Dual Immune Checkpoint Blockade and Hypofractionated Radiation in Patients with Salivary Gland Cancers

Protocol number: CA209-8G3

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TRIAL REGISTRATION NUMBER: NCT03749460

STUDY SYNOPSIS

Background

No therapeutic treatment standard exists for recurrent or metastatic salivary gland cancers. There is preliminary data that a minority of patients may respond to single agent pembrolizumab (Cohen, 2016). The dual inhibition of PDL-1 and CTLA-4 is an approach that has garnered significant enthusiasm, due to robust preclinical data showing synergistic antitumor efficacy.

This data is supported by prospectively collected clinical data, in immunotherapy naive melanoma patients, wherein improved objective response rates and progression free response rates were observed with the combination of nivolumab and ipilimumab compared to either agent (Larkin, 2015). Multiple ongoing studies in other tumor types are examining the activity of this combination.

The role of radiation therapy in transforming the tumor microenvironment to increase the activity of immune checkpoint inhibition is an area of significant scientific interest. There is preclinical data supporting that the exposure to immune checkpoint inhibitors prior to therapeutic radiation is associated with increased antitumor activity. The clinical observation of the abscopal effect further supports the potential clinical utility of radiation therapy in inducing responses to immune check point inhibition.

Hypothesis

Dual immune checkpoint blockade with nivolumab and ipilimumab combined with hypofractionated palliative radiation therapy is safe and well tolerated in patients with advanced salivary gland carcinomas.

Objectives:

Primary Objective:

Demonstrate that nivolumab, ipilimumab and hypofractionated palliative radiation therapy is safe and well tolerated in patients with advanced salivary gland carcinomas.

Secondary Objective(s):

1. Evaluate the objective response rate
2. Determine overall and progression free survival

Exploratory Objective(s):

Collect tumor and blood for correlative studies

Study Design

This is a single arm, open label, prospective study evaluating the safety and clinical efficacy of the combination of nivolumab, ipilimumab and hypofractionated palliative radiation therapy (SBRT) in patients with advanced salivary gland cancer.

Patients enrolled will receive the following treatment (see Section 5.1.1):

1. Nivolumab 3mg/kg IV Q 2 weeks x 12 doses followed by Nivolumab 480 mg IV Q4 weeks x 8 doses

2. Ipilimumab 1 mg/kg IV Q6 weeks x 4 doses

3. Hypofractionated radiation therapy (SBRT) given to a total dose of 24Gy given in 3 fractions every other day over 1 week and initiated 2 weeks after the first dose of nivolumab and ipilimumab. The target lesion will be a local/regional or metastatic disease site that per the multidisciplinary head and neck team, requires local control for palliation and/or prevention of impending symptoms.

Both nivolumab and ipilimumab have well established toxicity profiles as a single agent and in combination. However, since the combination of nivolumab, ipilimumab and palliative radiation has not previously been described or studied, the first 6 patients who will be enrolled in this study will represent the initial safety run-in phase. Patients will receive full dose nivolumab and ipilumumab. Enrollment will be halted until these first 6 patients complete the first 12 weeks of treatment and acute toxicities will be reviewed. If more than 2 DLTs (to be defined in Section 5.1.2) are noted in this 6 patient cohort, a dose modification will be implemented (Section 5.1.1) for the remaining 14 patients who will be enrolled in the expansion cohort. Enrollment period is 24 months and duration of the trial 48 months.

Study Population

The study aims to enroll patients with salivary gland carcinomas (WHO, 2005), who are not candidates for curative intent therapy and who have a target lesion (either local/regional or distant metastatic site involving the lung and/or bone), that requires local control for palliation, as determined by a multidisciplinary team.

Inclusion Criteria:

1. Histologically proven salivary gland carcinoma (WHO, 2005) arising from a previous head and neck primary site, and located within the head and neck region, lung or bone, and who are not candidates for curative intent therapy.

2. ≥18 years old at the time of signing informed consent.

3. Demonstrated disease progression during, or after discontinuation, of the most recent line of systemic therapy. For patients who have received no prior systemic therapy, demonstrated progression in the 3 months prior to trial participation assessed by the treating physician.

4. Have received any number lines of prior systemic therapy (including systemic therapy in the curative intent setting).

5. Have a lesion/s deemed suitable by the treating physicians for SBRT with the intent of palliation or prevention of symptoms. This lesion must be:

    a) 1-3 non-overlapping sites in the head and neck region OR

    b) metastatic lesions outside the H&N region in the lung or bone (a minimum of 1 and a maximum 5 lesions will be irradiated), provided there is no significant overlap between the lesions.

