he/she may be (but not necessarily) currently receiving treatment. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are allowed to enroll in this trial. For example, patients with early-stage skin cancers, prostate cancer under surveillance with non-rising PSA, or meningioma or thyroid papillary cancers which are under surveillance are eligible. For determinations of a specific clinical condition, please consult with the Principal Investigator.

2. Active, untreated central nervous system (CNS) metastases;

3. Prior treatment with any other anti-programmed cell death protein-1 (anti-PD-1), or PD Ligand-1 (PD-L1) or PD Ligand-2 (PD-L2), anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways, or cancer vaccine;

4. Prior systemic cytotoxic therapy, antineoplastic biologic therapy, or major surgery within 28 days of first dose of study medication;

5. Severe hypersensitivity reaction to treatment during prior administration of a monoclonal antibody (mAb) or history of allergy to any study drug component;

6. Has received a live-virus vaccination within 30 days of planned treatment start;

7. Condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration;

   Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

8. Any evidence of current interstitial lung disease (ILD) or pneumonitis or a prior history of ILD or pneumonitis requiring oral or IV glucocorticoids;

9. Active, known, or suspected autoimmune disease or any autoimmune condition that has required systemic treatment in the past 2 years (replacement therapies for hormone deficiencies are allowed);

   Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

10. Clinically active diverticulitis, intra-abdominal abscess, gastrointestinal (GI) obstruction, or abdominal carcinomatosis (known risks factors for bowel perforation);

11. Signs or symptoms of infection within 2 weeks prior to first day of study treatment.

12. Patients with active tuberculosis (clinical evaluation in line with local practice), or a known history of active tuberculosis that in the opinion of the treating investigator has a high risk of reactivation.

13. Received therapeutic oral or IV antibiotics within 2 weeks prior to first day of study treatment:

    Patients receiving prophylactic antibiotics (eg, to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible.

14. Known positive test for human immunodeficiency virus (HIV);

15. Known active hepatitis B or hepatitis C virus (HBV or HCV):

    Patients with past or resolved HBV infection (defined by a negative hepatitis B surface antigen [HBsAg] test and a positive anti-hepatitis B core antigen [anti-HBc]

antibody test) are eligible. HBV DNA must be obtained in these patients prior to first day of study treatment.

Patients who have been recently discovered to have HBV with positive HBsAg test and positive anti-HBc antibody test but who have been started on antiretroviral treatment with nondetectable HBV DNA are eligible. HBV DNA must be obtained in these patients prior to first day of study treatment.

16. Patients with known active hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection:

    Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

17. Prior radiation therapy of any type within 7 days of first dose of study medication;

18. Prior radiation therapy to head and neck region that would overlap with intended radiation treatment for nasopharyngeal carcinoma;

19. Medical contraindication to radiation treatment (e.g. active systemic sclerosis, other uncontrolled autoimmune condition)

20. Treatment with prohibited medications (including concurrent anticancer therapy including chemotherapy, radiation, hormonal treatment [except corticosteroids and megesterol acetate] ≤ 14 days prior to treatment.

21. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study;

22. Active, uncontrolled psychiatric disorders or substance (drug/alcohol) abuse that interfere with patient's safety, ability to provide informed consent, or ability to comply with the protocol.

23. Persons who are incarcerated or otherwise under compulsory detention by an authority are not eligible.

3.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment with nivolumab may continue from the specified initiation timepoint and for 3 months after chemoradiation or until:

- The patient or legally authorized representative withdraws consent.
- Progression of disease by RECIST 1.1 criteria.
- Any adverse event that in the opinion of the investigator would pose an unacceptable safety risk to the patient.
- Closure of the study

3.7 Duration of Follow Up

Patients will be followed for safety assessments for 100 days after completion of treatment or removal from study, or until death, whichever occurs first. All SAEs must be collected that occur within 100 days of discontinuation of dosing. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower. Patients will be followed for adverse events for up to 1 year. Survival and disease status information may also be collected from review of the electronic medical records, patient visits, or telephone calls. Survival and disease status will be collected until participant death, withdrawal, or if the participant is lost to follow-up.

3.8 Study Timeline

3.8.1 Primary Completion

It is expected that the study will reach primary completion 20 months from the time the study opens to accrual.

3.8.2 Study Completion

It is expected that the study will reach full completion 6 years from the time the study opens to accrual.

4 Study Drugs

At study sites, all study medication will be stored as described in the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Nivolumab (BMS-936558)

Classification:
Nivolumab is a fully human IgG4 anti-PD1 monoclonal antibody.

Mechanism of Action:

In vitro, nivolumab binds to PD-1 on activated human T cells with high affinity (half maximal effective concentration [EC50]: 0.64 nM by FACS analysis and 2.6 nM by Scatchard), and inhibits the binding of PD-1 to its ligands, programmed death-ligand-1 (PD-L1) and programmed death-ligand-2 (PD-L2) (half maximal inhibitory concentration [IC50] of ~1 nM)[1]. Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, inducible co-stimulator (ICOS), cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and B and T lymphocyte attenuator (BTLA). Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-α release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV)-re-stimulation assay with human peripheral blood mononuclear cell (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-α secretion from CMV specific memory T-cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejections and tumor growth delays in MC38 and SA1/N immunocompetent mouse tumor models.

Storage Conditions & Handling:

- Nivolumab has a concentration of 10mg/mL and is provided in a 10mL vial. Ten or five vials are provided in a carton.
- Store at 2-8°C (36-46°F), protect from light, freezing, and shaking.
- If any temperature excursions are encountered during storage, please report these to BMS for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.
- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

Use Time/Stability:

The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2°-°-8°C (, 36°-46°F) and used within 4 for up to 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of BMS-936558-01 injection in the IV bag should be inclusive of the includes the product administration period.

Preparation and Administration:

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles.

   *Note: Mix by **gently** inverting several times. **Do not** shake.*

2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV. bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection

3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*

   Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL [IBV13 Addendum Section 3.2.2]

Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.

4. Attach the IV bag containing the nivolumab solution to the infusion set and filter.

5. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

4.2 Drug Accountability

The Investigational Pharmacist will manage drug accountability records.

After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs. For further information, please either discuss with the protocol manager or refer to Destruction policies and procedures

4.3 Drug Ordering

Participating sites will obtain nivolumab directly from Bristol-Myers-Squibb as study supply.

Initial Orders

- *Following submission and approval of the required regulatory documents, a supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial. The first request may take place upon screening of the first patient*

- *The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.*

- *Pharmacy supplies that are not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing*

Re-Supply

- *Drug re-supply request form should be submitted electronically business days before the expected delivery date. Deliveries will be made Tuesday through Friday.*

- *When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.*

Drug Excursions

- *Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form*

4.4 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per institutional standards, adhering to applicable local and federal laws.

5 Treatment Plan

5.1 Dosage and Administration

Treatment will be administered on an outpatient basis.

Table 5.1 Regimen Description

Study Drug	Dose	Route	Schedule	Cycle Length
Radiation	2.12 Gy / fraction	External	Daily, Monday-Friday	33 fractions
Cisplatin	40 mg/m^2	Intravenous, over 30-60 minutes	Every 7 days	7 days
Nivolumab	240 mg	Intravenous, over 60 minutes	Every 14 days	14 days

5.1.1 Other Modality(ies) or Procedures

5.1.1.1 Radiation therapy

Radiation therapy of the patients' nasopharyngeal cancer will be carried out in accordance with institutional standard practice and standard-of-care guidelines.

Associated imaging and plans (planning CT and associated RTst and RTDOSE files) should be transmitted in anonymized DICOM format for central archiving. These data must be anonymized and labeled clearly by patient study number prior to transmittal. The data may be transmitted electronically or batch-mailed on a CD-ROM to the attention of the Principal Investigator at the UCSF Department of Radiation Oncology.

Dose Specifications

Treatment will be delivered once daily, 5 fractions per week, over approximately 6 weeks and 3 days. All targets will be treated simultaneously. To treat gross disease, PTV_{6996} (CTV_{6996} + margin) will receive 69.96 Gy in 33 fractions at 2.12 Gy per fraction. The PTV_{5940} (CTV_{5940} + margin) to the high-risk subclinical region will receive 59.4 Gy. The CTV_{5940} typically includes the primary site CTV as well as the neck CTV where there are gross nodes present; typically this CTV would include a 5 mm expansion around any GTV in addition to the high risk areas of the neck, but the expansion from the GTV may be reduced or omitted in cases where a critical structure would exceed tolerance due to the CTV expansion (e.g. the brainstem or optic chiasm or nerve). If the treating physician would like to treat all sites such as primary, upper neck, and lower neck with a single IMRT plan, the low neck which is considered low risk may receive 54.12 Gy at 1.64 Gy per fraction. This is known as PTV_{5412} (CTV_{5412} + margin). However, if there are gross nodes in the low neck, the surrounding subclinical region must receive 59.4 Gy in this case, as it is still considered high risk due to the presence of gross nodes in the same region.

The uninvolved low neck or supraclavicular field also may be treated independent of the IMRT plan with conventional AP or AP/PA fields, with a half-beam block superior to the isocentric junction with the IMRT plan, and will receive 28 fractions of 1.8 Gy/fraction, for a total of 50.4 Gy. If all involved adenopathy is confined only to level 2 of the neck and no lower, the low neck dose may be as low as 45 Gy in 25 fractions of 1.8 Gy/fraction. If using a single AP field, the prescription depth is dependent on the thickness of the low anterior neck, which is typically at a depth of 3 cm. For AP/PA fields, the prescription point will be at midplane for an AP field or midline for AP/PA fields. The investigator should place a midline cord block. However, if there are grossly involved nodes in the low neck, these nodes should receive the same dose as the $PTV_{69.96}$, except for small volume lymph nodes which can be prescribed a total dose of 62.7 Gy (optional $PTV_{62.70}$ to be used at investigator's discretion). Should the treating physician choose to use a low anterior neck field in the presence of gross nodal disease, electrons or photons can be used to boost these nodes.