    Patients should have RECIST 1.1 criteria measurable disease in addition to the lesion/s treated with SBRT. If the site/s of SBRT were previously radiated to high dose RT (>50Gy), there should be >6 month time interval between the last dose of radiation and the start of SBRT.

6. Have the ability to tolerate required SBRT-related procedures (e.g.: lie flat and hold position for treatment) as determined by the treating physician

7. Be willing and able to provide written informed consent for the trial and comply with the study visit requirements

8. Have measurable disease based on RECIST 1.1. (in addition to the lesion/s that will be treated with stereotactic radiation therapy)

9. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion. Tissue requirement will be waived if deemed contraindicated or not clinically available/accessible for resection per the treating physician (PI approval required).

10. Have a performance status of 0 or 1 on the ECOG Performance Scale.

11. Demonstrate adequate organ function as defined in below, based on screening labs should be performed within 28 days of treatment initiation.

- Hemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
- Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
- Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance.

12. Evidence of post-menopausal status OR negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone

levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, or hysterectomy).

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

13. Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

14. Female subjects of childbearing potential should be willing to use 1 method of highly effective birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 180 days after the last dose of study medication (Reference Section 8.1). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

15. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 180 days after the last dose of study therapy.

16. Patient is ≥ 5 years free of another primary malignancy, except: a) if the other malignancy is basal cell carcinoma or cervical carcinoma in situ or b) if the other primary malignancy is not considered clinically significant and is requiring no active intervention

Exclusion Criteria:

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

2. Has a target lesion/s for SBRT that demonstrate any of the following:
   a. located within 2 cm of the proximal bronchial tree
   b. > 5 cm (> 50 cc) in greatest dimension

3. Has a target lesion/s in a region that previously received high dose RT (>50 Gy) demonstrating any of the following:
    a. carotid artery encasement (> 180 degrees)
    b. unprotected carotid artery (i.e. skin is directly over the carotid without intervening soft tissue, especially after prior neck dissection without a vascularized free flap) (a&b due to risk of carotid blow out)
    c. skin infiltration by tumor (due to risk of fistula)
    d. located in the larynx/hypopharynx primaries (due airway threat)
    e. treated with high dose radiation therapy (>50 Gy) within 6 months or less of trial enrollment

4. Prior receipt of an anti-PD-1, anti-PDL1 or anti-CTLA4 immune checkpoint inhibitor.

5. Current or prior use of immunosuppressive medication within 14 days before the first dose of nivolumab or ipilimumab. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

6. Has received a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

7. Has received prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    -Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    -Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

9. Has known brain metastases or spinal cord compression unless the patient is stable (asymptomatic; no evidence of new or emerging brain metastases; and stable and off steroids for at least 14 days prior to start of study treatment). Following radiotherapy and/or surgery of the brain metastases patients must wait 4 weeks following the intervention and before initiating study treatment with imaging to confirm stability.

10. Has an active autoimmune disease requiring systemic treatment within the past 2 years or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement will not be excluded from the study.

11. Has a history of or evidence of active interstitial lung disease or non-infectious pneumonitis.

12. Has an active infection requiring systemic therapy.

13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 180 days after the last dose of trial treatment.