Description of margin: The PTV volumes consist of a 3 mm expansion from the CTV volumes. However, in cases where a critical structure would exceed tolerance due to the PTV expansion (e.g. the brainstem or optic chiasm or nerve), the PTV expansion can be reduced or omitted for safety, at the treating investigator's discretion.

Technical Specifications

Intensity modulated radiation therapy (IMRT) and image-guidance (IGRT) are mandatory for this study. Megavoltage equipment capable of delivering static-gantry intensity modulation beams with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. Other techniques are acceptable as long as dose specifications and constraints are satisfied. This includes tomotherapy and Volumetric Modulated Arc Therapy (VMAT) techniques.

IGRT specifications

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac
- Linear-accelerator mounted kV and MV helical conebeam CT images
- Linear-accelerator mounted MV CT images (e.g. Tomotherapy)
- Other Mechanism, after discussion with the PI

Required Critical Normal Tissue Constraints

	Per protocol	Acceptable	Unacceptable
Maximum dose to 0.03 cc of BrainStem	54 Gy	54-60 Gy	>60 Gy
Maximum dose to 0.03 cc of Spinal Cord	≤45 Gy	45-50 Gy	>50 Gy
Maximum dose to 0.03 cc of Optic Nerves and Chiasm	≤54 Gy	54-56 Gy	>56 Gy

Maximum dose to 0.03 cc of Mandible and TM joint	≤70 Gy	70-75 Gy	>75 Gy
Maximum dose to 0.03 cc of one Temporal Lobe	≤70 Gy	70-72 Gy	>72 Gy
Mean dose to one of Parotid glands	≤26 Gy	26.1-33 Gy	>33 Gy

Recommended dose constraints for other normal tissues

Oral cavity (excluding PTV's)	Mean dose less than 40 Gy
Each cochlea	Maximum dose less than 55 Gy
Eyes	Max dose less than 55 Gy
Lens	Max dose less than 15 Gy
Glottic Larynx	Mean dose less than 40 Gy
Esophagus, Postcricoid pharynx	Mean dose less than 50 Gy
Brachial plexus	Mean dose less than 66 Gy

5.1.1.2 Cisplatin chemotherapy

Weekly cisplatin chemotherapy will be delivered in accordance with institutional standard practice and standard-of-care guidelines.

Cisplatin: 40 mg/m^2/day, weekly during radiation

No concurrent cisplatin will be administered after the final week of radiation, but the final dose of cisplatin may be administered following the last dose of radiation if it is administered within the same calendar week. **Cisplatin should be ideally be administered on Mondays or Tuesdays to maximize overlap of daily radiation with cisplatin exposure**. Administration on Wednesday or Thursday concurrent with that day's radiation dose is acceptable. Investigators should strive to administer cisplatin on the same day each week but variance of 1 day is acceptable for vacations, holidays, etc. If radiation treatments are held for toxicity, cisplatin dosing should also be held.

Guidelines for Administration of Cisplatin Concurrent with Radiation

Many institutions will have standard guidelines for the administration of cisplatin at the doses used in this study. **For purposes of this protocol, individual investigators may use these local guidelines for cisplatin administration. One possible approach is outlined below.** This may need to be modified based on local guidelines and patient related factors (e.g. the substitution of normal saline in diabetic patients). Similarly, the anti-emetic regimen for this combination is to be determined by the local investigator.

- *Low-dose Cisplatin anti-emetic administration guidelines*: 5-HT3 antagonists (e.g. ondansetron 16 mg PO prior to cisplatin and 8 mg PO up to 3 times daily on days 2 and 3 following cisplatin weekly. Use of other anti-nausea meds such as fosaprepitant or aprepitant (these are strongly encouraged), lorazepam, metoclopramide, or prochlorperazine is left to the discretion of the investigator.

- Use of dexamethasone or other corticosteroids are highly discouraged but may be used at investigator's discretion for unusual conditions such as highly refractory nausea unresponsive to above-listed interventions, immune-treatment-related toxicity requiring steroids for management, or airway compromise or other emergent conditions.

- *Low-dose Cisplatin pre-hydration guidelines*: Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin. Mannitol 12.5 gm IV immediately prior to cisplatin.

- *Cisplatin administration*: Cisplatin, 40 mg/m2 over 30-60 minutes IV in 250 cc NS. See above discussion on scheduling and number of doses concurrent with radiation.

- *Cisplatin post-hydration guidelines*: Following the end of the cisplatin administration, an additional liter of ½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol is infused over 2 hours. On the second and third day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS.

5.2 Dose Modifications and Dosing Delays

5.2.1 Dose Delays of Nivolumab

No dose escalation or dose reduction of nivolumab from the patient's starting dose is allowed. Dose delays are allowed for an individual patient at the investigator's discretion to allow for resolution of toxicities as described below.

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.

Specific management algorithms for immune-related toxicities are given in Appendix

5 and should be referenced in case of any immune-related AE.

If dosing with study drug is delayed for > 28 consecutive days due to toxicity, protocol therapy should be discontinued unless otherwise agreed between the investigators and Principal Investigator.

For patients expected to 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 or visit delays for public holidays or weather conditions do not constitute a protocol violation.

The following dose delay rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v5.0).

Nivolumab administration should be delayed for CTCAE v5.0 toxicities as indicated in the tables below that in the opinion of the treating physician are **related to the study drug**.

Dosing Delays for General and Immune-Related Adverse Events

Algorithms in tables which follow and Appendix 5 should be consulted for specific immune-related AEs and followed preferentially rather than this general guideline.

Grade of Event	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 Resume at same dose schedule when toxicity ≤ Grade 1
Grade 3	Hold* until ≤ Grade 2 Resume at same dose schedule when toxicity ≤ Grade 2
Grade 4	Off protocol therapy

*Patients requiring a delay of > 28 days should go off protocol therapy

Please note nivolumab therapy will not be delayed for the following:

- Grade 2 weight loss;
- Grade 2 or 3 nausea that in the opinion of the investigator is related to cisplatin;
- Grade 3 radiation dermatitis;
- Any Grade 2-3 mucositis, dysphasia, or pharyngolaryngeal pain that in the opinion of the treating physician is related to radiation therapy for head and neck cancer;
- Grade 2 hypokalemia or hypomagnesemia that in the opinion of the investigator is related to cisplatin;
- Grade 2 or greater hearing impairment that in the opinion of the treating physician is related to cisplatin;
- Grade 3 or 4 isolated lymphopenia;
- Grade 3 isolated anemia if, in the opinion of the treating physician, the anemia is not related to the study drug (e.g. related to chronic disease, iron deficiency, radiotherapy).

Skin Rash and Oral Lesions	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose*

Grade 2	No change in dose; see guidelines for management in Appendix 5.
Grade 3	Hold* until ≤ Grade 1; see guidelines for management in Appendix 5. Resume at same level at investigator discretion
Grade 4	Off protocol therapy

*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphagoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.

Liver Function AST/ALT/T. Bili *	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change.
Grade 2	Hold until UNL or baseline. Resume at same dose schedule; see guidelines for management in Appendix 5.
Grade 3	Off protocol therapy; see guidelines for management in Appendix 5.
Grade 4	Off protocol therapy see guidelines for management in Appendix 5.

Continued treatment of active immune-mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.

Renal Function Serum Creatinine	**Management/Next Dose for Nivolumab**
≤ Grade 1	Continue treatment.
Grade 2	Hold until UNL or baseline. Resume at same dose schedule; see guidelines for management in Appendix 5.
Grade 3	Hold until UNL or baseline. Resume at same dose schedule; see guidelines for management in Appendix 5.
Grade 4	Off protocol therapy

For Grade 2 or greater, consider renal biopsy.

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose; see guidelines for management in Appendix 5.
Grade 2	Hold until Grade 0 or baseline; see guidelines for management in Appendix 5.
Grade 3	Off protocol therapy; see guidelines for management in Appendix 5.
Grade 4	Off protocol therapy; see guidelines for management in Appendix 5.

See GI AE Algorithm for management of symptomatic colitis (in IB).
Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution.
Patients with persistent symptoms greater than 14 days who require steroids should be taken off study treatment.
Please evaluate pituitary function prior to starting steroids if possible without compromising acute care.
Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold dose until grade 0.

Grade 2	Hold until Grade 0. Resume at same dose schedule if asymptomatic.
Grade 3	Hold* until Grade 0. Resume at same dose schedule if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment.*
*Grade 4	Off protocol therapy

Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur during the period of steroid withdrawal and with other immune-mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated.
For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm (in Appendix 5).
*Excluding asymptomatic amylase and lipase increases

Pneumonitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold dose pending evaluation and resolution to ≤ Grade 0 or baseline including baseline pO2. Resume no change in dose after pulmonary and/or ID consultation.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation if lymphocytic pneumonitis is excluded. Off study if grade 2 symptoms do not improve or worsen after 2 weeks of steroids and dose delay; see guidelines for management in Appendix 5.
Grade 3	Off protocol therapy; see guidelines for management in Appendix 5.
Grade 4	Off protocol therapy; see guidelines for management in Appendix 5.

Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.

Other GI N-V	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose schedule after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose schedule. If symptoms do not resolve within 7 days

	with symptomatic treatment patients should go off protocol therapy.
Grade 4	Off protocol therapy.

Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.

Fatigue	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose.
Grade 2	No change in dose.
Grade 3	Hold until ≤ Grade 2. Resume at same dose schedule.

Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation.

Neurologic events	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose.
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1; see guidelines for management in Appendix 5. Resume at same dose schedule for peripheral isolated n. VII (Bell's palsy); see guidelines for management in Appendix 5.
Grade 3	Off protocol therapy; see guidelines for management in Appendix 5.
Grade 4	Off protocol therapy; see guidelines for management in Appendix 5.

*Patients with any CNS events including aseptic meningitis, encephalitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be off study.

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab**

Discontinue protocol therapy for grade 4 hypophysitis and grade 3 or greater adrenal insufficiency. Note that protocol-specific actions and management are not strictly by CTCAE grade; see guidelines for management in Appendix 5 for recommendations on I-O therapy and management of adverse events.

Fever	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold until ≤ Grade 1. Resume at same dose schedule.
Grade 2	Hold until ≤ Grade 1. Resume at same dose schedule.
Grade 3	Hold until ≤ Grade 1. Resume at same dose schedule.
Grade 4	Off treatment

Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever **See detailed section below with instructions for management of infusion reactions.**

ALL OTHER EVENTS	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline.** When resolved or following steroids, resume at same dose schedule.
Grade 3	Any grade 2 or 3 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 requires treatment discontinuation. Any other immune-related grade 3 toxicity not covered in the tables above would require that the patient go off protocol therapy with the following exceptions: • Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, not associated with underlying organ pathology, that does not require treatment except for electrolyte replacement OR hormone/steroid replacement **does not** require treatment discontinuation.
Grade 4	Off protocol therapy (except for drug-related laboratory abnormality or electrolyte abnormality, not associated with underlying organ pathology, that does not require treatment except for electrolyte replacement OR hormone/steroid replacement does not require treatment discontinuation).

** Immunologically mediated

Criteria to Resume Nivolumab

Patients may resume treatment with nivolumab when the drug-related AE(s) resolve to the grade specified in the tables above and as detailed in Appendix 5.

If the criteria to resume treatment are met, the patient should restart treatment at the next scheduled time point (two-week interval) per the protocol.

Discontinuation Criteria

Treatment with nivolumab should be permanently discontinued as specified in the tables above and guidelines for management in Appendix 5. Additional criteria for discontinuation include:

- 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;
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation;
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation;
- Any Grade 4 drug-related adverse event or laboratory abnormality, with the exception of those noted below:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset;
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
    - Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality not associated with underlying organ pathology that does not require treatment except for electrolyte replacement OR hormone/steroid replacement **does not** require treatment discontinuation.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing;
- A delay in nivolumab treatment of 28 days.

Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, 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 CTCAE v5.0 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 patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms (Moderate reaction requires therapy or infusion interruption but

responds promptly to symptomatic treatment [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours): Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor patient 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 patient 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 patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated): Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the patient 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. Patient 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 patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

5.2.2 Cisplatin (CDDP) Dose Modifications During Concurrent Radiation

Patients will be examined and graded for subjective/objective evidence of developing toxicity weekly according to CTCAE v5.0 while receiving concurrent cisplatin with radiotherapy.

Treatment interruptions are allowed if there is symptomatic mucositis or skin reaction that, in the judgment of the clinician, warrants a break. For chemotherapy attributable AEs requiring a break in treatment, resumption of concurrent CDDP may begin when AEs have recovered to the levels specified below. If an AE does not resolve to the levels specified in the sections below prior to the calendar week of the last radiation treatment, treatment off protocol can continue according to the judgment of the treating physician.

There will be no dose re-escalation for concurrent cisplatin. If a patient requires >2 dose reductions then the patient should discontinue protocol therapy. For Grade 4 toxicity, protocol therapy is discontinued. If dosing with study drug is interrupted for > 28 consecutive days due to toxicity, protocol therapy should be discontinued unless otherwise agreed between the

investigators before reintroduction of study drug.

Chemotherapy dosage modifications are based upon lab values obtained within the 24 hours prior to cisplatin and interim non-hematologic toxicities during the week prior to a particular cisplatin dose.

The dose modifications for cisplatin (below) are intended to be permanent (i.e., if the patient's dose is reduced to dose level -1, it remains at the reduced dose level) unless adverse events (AEs) are ongoing requiring further reduction.

Cisplatin Dose Modifications for Hematologic Adverse Events during Concurrent Radiation

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

Chemotherapy must not be administered until the ANC is ≥ 1,000 and platelets are ≥ 75,000. If not, delay 7 days. Cisplatin should be held every week until the above ANC and platelet parameters are met. Dose reductions when cisplatin is resumed after delay for low ANC or platelets will be as follows, based upon counts at time cisplatin was held.

ANC		**Platelets**	**Reduction**
≥ 1000 mm^3	and	≥ 75,000	None
< 1000 mm3	or	< 75,000	One dose level

Note: **Hematologic growth factors for neutropenia or anemia are not allowed during concurrent cisplatin and radiation treatment.**

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

Neutropenic Fever: If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200, hold treatment until ANC ≥ 1200, then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction. Febrile neutropenia is fever of unknown origin without clinically or microbiologically documented infection; ANC < 1.0 x 10e9L, fever > 38.5°C.

Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is < 75,000, hold treatment until platelets are > 75,000, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a 25% dose reduction.

Renal Adverse Events: Cisplatin should be administered on the scheduled day of treatment using the following guidelines:

Note: If creatinine is > 1.2 mg/dl, clearance must be done in order to make dose adjustment. If the calculated nomogram is 50 mL/min or above, a 24-hour urine collection is not needed, but if the nomogram calculation is less than 50 mL/min, a 24-hour urine collection is mandated.

Once the creatinine has met the above parameters, cisplatin may be restarted with the modifications below, based on the creatinine at the time the cisplatin was held: In general, cisplatin should be held for weekly intervals (rather than restarting cisplatin later in the same week that a dose limiting AE is seen).

Cisplatin dose modifications for creatinine during concurrent radiation			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction
≤ 1.2	or	> 50	100%
> 1.2	and	40-50	50%
		< 40	Discontinue drug

Neurologic (neuropathy) adverse events: If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin.

Grade (CTCAE v5.0)	**Dose Reduction**
0-1	None
2	One dose level
3-4	Discontinue drug

Ototoxicity: For new clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living, treat at 50% dose reduction. For hearing loss requiring a hearing aid, discontinue cisplatin. Continue radiation. If the physician is unsure about the severity of the hearing loss, an audiogram is encouraged.

All Other Non-Hematologic Adverse Events Attributable to Cisplatin during Concurrent Radiation: For all other non-hematologic adverse events in which toxicity is ≥ grade 2 (CTCAE v5.0), investigators are advised to evaluate and manage correctable issues promptly to prevent worsening of toxicity. For these events in which toxicity is ≥ grade 3, investigators should hold cisplatin, with weekly re-evaluation until AE grade falls to 0-1, then restart cisplatin at one lower dose level.

Note: Grade 3 mucositis is commonly experienced by head and neck cancer patients; the investigator generally would not hold the cisplatin dosing in this case, unless there is unusual concern for progression to grade 4 mucositis. Grade 4 mucositis will require a cisplatin dose reduction.

If a weight change of ≥ 10% occurs, the cisplatin dose should be adjusted.

5.3 Monitoring and Toxicity Management

Each patient receiving nivolumab will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity. Toxicity will be assessed according to the NCI CTCAE v5.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

Management of any grade 3 or higher toxicity should be discussed with the PI of the study.

5.4 Permitted Concomitant Therapy Requiring Caution and/or Action

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 30 days before the first dose of study treatment through 30 days after the date of the last dose of study treatment are to be recorded in the case report forms.

- Antiemetics and antidiarrheal medications are allowed in accordance to standard clinical practice if clinically indicated;

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are generally not to be used in this protocol. Note that hematologic growth factors are not allowed during concurrent cisplatin and radiation treatment. If hematologic growth factors must be used outside of the radiation phase of treatment, they should be used per clinical guidelines (eg, American Society of Clinical Oncology [ASCO] or [European Society for Medical Oncology] ESMO guidelines);

- Transfusions, hormone replacement, and short term higher doses of corticosteroids should be utilized as indicated by standard clinical practice

5.5 Prohibited Concomitant Therapy

The following medications are prohibited during the treatment and follow-up phases (before recurrence) of the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.4)
- Any concurrent anti-neoplastic therapy (including, but not limited to chemotherapy, hormonal therapy, immunotherapy, or radiation therapy), other than those allowed in the protocol.

5.5.1 Other Anticancer or Investigational Therapies

No other anti-cancer therapies (including non-platinum chemotherapy, radiation, hormonal treatment [except Corticosteroids, bisphosphonates, or denosumab], antibody or other immunotherapy or other experimental drugs) of any kind will be permitted while the patient is participating in the study.

Patients experiencing unacceptable toxicity due to cisplatin may be switched to carboplatin by the treating physician after consulting with the Study Chair. Carboplatin should be administered weekly at AUC 2, further modifications to the regimen should be discussed with the study chair.

5.5.2 Hormonal Contraception Allowed/Excluded

The use of oral contraceptives is allowed during the study.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Section 6 Schedule of Study Procedures and Assessments. Screening assessments must be performed within 30 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ± 3 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.1.1 Pretreatment Period

During the Pre-Treatment Period, subjects are consented and qualified (screened) for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/ethics committee (EC) policies.

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening and on Study Day 1 before study treatment administration. The following assessments will be conducted before subjects receiving their first dose of nivolumab on this protocol:

6.1.1.1 Screening Assessments

Patients will undergo screening assessments within 30 days before receiving the first dose of nivolumab, unless otherwise noted. Study procedure-related AEs that occur after signing of the

Informed Consent Form (ICF) and before administration of nivolumab will also be collected.

The Screening procedures and assessments must be completed within 30 days prior to the Cycle 1 Day 1 Visit, unless otherwise noted.