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

17. Has evidence of acute or chronic hepatitis B, or hepatitis C

18. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

19. Has a history of primary immunodeficiency or an allogeneic organ transplant

20. Known history of previous clinical diagnosis of tuberculosis

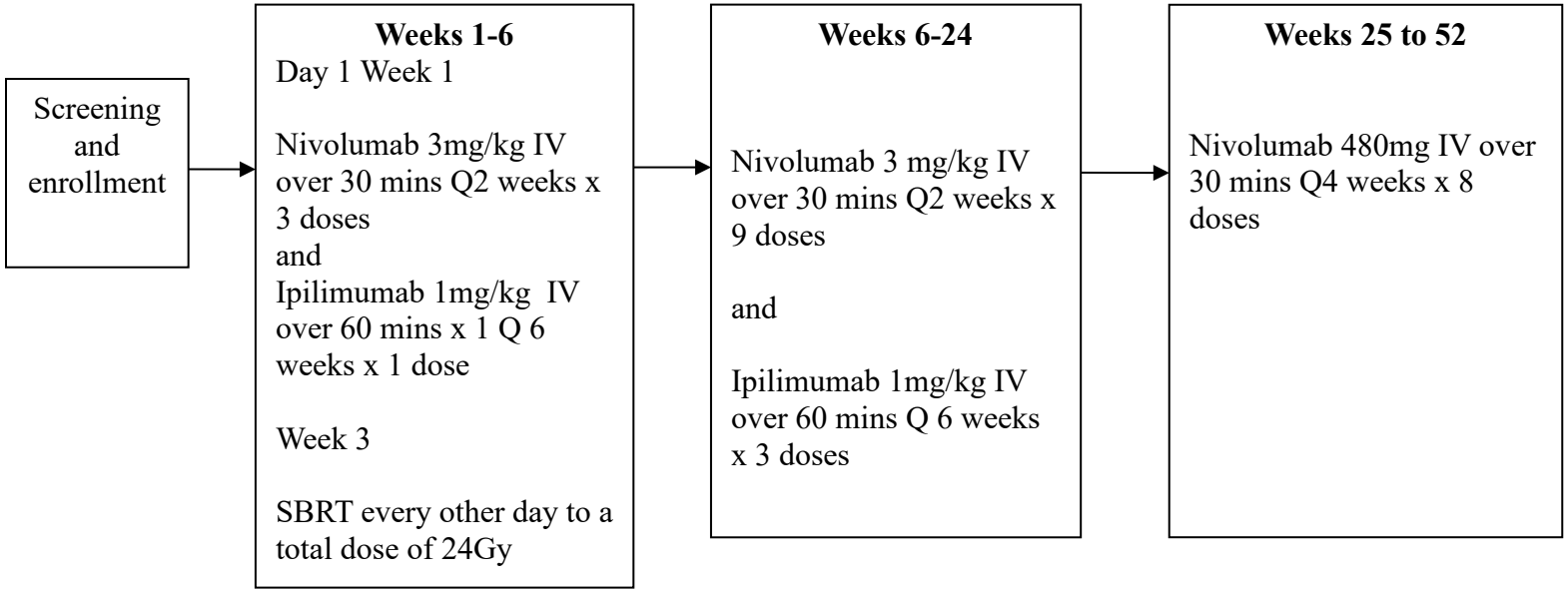
21. Uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, seizures

Statistical Plan

There are multiple ongoing studies in various tumor types exploring the activity of nivolumab and ipilimumab. In a published report of the combination in patients with advanced NSCLC treated on a phase I study (Checkmate 012), treatment related serious adverse events were observed in 28% of patients (Hellmann Lancet Oncol, 2017). This study plans to accrue 20 patients, a sample size that would allow us to estimate grade 3 or higher acute drug related toxicity rate of 30% with a confidence interval of 20% (95% confidence level) or an upper bound of 50%. This would allow us to reasonably exclude a clinically significant increase in toxicity with the addition of radiation therapy to the nivolumab and ipilimumab combination as defined by the upper bound of the confidence interval.

Toxicities will be summarized as the number and percentage of patients with each type of toxicity. Responses will be summarized as frequencies and percentages. The Kaplan Meier method will be used to estimate overall survival and progression free survival. Outcomes will be calculated from the date of study entry to the date of the corresponding event. We will use multivariate statistics to test the hypotheses that pretreatment intratumoral immune cell phenotype and PD-L1expression predict response response to therapy, and that therapy alters systemic immunophenotype.

Study Schema



Note: refer to Dosing and Administration (Section 5.1.1) for further details on treatment scenarios.

Number of Centers: 1

Number of Subjects: A maximum of 20 subjects will be enrolled.

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
B-HCG	Beta-Human Chorionic Gonadotropin
BMS	Bristol-Myer Squibb
BrdU	Bromodeoxyuridine
C	Cycle
CBCT	Cone Beam Computed Tomography
CD	Cluster of differentiation
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CR	Complete response
CRF	Case Report Form

Abbreviation or special term	Explanation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
DSMC	Data and Safety Monitoring Committee
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic
ERC	Ethics Review Committee
ESR	Expediated Safety Report
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FNA	Fine Needle Aspiration
GI	Gastrointestinal
GTV	Gross Target Volume
Gy	Gray
hCG	Human chorionic gonadotropin

Abbreviation or special term	Explanation
HA	Health Administration
H&E	Hematoxylin & Eosin
HIV	Human immunodeficiency virus
H&N	Head and Neck
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Investigational Drug
IDL	Intermediate Density Lipoprotein
IDO	Indoleamine-pyrrole 2,3-dioxygenase
IEC	Independent Ethics Committee
IFN	Interferon
IGTV	Internal Gross Tumor Volume
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IGRT	Image guided RT
IGTV	Internal Gross Tumor Volume
IHC	Immunohistochemistry
ILS	Interstitial lung disease
IMRT	Intensity-Modulated Radiation Therapy