- Physical examination
- Weight
- Vital signs
- Complete medical history
- Baseline conditions assessment
- Disease Assessment
- ECOG Performance status
- History of prior treatments and any residual toxicity relating to prior treatment
- Concomitant medications and procedures
- Biopsy or archived tissue procurement
    - Archived tissue: If no intervening treatment received, adequate tissue available, and performed within 90 days of day 1 (cycle 1 day 1) of study treatment; otherwise, fresh biopsy required. See Appendix 4.
- Complete blood count (CBC) with differential and platelet count (within 14 days of Cycle 1 Day 1)
- Serum chemistry assessment (within 14 days of Cycle 1 Day 1), including:
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, total protein, albumin, calcium, phosphorus, magnesium, blood urea nitrogen (BUN), creatinine, glucose (fasting), potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides).
- Serum or urine pregnancy test within 7 days prior to the start of study drug in pre-menopausal females.
- TSH evaluation (within 14 days of Cycle 1 Day 1)
- Urinalysis (within 14 days of Cycle 1 Day 1)
- MRI of nasopharynx, face, and neck within 60 days prior to start of study drug.
- Whole body PET-CT of top of head to mid-thigh (preferred) or CT of chest, abdomen, and pelvis within 60 days prior to the start of study drug.
- Research blood draw: collection of peripheral blood for EBV DNA and correlative biomarker studies.
- All blood draws may be done within 7 days prior to start of therapy unless otherwise specified.
- Contraceptive counseling
- Serum pregnancy test (by local laboratory) ≤ 1 days prior to the first day of dosing for women of childbearing potential. If the serum pregnancy test results are not available on C1D1, a urine pregnancy test can be performed on C1D1 to confirm that the patient is not pregnant prior to dosing.
- Baseline quality of life assessments

For each subject, the Pre-Treatment Period ends upon receipt of the first dose of study treatment or final determination that the subject is ineligible for the study.

The following assessments are not required but highly recommended:

- Audiogram;
- Speech and swallowing consultation with formal assessment by modified barium swallow;
- Dental evaluation and counseling in preparation for radiation therapy;
- Nutritional evaluation

6.1.2 Treatment Period

During the Treatment Period subjects will receive nivolumab until the period of adjuvant therapy is complete, disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) such as subject withdrawal. Subjects should be instructed to immediately inform the principal investigator (PI) of any AEs. Patients will be monitored for AEs from the time the first dose of nivolumab is administered through 30 days after the last dose.

Nivolumab will be administered to patients every 2 weeks through the intravenous route. Each 14-day period of treatment represents 1 cycle, with dosing initiated on C1D1. No dose escalation beyond the starting dose is allowed.

Patients will undergo serial assessments for anti-tumor efficacy and drug safety. Tumor samples will be collected at baseline and after the first cycle of nivolumab at the investigator's discretion. Serial blood sampling will be conducted for longitudinal immunologic assessment (see Appendix 4). Radiologic scans will be acquired by the investigative site and evaluated locally for patient treatment decisions. Patients will be followed with monthly clinical and laboratory assessments while on protocol-mandated treatment, as well as routine physical examinations every 3 months and scans at the end of treatment and 12 months to assess for disease status for a 1 year period following completion of all treatment.

6.1.2.1 Study Procedures

Table 6.1 summarizes the procedures and assessments to be performed for all patients. Before enrolling a patient, all eligibility criteria must be satisfied.

- Physical examination
- Weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Disease Assessment
- Concomitant medications and procedures
- Serum chemistry
- Complete blood count (CBC) with differential and platelet count
- Research tissue procurement: collection of biopsy tissue from accessible sites (see schedule)
- Research blood draw: collection of peripheral blood for EBV DNA and correlative biomarker studies (see schedule)
- AE monitoring
- TSH evaluation
- Quality of life assessments (see schedule)
- Administration of intravenous (IV) nivolumab
    - 72-hour window of scheduled nivolumab administration allowed

Study visits will be required on the first day of each cycle.

6.1.3 End-of-Treatment Study Procedures

After having received the last dose of nivolumab on this study, all patients will remain in the study to be followed for safety until the EOT Visit. The EOT Visit should occur 28 (± 7) days after the last dose of nivolumab. Patients with ongoing SAEs will be followed until either resolution or stabilization of the event(s) has been determined. Please see Table 6.1 for details of assessments.

- Physical examination
- Weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Disease Assessment
- Concomitant medications and procedures
- Serum chemistry
- Fasting glucose
- Complete blood count (CBC) with differential and platelet count
- MRI of nasopharynx, face, and neck.
- Whole body PET-CT (top of head to mid-thigh).
- Blood sampling for EBV DNA and exploratory research (see schedule)
- AE monitoring
- Quality of life assessments (see schedule)
- TSH evaluation
- Measurable Disease

6.1.4 Post-treatment/Follow-Up Visits

After completion of all treatment, patients will be followed at 1, 3, 6, and 12 months +/- 1 week for up to 1 year or until disease progression. Please see Table 6.1 for details of assessment.

- Physical examination
- Weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Concomitant medications and procedures
- Serum chemistry
- Fasting glucose
- Complete blood count (CBC) with differential and platelet count
- MRI of nasopharynx, face, and neck, if applicable (see schedule)
- Whole body PET-CT (top of head to mid-thigh), if applicable (see schedule)
- Blood sampling for EBV DNA and exploratory research, if applicable (see schedule)
- AE monitoring
- Quality of life assessments, if applicable (see schedule)
- TSH evaluation

6.1.5 Long Term/Survival Follow-up Procedures

Survival follow-up information may be collected via telephone calls or medical records review for an additional 4 years. Survival and disease status will be collected during this period until participant death, withdrawal, or if the participant is lost to follow-up. .

6.1.6 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

Table 6.1 Schedule of Study Procedures and Assessments

Table 6.1 Schedule of Procedures and Assessments						
Test/study	**Screening**	**Cycle 1 to Cycle 5[a]**	**Cycle 6[f] and future cycles**	**End of Treatment[s]**	**Follow-up visits[t]**	**Survival Follow-up[v]**
	Day -30 to -1	**Day 1 (+/- 3)**	**Day 1 (+/- 3)**	**28 days (+/- 7) after last dose**	**12 month Follow-up**	**48 Month Follow-up**
Informed consent	X					
Baseline conditions[b]	X					
Quality of life assessments[c]	X		X	X	X	
AE assessment[d]		X	X	X	X	X[v]
Concomitant medications and procedures	X	X	X	X	X	
Treatment/Drug Administration[f]						
Nivolumab		X	X			
Radiation therapy		X				
Cisplatin		X				
Clinical procedures[g]						
Physical exam[h]	X	X	X	X	X	
Vital signs	X	X	X	X	X	
Medical history	X	X				
Disease assessment[i]	X	X		X	X	
ECOG	X	X	X	X	X	
Measurable disease[j]	X	X		X	X	
Biopsy or archived tissue procurement[k]	X	X				
Laboratory procedures[l]						
CBC w/ Diff[m]	X	X[u]	X	X	X	
Blood chemistry[n]	X	X[u]	X	X	X	
Fasting Glucose[n]	X	X[u]	X	X	X	
TSH evaluation[n]	X	X[u]	X	X	X	
Urinalysis[n]	X					
Pregnancy test (Serum or urine HCG)[o]	X					
Tissue for exploratory research[p]	X	X				

Table 6.1 Schedule of Study Procedures and Assessments

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Test/study	**Screening**	**Cycle 1 to Cycle 5[a]**	**Cycle 6[f] and future cycles**	**End of Treatment[s]**	**Follow-up visits[t]**	**Survival Follow-up[v]**
	Day -30 to -1	**Day 1 (+/- 3)**	**Day 1 (+/- 3)**	**28 days (+/- 7) after last dose**	**12 month Follow-up**	**48 Month Follow-up**
Blood for exploratory research[q]	X	X	X	X	X	
Imaging procedures[r]						
Whole body PET-CT[r]	X			X	X	
MRI[r] nasopharynx/face/neck	X			X	X	

[a] Each 14-day period of treatment will represent 1 cycle and begins from C1D1.
[b] Baseline conditions assessment
[c] As part of efficacy assessments, quality of life by FACT-NP, FACT-Taxane, HHIE-S, and EuroQOL EQ-5D will be administered at baseline, at cycle 6, at end of treatment and at all followup visits. Survey's not available in the patient's language may be administered by the study staff in an interview format with a translator, however failure to obtain any individual quality of life survey not available in the patient's language will not be considered a protocol deviation.
[d] Toxicity will be assessed by CTCAE v5.0
[f] There is a 72 hour window of scheduled nivolumab administration. **In Dose Schedule 1**: Nivolumab will be administered on C1D1 for priming and then q14 days beginning C2D1, concurrent with chemoradiation, until C5D1. Nivolumab will not be administered on C6D1 to allow for any resolution of toxicities. Beginning C7D1, adjuvant nivolumab q14 days will be administered until C12D1. **In Dose Schedule 2:** Nivolumab will be administered on C1D1 concurrent with chemoradiation (no priming), and then q14 days until C4D1. Nivolumab will not be administered on C5D1 to allow for any resolution of toxicities. Beginning C6D1, adjuvant nivolumab q14 days will be administered until C11D1. **In Dose Schedule 3:** Nivolumab will not be administered until after completion of chemoradiation. Beginning C6D1, adjuvant nivolumab q14 days will be administered until C11D1. Immune-related toxicities should be at grade 1 or lower prior to starting a patient on the adjuvant phase of therapy; if not, initiation of the adjuvant phase should be delayed until resolution of toxicities.
[h] Physical Exam includes weight measurements
[i] Disease-specific criteria (for CRF purposes, e.g.: GU assessment, BR disease Eval, AML-MDS Summary, etc.)
[j] Measurable disease will be assessed using RECIST 1.1 criteria
[k] For the **baseline** tissue collection, if a biopsy was performed within 90 days prior to C1D1, and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided. **Repeat biopsy** will be at the discretion of the investigator, and timing will depend on Dose Schedule. **In Dose Schedule 1:** Tumor tissue post-nivolumab during cycle 1 AND after first week of radiation therapy. **In Dose Schedule 2 and 3:** Tumor tissue after first week of radiation therapy only. See appendix 4 for further details.
[l] All blood draws may be completed within 7 days prior to start of therapy unless otherwise specified; screening labs must be completed within 14 days of Cycle 1 Day 1.
[m] Hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential
[n] Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, total protein, albumin, calcium, phosphorus, magnesium, blood urea nitrogen (BUN), creatinine, glucose fasting), potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides), thyroid stimulating hormone (TSH).
[o] **Pre-menopausal females**: serum or urine pregnancy test within 7 days prior to start of study drug. Serum pregnancy test by local laboratory ≤ 1day prior to C1D1 for women of childbearing potential. If the serum pregnancy test results are not available on C1D1, a urine pregnancy test can be performed on C1D1 to confirm that the patient is not pregnant prior to dosing.
[p] See Appendix 4 for details on tissue specimen collection and processing.
[q] Collection of peripheral blood for correlative biomarkers and peripheral immune changes must be collected with every cycle of nivolumab. Blood will also be collected in post-treatment followup to 1 year.
[r] Imaging with MRI nasopharynx/face/neck and whole body PET-CT will be performed at screening and at end of treatment and at 1 year followup, with further imaging to be performed as clinically indicated.

- If a whole body PET-CT (top of head to mid-thigh) scan (preferred) or a CT of the chest, abdomen, and pelvis was performed within 60 days prior to C1D1, then a repeat scan is not required provided the images are adequate for analysis. PET-CT is required after protocol treatment completion.

- MRI scan of nasopharynx/face/neck required within 60 days prior to C1D1 and after protocol treatment completion.

[s]All patients to be followed for safety until the EOT visit. This visit should occur 28 (+/-7) days after the last dose of nivolumab. Patients with ongoing SAEs will be followed until either resolution or stabilization of the event(s) have been determined.

[t] After completion of all treatment, patient will be followed at 1, 3, 6, 9 and 12 months +/- 1 week for up to 1 year.

[u] Fasting lipid panel and TSH blood tests will not be performed on day 8. Only CBC with differential and blood chemistry tests including non-fasting glucose are required on day 8 of Cycles 2, 3, and 4.

[v] Survival follow-up information may be collected via telephone calls, and/or review of the medical record, every 3 months for an additional 4 years. Survival and disease status will be collected until participant death, withdrawal, or if the participant is lost to follow-up.

6.2 Prohibited Medications

Permitted Therapy

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

Intravitreal injections of vascular endothelial growth (VEGF) inhibitors are permitted if used according to the approved ocular indication, such as macular degeneration.

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy (or Activity)

7.1.1 Antitumor Effect – Solid Tumors

A secondary measure of response to neoadjuvant therapy in this study will be determined by RECIST 1.1 criteria according to the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria (or International Workshop on Chronic Lymphocytic Leukemia [IWCLL]). RECIST 1.1 will also be used to determine whether the patient has progressive disease in the adjuvant portion and follow-up portion of the study in accordance with standard of care practices.

7.1.2 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

7.1.2.1 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Bone lesions may be measureable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease (Tumor Markers)

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by e.g. PSA, CA-125, CA19-9, CEA)

7.1.2.2 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

PET-CT

PET-CTs for a given patient should be performed at the same institution and on the same scanner if possible. Patient should fast for at least 6 hours before undergoing scanning and measured serum glucose must be < 200 mg/dL. Patients can be on oral hypoglycemic but not insulin. PET should be obtained 50-70 minutes after tracer injection. The same amount of radioactivity +/- 20% should be injected for a given patient pre- and post- nivolumab treatment.

Conventional CT

CTs should be performed with cuts of 10 mm or less in slice thickness contiguously.

Cytology, Histology

Any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease or progressive disease.

7.1.2.3 Response Criteria

Objective Response

Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD)

At least a 20% increase in the sum of the SLD of target lesions, taking as reference the smallest sum SLD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of one or more new lesions.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR)

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

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response (BOR)

The best overall response is the best response recorded from the first day of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 7.2 Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	> 4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	> 4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once > 4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

Duration of Response

Duration of overall response

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

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

Duration of stable disease

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

Metabolic Response

Summarized in Table 7.1 and in reference[36].

7.2 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v5.0 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events.

For multicenter studies, the Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g.,

an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.3.2.3 Serious

- An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life function
- Is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Note: The following hospitalizations are not considered SAEs in BMS clinical studies:

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

<u>Potential Drug Induced Liver Injury (DILI)</u>

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:

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

7.3.2.4 Life-threatening

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

7.4 Recording of an Adverse Event

Grade 1-5 adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v5.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

NONSERIOUS ADVERSE EVENT

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

- Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

Nonserious Adverse Event Collection and Reporting

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

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

Laboratory Test Abnormalities

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

The following laboratory abnormalities should be documented and reported appropriately:

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

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

- any laboratory abnormality that required the subject to receive specific corrective therapy.

Pregnancy

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

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

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]

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

Overdose

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

Other Safety Considerations

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

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.6 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board (IRB) and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Phase 2 or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center please refer Appendix 4 Multicenter Institutional Studies.

7.7 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Institutional Review Board

The Principal Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

Suspected adverse reaction (as defined in 7.3)

Unexpected (as defined in 7.3)

Serious (as defined in 7.3)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

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
[redacted]
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
[redacted]

Reporting to Pharmaceutical Companies providing Study Drug

All 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 on a Pregnancy Surveillance Form.

SAE Email Address: [redacted]

SAE Facsimile Number: [redacted]

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

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

All SAEs should be followed to resolution or stabilization.

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

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

8.1.1 Primary Endpoint:

The primary objective of this study is to establish the feasibility of completing a combined chemoradiation-nivolumab regimen followed by adjuvant nivolumab. Feasibility of completing adjuvant phase therapy is a key relevant clinical question in ongoing NPC research, as the efficacy of the current standard of care of platinum-based concurrent and adjuvant phase chemotherapy is in question but its toxic effects are severe, resulting in frequent early discontinuation of adjuvant therapy. Adjuvant nivolumab is likely to be much more tolerable and feasible and if feasibility of the program is established, this will open the possibility of testing its efficacy in various subsets of patients.

Feasibility of treatment completion: The primary endpoint of the study will be the rate of completion of all adjuvant immunotherapy, in comparison to the rate of completion of a standard adjuvant cisplatin-based platform. The rate of completion of all adjuvant therapy by patients treated at the MTD schedule will be determined and compared to a historical control rate of 52%.

8.1.2 Secondary Endpoints

Efficacy: ORR as assessed by the study investigator by RECIST 1.1 criteria. The ORR is defined as the best overall response (BOR) recorded from the first day of treatment until time of assessment.

Safety and tolerability: Evaluate the number and frequency of Adverse Events (AEs) as determined by National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0 by investigator assessment.

- To determine the clinical response as judged by the investigator;
- To determine the overall response rate from the first day of treatment to 1 year post-treatment, as determined by RECIST 1.1 criteria;
- To determine the locoregional control rate at 1 year post-treatment;
- To determine the distant metastasis rate at 1 year post-treatment;
- ;
- To determine the rate of EBV DNA clearance at end of chemoradiation and at 1 year post-treatment;
  To determine the acute and late toxicity rates according to CTCAE v5.0, including immune-related adverse events (AEs);
- To assess patients' quality of life from baseline through 1 year post-treatment;

8.1.3 Correlative Studies

Exploratory studies

- To determine the overall survival rate at 5 year post-treatment

When adequate tissue is available, To determine whether PDL1-positive immunohistochemistry and novel quantitative assays correlate to clinical outcome;

- To determine if the density of infiltrating CD3+ T cells/μm2 correlates to clinical outcome;
- To monitor immune changes by flow cytometry in the circulating T cell response to EBV antigens;
- To compare the change in the circulating T-cell repertoire by TCR sequencing and single-cell T-cell profiling;
- To quantify treatment-induced changes over time in the circulating T cell immune response to EBV using TCR sequencing and enzyme-linked immunospot (ELISPOT) assays**.**

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

We expect the true completion rate of this combined chemoradiation-nivolumab regimen followed by adjuvant nivolumab to be 70%, versus the null hypothesis of 50% (the rate of completion of a standard adjuvant cisplatin-based platform is 52%).

Simon's two-stage design will be used to test this endpoint. In the first stage, 22 patients will be accrued. If 11 or fewer completions, the study will be stopped. Otherwise, 18 additional patients will be accrued for a total of 40 participants.. The null hypothesis will be rejected if 26 or more completions are observed in 40 patients. This design yields a type I error rate of 0.05 and power of 80% when the true completion rate is 0.7.

8.2.2 Run-in phase

Six patients will be enrolled for the initial run-in phase, with nivolumab dosing of 240 mg. Enrollment will cease until all 6 patients have completed concurrent chemoradiation and nivolumab. If 3 or more of the first 6 patients experience grade 3-4 immune related toxicity or other DLT during concurrent chemoradiation and nivolumab therapy, then the run-in will restart at dose schedule 2 with 6 additional patients. In dose schedule 2, patients will start nivolumab

concurrent with chemoradiation and will not start nivolumab prior to chemoradiation. If 3 or more of the first 6 patients experience grade 3-4 immune related toxicity or other DLT during concurrent chemoradiation and nivolumab at dose schedule 2, then the dose schedule will be changed to dose schedule 3 and the run-in will restart at dose schedule 3 with 6 additional patients. In dose schedule 3, patients will start nivolumab in the adjuvant phase only and will not receive nivolumab before or during chemoradiation, and the toxicity of nivolumab will be assessed during the adjuvant phase. No dose escalation or reduction will be allowed in the run-in phase. Dose modifications of nivolumab are not permitted from the standard dose of 240 mg every 14 days.