Abbreviation or special term	Explanation
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
mAB	Monoclonal Antibody
MLC	Mixed Lymphocyte Culture
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NBF	Neutral Buffered Formalin
NSCLC	Non–small-cell lung cancer
OAR	Organ at Risk
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PET	Positron Emission Tomography

Abbreviation or special term	Explanation
PFS	Progression-free survival
PRV	Planning organ at Risk Volume
PT	Prothrombin Time
PTV	Planning Target Volume
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RT	Radiation Therapy
SAE	Serious adverse event
SBRT	Stereotactic Body Radiation Therapy
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SRC	Scientific Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
T_4	Thyroxine
TSC	Tumor Slice Culture
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
VEGF	Vascular Endothelial Growth Factor
VMAT	Volumetric Modulated Arch Radiotherapy
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

Abbreviation or special term	Explanation
XRT	Radiotherapy

1. INTRODUCTION

Salivary gland carcinomas represent <5% of all head and neck malignancies and are characterized by marked morphologic and biologic diversity. These arise from the secretory acini and associated myoepithelial cells in the three paired major salivary glands, and minor salivary glands located throughout the upper aerodigestive epithelium. The current WHO histological classification identifies 24 subtypes, with the most common being adenoid cystic carcinoma, mucoepidermoid carcinoma, salivary duct carcinomas and adenocarcinomas (Barnes, 2005). The current standard of care for early or locally advanced disease is curative intent resection followed by adjuvant radiation for tumors at high risk for recurrence (Schroeder, 2008).

Currently, there is no standard of care for the treatment of incurable (unresectable and metastatic) salivary gland malignancies. Clinical trials that have examined the activity of systemic therapy have been difficult to interpret due to small numbers, heterogeneous patient populations, and the frequent observation of prolonged stable disease, a likely reflection of the indolent biology of certain salivary gland tumors, such as adenoid cystic carcinomas. Historical regimens tested more than 20 years ago have employed cisplatin and cisplatin-based combinations (response rates of 20% or lower) (Laurie, 2006). Two of the largest contemporary studies conducted in North America have examined single agent paclitaxel (response rate 26% in non-adenoid cystic carcinoma subtypes, 0 in adenoid cystic carcinomas), and a gemcitabine carboplatin combination (response rate 24%) (Gilbert, 2006; Laurie, 2010). In these two studies median progression free survival was 5-6 months and median overall survival was 12-14 months, (KM estimates of 1year overall survival 50%, 3year overall survival 25%). Even lower response rates have been demonstrated with prospective evaluation of the activity of various molecular targeted agents such as trastuzumab, gefitinib, imatinib and lapatinib, with essentially no objective response rates noted (Haddad, 2003; Jakob, 2014; Pfeffer, 2007; Agulnik 2007).

The experience with immune checkpoint inhibitors in this rare disease is limited. Preliminary reports on the anti-PD1 monoclonal antibody pembrolizumab, demonstrated an objective response in approximately 10% of patients with salivary gland cancers, among a

population enriched for >1% PDL1 tumor expression (Cohen, 2016). There is increasing interest in exploring the efficacy of immune checkpoint inhibition in this population.

The dual inhibition of PDL-1 and CTLA-4 is an approach that has garnered significant enthusiasm, due to robust preclinical data showing synergistic antitumor efficacy. This data is supported by prospectively collected clinical data, in immunotherapy naive melanoma patients, wherein improved objective response rates and progression free response rates were observed with the combination of nivolumab and ipilimumab compared to either agent alone (Larkin, 2015). Multiple ongoing studies in other tumor types are examining the activity of this combination.

The role of radiation therapy in transforming the tumor microenvironment to increase the activity of immune checkpoint inhibition is an area of significant scientific interest. There is preclinical data supporting that the exposure to immune checkpoint inhibitors prior to therapeutic radiation is associated with increased antitumor activity (Twyman-Saint Victor, 2015). The clinical observation of the abscopal effect further supports the potential clinical utility of radiation therapy in inducing responses to immune check point inhibition (Postow, 2012).

Therefore this clinical trial aims to examine the safety and efficacy of dual immune checkpoint blockade and palliative hypofractionated radiation therapy in salivary gland carcinomas. Our institution has had prior experience with implementation and completion of clinical trials in this rare disease.

2. STUDY OBJECTIVES

2. 1 Primary Objective:

To demonstrate that nivolumab, ipilimumab and hypofractionated palliative radiation therapy is safe and well tolerated in patients with advances salivary gland carcinomas.