The run-in will cease when 4 or more patients have completed chemoradiation and nivolumab therapy at the same nivolumab dose schedule without experiencing grade 3-4 toxicity or other DLT (this will be considered the maximally tolerated dose), or alternatively, if 3/6 patients have experienced grade 3-4 toxicity at dose schedule 3 during administration of adjuvant nivolumab (in which case the entire study will terminate). Therefore, a minimum of 6 patients and a maximum of 18 patients will be enrolled in the run-in phase.

DLT criteria are grade ≥3 immune-related adverse events, need to hold nivolumab for >28 days due to toxicity, and for patients receiving concurrent nivolumab with chemoradiation, inability to complete chemoradiation or need to hold chemoradiation for >3 days due to immune-related toxicity.

8.2.3 Expansion phase

Sample size for the expansion cohort will be a minimum of 9 patients and a maximum of 22 patients (Simon's two-stage design, see statistical plan).

The 6 patients treated at the final dose from the run-in cohort will be included in statistical comparisons. This would yield a minimum total sample size of 15 patients, and a maximum sample size of 28 patients treated at the MTD schedule across the run-in and expansion phases, assuming 6 patients treated at the MTD schedule in the run-in and 22 patients treated at MTD schedule in the expansion cohort.)

The rate of completion of all adjuvant therapy by patients treated at the MTD schedule will be determined and compared to a historical control rate of 52%.

8.2.4 Statistical plan

Simon's two-stage design[37] will be used to test the primary endpoint for the phase II study. The null hypothesis that the completion rate is 0.5 will be tested against a one-sided alternative 0.7. In the first stage, 15 patients will be accrued (including 6 patients at MTD schedule from the run-in phase). If there are 7 or fewer completions in these 15 patients, the study will be stopped. Otherwise, 13 additional patients will be accrued for a total of 28 patients accrued in the expansion phase. The null hypothesis will be rejected if 18 or more completions are observed in 28 patients. This design yields a type I error rate of 0.09 and power of 80% when the true completion rate is 0.7.

We propose that the final decision about the direction of future strategy and additional expansion studies should be made based on careful analysis of subpopulations with particular attention to feasibility, toxicity, and observed immodulatory responses.

8.2.5 Replacement Policy

A maximum of 40 evaluable patients will be enrolled in the study using a Simon's two-stage design for the primary endpoint. An evaluable patient will be defined as one who receives any amount of study drug. If a patient drops out of the study before receiving nivolumab, a replacement patient will be allowed.

8.2.6 Accrual estimates

A maximum of 40 evaluable patients will be enrolled in the study using a Simon's two-stage design for the primary endpoint. At UCSF, approximately 20 NPC patients are treated with definitive radiation therapy yearly and we plan to partner with other high accruing centers. Thus we expect to be able to complete accrual to this study within a reasonable time frame.

It is anticipated that accrual will be completed in approximately 18 months, with each patient treated for approximately 6 months and then followed for 12 months after completing protocol therapy. The total study duration is expected to be about 3 years. If a longer duration of clinical follow-up is desired (such as 2 or 3 years), the timeline would lengthen by an additional year but that follow-up is at the discretion of the treating investigators and not mandated by the study.

8.3 Interim Analyses and Stopping Rules

There is no interim analysis planned. There is a safety run-in which will be evaluated prior to continuing into the expansion phase. Safety of the study will be continuously assessed by the PI and the data safety monitoring committee (DSMC). The study may be stopped early if there is deemed to be an unacceptable safety risk by either the PI or the DSMC.

8.4 Analysis Plans

8.4.1 Analysis Population

Primary endpoint will determined in patients who receive the study drug for a minimum of 1 cycle (or 14 days) at the MTD schedule.

8.4.2 Primary Analysis (or Analysis of Primary Endpoints)

Rate of completion of all adjuvant immunotherapy is defined as completion of all post-chemoradiation cycles of nivolumab, per protocol.

8.4.3 Secondary Analysis (or Analysis of Secondary Endpoints)

Objective Response Rate (ORR): The ORR is based on the best overall response (BOR) recorded from the first day of treatment until time of assessment. The frequency and percentages of patients with a best overall response rate of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) will be determined.

Locoregional Control (LRC) Rate: Duration of LRC will be calculated as 1+ the number of days from the first day of treatment to time of documented locoregional clinical or radiographic relapse, progression or death due to any cause. For patients who continue treatment post-progression, the date of clinical or radiographic relapse or progression will be used for analysis. The Kaplan-Meier analysis will be used to calculate the mean LRC rate with 95% confidence interval.

Distant Metastasis (DM) Rate: Time to DM will be calculated as 1+ the number of days from the first day of treatment to documented clinical or radiographic progression at a distant metastatic site, or death due to any cause. Pathologic confirmation is not required to document the date of distant progression. For patients who continue treatment post-progression, the date of clinical or radiographic progression will be used for analysis. The Kaplan-Meier analysis will be used to calculate the mean DM rate with 95% confidence interval.

8.4.4 Other Analyses/Assessments

Correlative and exploratory analyses will be performed as described in 8.1.3.

8.5 Evaluation of Safety

Safety analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v5.0.

The safety population will consist of all subjects who receive any amount of study treatment. Safety will be assessed by evaluation of AEs. All safety analyses will be performed using the safety population. Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity grade and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) CTCAE v5.0. Listings of AEs will be provided.

Separate tables will present the following by dose group and study phase:

- All treatment-emergent AEs
- Treatment-emergent AEs by CTCAE grade
- Grade 3 or greater treatment-emergent AEs
- Treatment-related, treatment-emergent AEs
- Dose-limiting toxicity AEs
- Serious treatment-emergent AEs
- Treatment-emergent AEs with an outcome of death
- Treatment-emergent AEs leading to discontinuation of nivolumab.
- Treatment-emergent AEs resulting in interruption or reduction or delay of nivolumab.

8.6 Study Results

Study results will be submitted to drug manufacturer (BMS), as well as presented at national or international oncology conferences, and published in peer-reviewed scientific journals.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH), WHO and local directives including all applicable regulatory requirements.

The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval before initiation of the study. Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF Institutional Review Board. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

Informed consent will be obtained by personnel who are qualified by education, training, and experience to perform their respective tasks and that the study will not use the services of study personnel for whom sanctions have been invoked or where there has been scientific misconduct or fraud. Signed, dated Informed Consent will be obtained from each of the participants. Investigators will ensure that subjects--or, in those situations where consent cannot be given by subjects, their legally acceptable representatives--are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. The approved informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki. The informed consent will include

relevant safety information regarding dose/schedule of investigational products and any other drugs/procedures. BMS and health authorities will have direct access to study records. The informed consent will disclose BMS support of the study (e.g., study drug, funding).

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 Data and Safety Monitoring Plan for a Multicenter Institutional Study (For Run-In Phase) and Data and Safety Monitoring Plan for Multicenter Institutional Study (Phase 2 or 3 Institutional Study) – For Dose Expansion Phase for additional information.

9.8 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center for Phase II studies will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment.

The following issues will be discussed as appropriate:

- Enrollment information
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the

physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

9.9 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

9.10 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF IRB. Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional

- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendices

Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Multicenter Institutional Studies

Data and Safety Monitoring Plan for a Multicenter Institutional Study (For Run-In Phase)

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data in each cohort.
- Review of serious adverse events.
- Approval of dose escalation by DSMC Chair or Vice Chair.
- Real time monitoring (depending on study accrual).
- Minimum of a yearly regulatory audit.

2. Monitoring and Reporting Guidelines

The data is monitored by a DSMC monitor once a month as patients are enrolled and includes all visits through the first post-Dose Limiting Toxicity (DLT) period. At the time of dose escalation, a written report will be submitted to the DSMC Chair outlining the cohort dose, all adverse events and serious adverse event reports, and any Dose Limiting Toxicity as described in the protocol. The report will be reviewed by the DSMC Chair or qualified alternate and written authorization to proceed or a request for more information will be issued within two business days of the request. The report is then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair's decision, further study accrual is held while further investigation takes place.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and patient safety and discuss each patient's treatment at weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Cohort updates (i.e., DLTs).
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information).
- Protocol violations.
- Other issues affecting the conduct of the study.

Dose Level Considerations

The PI/Study Chair, participating investigators, and research coordinators from each site will review enrollment for each dose level cohort during the regularly scheduled conference calls. The dose level for ongoing enrollment will be confirmed for each patient scheduled to be enrolled at a site. Dose level assignments for any patient scheduled to begin treatment must be confirmed by the UCSF Coordinating Center via e-mail.

If a Dose Limiting Toxicity (DLT) arises in a patient treated at a participating site, all sites must be notified immediately by the UCSF Coordinating Center. The Study Chair has 1 business day (after first becoming aware of the event at either the UCSF Coordinating Center or the participating site) in which to report the information to all participating sites. If the DLT occurs at a participating site, the local investigator must report it to the UCSF Coordinating Center within one business day, after which the UCSF Coordinating Center will notify the other participating sites.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines.The data (i.e., redacted copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and FDA guidelines.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All clinically significant adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse Events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center's Site Committee. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 1 business days of becoming aware of the event. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

FDA website for guidance in reporting serious adverse events:
www.fda.gov/Safety/MedWatch/HowToReport/default.htm
Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within 10 business days of becoming aware of the event or during the next scheduled conference all, whichever is sooner. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the

Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The reporting procedure is by communication via e-mail, with a copy of the e-mail to the DSMC Manager.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator's Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail and the IRB must be notified via 10 business days via an iRIS Reporting Form.

Data and Safety Monitoring Committee Contacts:

Thierry Jahan, MD (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

DSMC Monitors
[redacted]
UCSF HDFCCC
San Francisco, CA
94143

Data and Safety Monitoring Plan for Multicenter Institutional Study (Phase 2 or 3 Institutional Study) – For Dose Expansion Phase

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monthly monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

All institutional Phase 2 or 3 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

<u>Multicenter communication</u>

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be sent electronically or faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

Adverse Event Monitoring

All Grade 3-5 Adverse Events, whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the IRB must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair: Thierry Jahan, MD
Phone: [redacted]
Email: [redacted]
Address: [redacted]
UCSF
San Francisco, CA 94115

DSMC Monitors
[redacted]
UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, CA 94115

* DSMP approved by NCI 09/February2012

Appendix 3 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Multicenter Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iRIS:

- UCSF IRB approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- UCSF IRB approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to the UCSF IRB with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e., Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- BMS pregnancy reporting forms, if applicable
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s)
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s) – Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for Investigational New Drug Application
- Site Initiation Visit (SIV) minutes and correspondence with Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and Single Patient Exception (SPE) reports to IRB with supporting fax documentation for Participating Site(s)
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s)
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s)
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges for the Participating Site(s)
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study)
- Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor for the Participating Site(s)

27 April 2012

3. Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)

Directions:

1) Fax the documents listed below to the UCSF Coordinating center [redacted] *or*

2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

1572

☐ PI and Sub investigators:

CV and Medical license

Financial disclosure form

NIH or CITI human subject protection training certification

☐ Laboratories

CLIA and CAP

CV of Lab Director and Lab Licenses

Laboratory reference ranges

Local Institutional Review Board

☐ IRB Approval letter

☐ Reviewed/Approved documents

- Protocol version date: _____
- Informed consent version date: _____
- Investigator Brochure version date: _____
- HIPAA

☐ Current IRB Roster

Other

☐ Delegation of Authority Log

- Include NIH or CITI human subject protection training certificates or GCP training certification

☐ Pharmacy

- Drug destruction SOP and Policy

☐ Protocol signature page

☐ Executed sub contract

27.apr.2012

Appendix 4 Specimen and Blood Collection

A. For tissue analysis:

Immunohistochemistry (IHC) analyses will be performed on the following diagnostic biopsy tissue specimens.

1. Baseline biopsy tissue (nasopharyngeal tumor tissue, core biopsy) is required to be submitted. Fresh nasopharyngeal tumor tissue obtained from a biopsy within 90 days prior to C1D1 is preferred but archival blocks of tissue are acceptable.

   Acquisition of representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks preferred) or at least 15 slides, with an associated pathology report, is required.

   Criteria for fresh tissue collection: 1) exophytic mass or tumor, or 2) amenable to cup forceps or ultrasound guided core biopsy. At least three cores should be obtained. A fine needle aspirate is not acceptable.

   If tumor may not be able to obtained from the primary site safely at all initial and subsequent tissue collection timepoints, then tissue from another anatomic area (e.g. core biopsies of neck) should be substituted. Every effort should be made to biopsy at baseline and subsequently from the same tissue site, e.g. always from the primary nasopharyngeal tumor or always from the neck.

2. 1 – 2 further tumor samples should be collected (if deemed appropriate by the investigator) as follows:

   a) Dose Schedule 1: (1) After the first cycle of nivolumab AND (2) after the first week of radiation therapy.

   b) Dose Schedule 2 and 3: (1) After the first week of radiation therapy.

See above for specifications of criteria for tissue collection. These samples should be collected from the same site that was biopsied at baseline.

See Laboratory Manual for processing and submission of paraffin-embedded tissue.

Formalin Fixed Paraffin Embedded (FFPE) tissue is stored at room temperature. These tissue samples may be batch-shipped to the UCSF Cancer Immunotherapy Lab for analysis.

B: For blood analyses:

All patients will have 4 (four) 10mL green top tubes and a purple top EDTA of blood specimens collected at baseline, at cycle 7 day 1 prior to initiation of adjuvant-phase nivolumab (whether nivolumab is actually given or not), and at 1 year followup. The purple top tube of blood will be reserved for EBV DNA testing in addition to immunologic correlative analyses.

Other than these three time points, 4 (four) 10mL green top tubes of blood specimens will be collected on day 1 and before administration of each nivolumab cycle. In addition, 4 (four)

10mL green top tubes of blood specimens will be collected at time of treatment discontinuation, and 4 (four) 10mL green top tubes of blood specimens will be collected at each regular post-treatment follow-up (at 1, 3, 6, 9 months post-treatment).

	# of green + purple top tubes
Baseline or before treatment on C1D1	4 (40mL total) + 1 (10mL total)
Day 1 of each cycle (before administration of study therapies)	4 (40mL total)
Day 1 of cycle 7	4 (40mL total) + 1 (10 mL total)
Treatment discontinuation	4 (40mL total)
Follow-up at 1, 3, 6, 9 months post-treatment	4 (40mL total)
Follow-up at 12 months post-treatment	4 (40mL total) + 1 (10 mL total)

See Laboratory Manual for processing and submission of blood samples.

Blood samples should be stored at room temperature no longer than 24 hours.

Peripheral blood mononuclear cells (PBMCs) and plasma should be isolated within 24 hours of blood collection and stored at -80°C. These samples may be batch-shipped to the UCSF Cancer Immunotherapy Lab for analysis.

C. Specimens saved for future research:

Excess blood and tissue samples remaining after all study procedures have been performed will be banked for future research. Samples will be stored indefinitely, and will be located at the Cancer Immunotherapy Lab at UCSF:

Cancer Immunotherapy Lab (CIL)

[redacted]

University of California, San Francisco

[redacted]

San Francisco, CA 94143

[redacted]

The patient consent form will include a specimen banking consent section. Study participants will be able to withdraw consent for specimen banking at any time by sending written correspondence to the principal investigator.

Appendix 5 Management Algorithms

As detailed in Investigator Brochure v15.0 for nivolumab (BMS-936558/MDX1106), appendix 3 Management Algorithms.

GI Adverse Event Management Algorithm

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

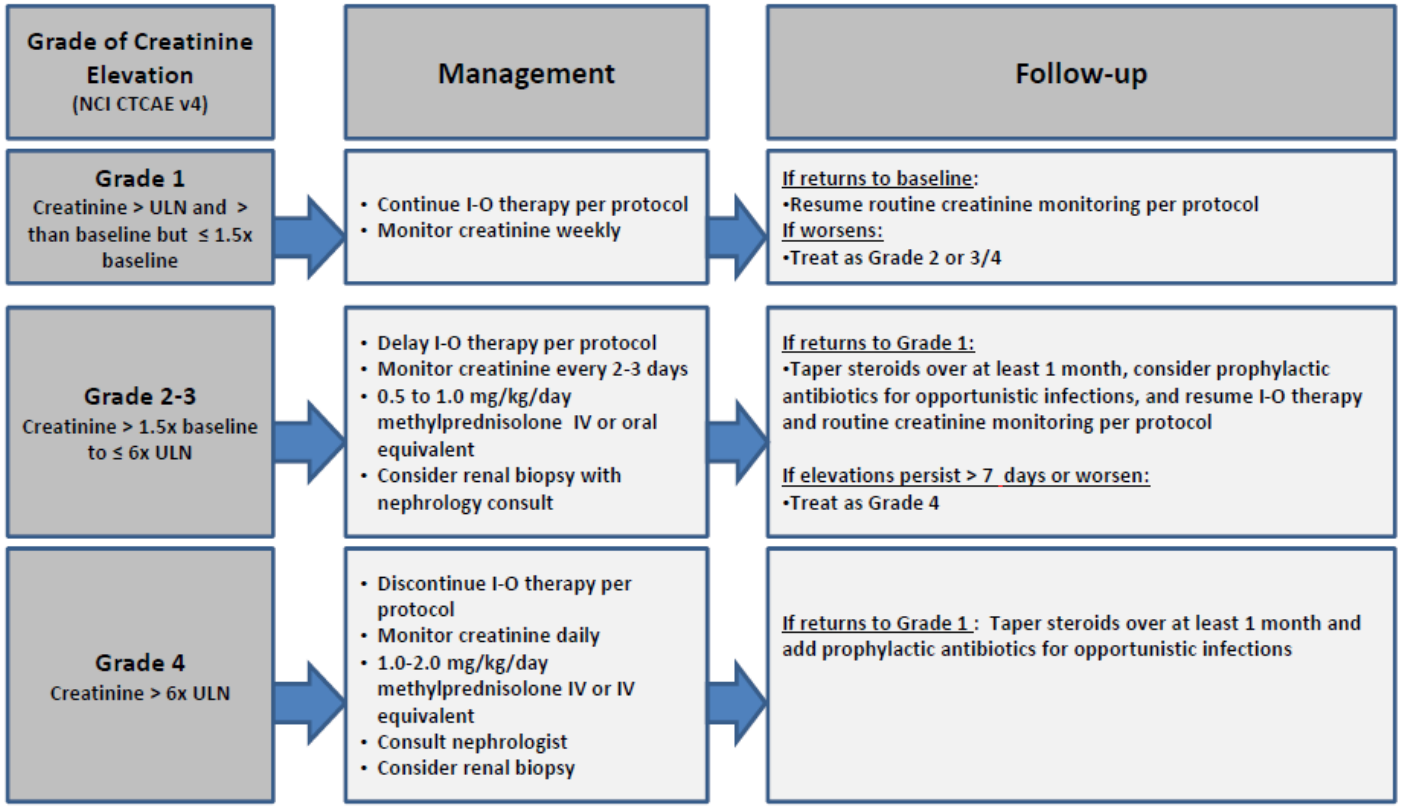
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

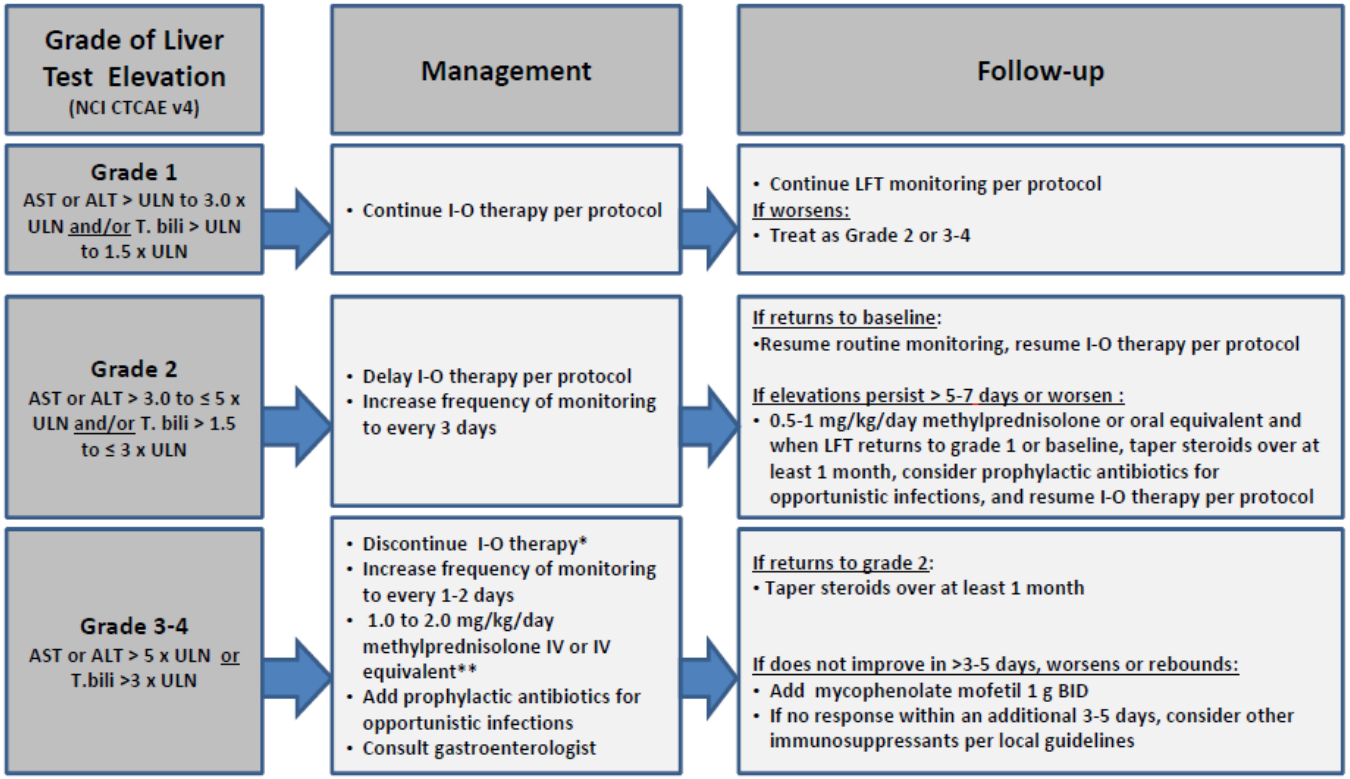
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

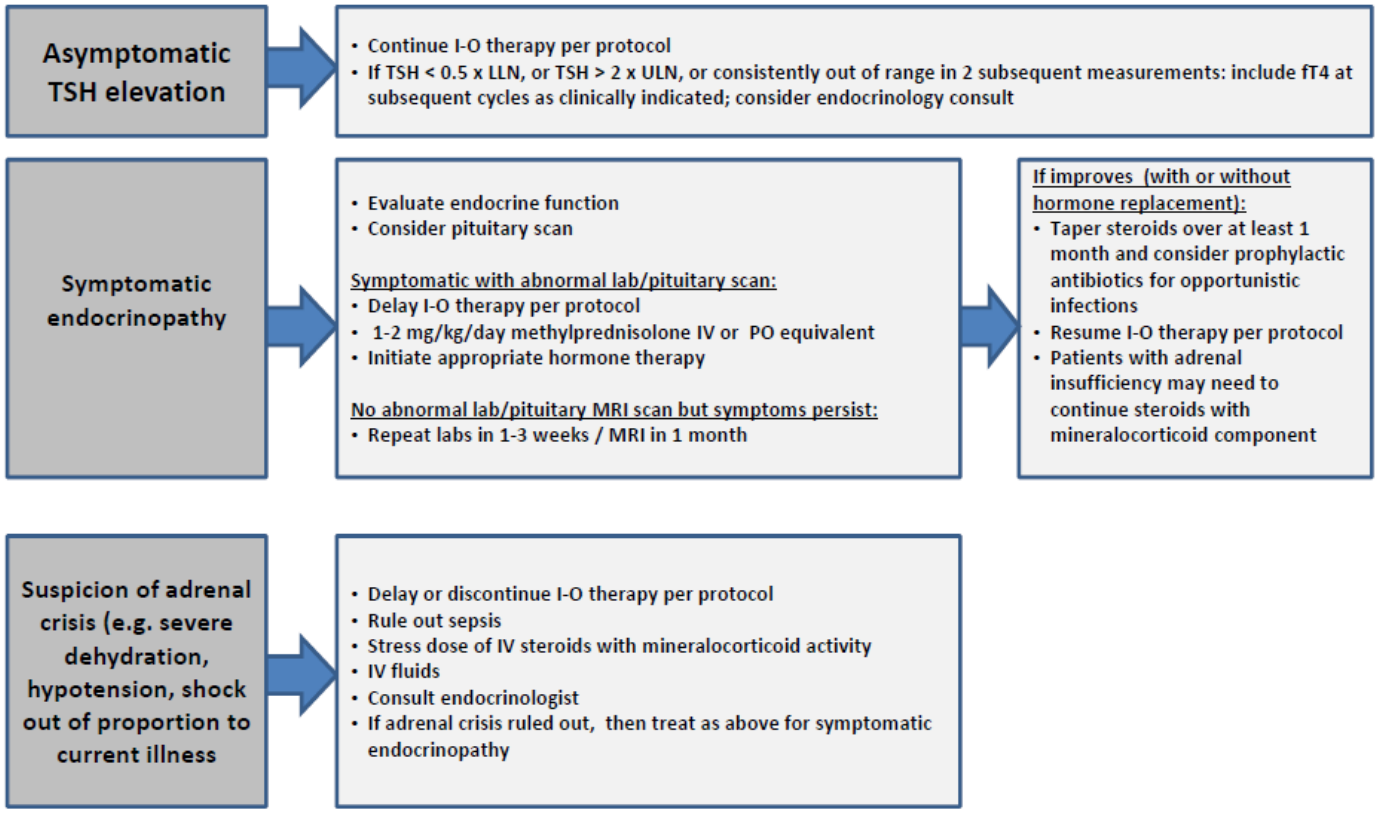
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

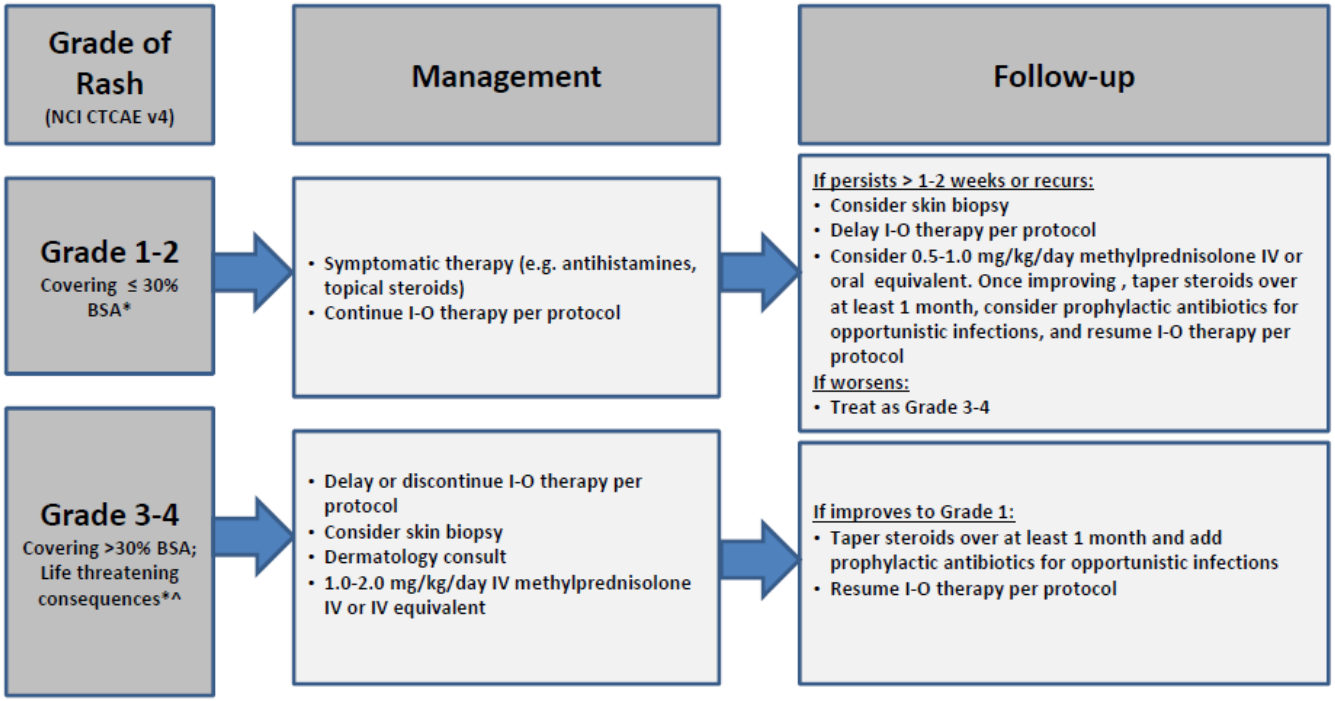


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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

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

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

Updated 05-Jul-2016