2.2 Secondary Objective(s):

1. Evaluate the objective response rate according to RECIST 1.1
2. Determine overall and progression free survival

2.3 Exploratory Objective(s):

Collect tumor and blood for correlative studies

3. ETHICAL CONSIDERATIONS

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

The protocol will be approved and reviewed by the Cancer Consortium Scientific Review Committee (SRC) and the Institutional Review Board (IRB). Once activated, the protocol will be reviewed at least annually by both institutional entities.

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the Cancer Consortium IRB and SRC. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation.

Trial oversight will be carried out by the Protocol Director, Dr. Cristina Rodriguez, and her research staff, who will be qualified by education, training and experience to perform their respective tasks, (services of personnel for whom sanctions have been invoked for scientific misconduct or fraud will not be used). They will meet weekly to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is

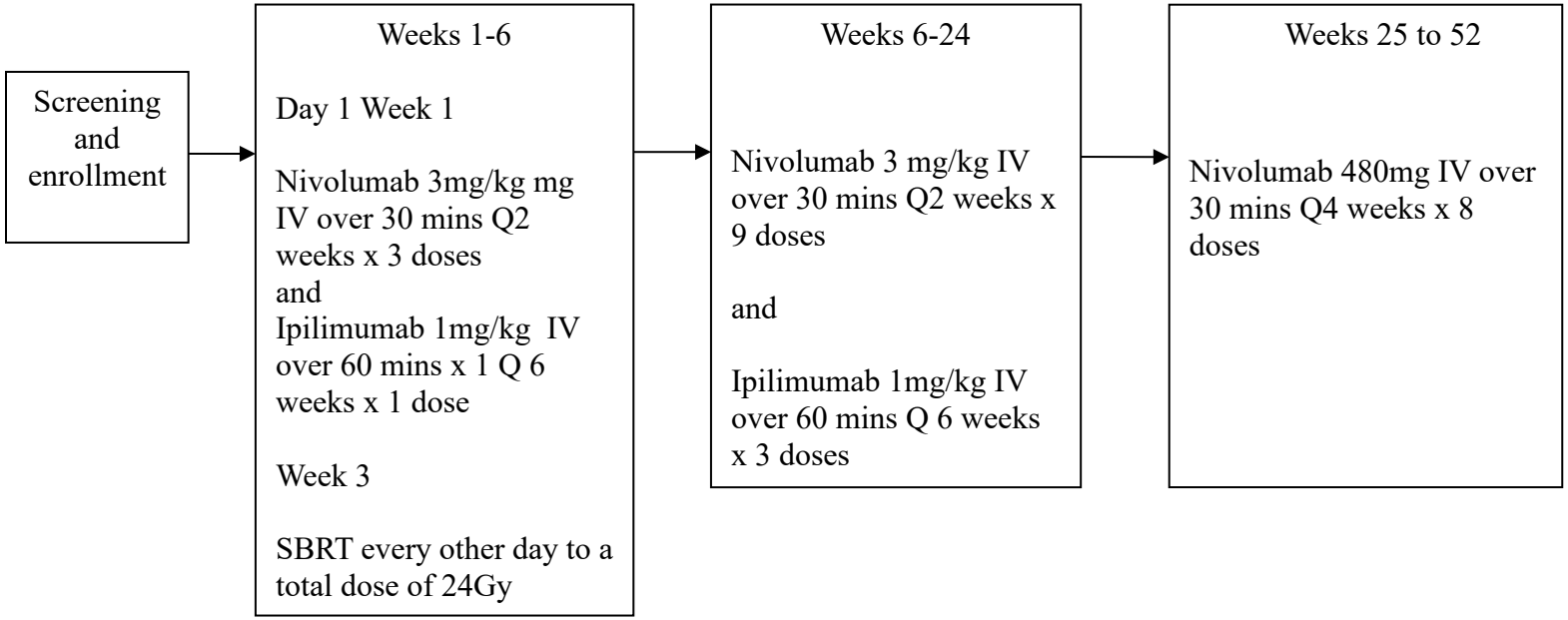
available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above.

4. INVESTIGATIONAL PLAN/STUDY DESIGN

4.1 Study Design Overview

This study will be carried out as a single institution, single arm phase I/II unblinded trial. A maximum of 20 patients will be enrolled. Each patient will be treated with nivolumab, ipilimumab and stereotactic body radiation therapy. Nivolumab will be continued for a total of 12 cycles, unless evidence of unacceptable toxicity, disease progression or withdrawal of patient consent were to occur.

4.2 Study Schema



Note: refer to Dosing and Administration (Section 5.1.1) for further details on treatment scenarios.

Both ipilimumab and nivolumab are FDA approved, and the safety profile of both agents have been extensively studied. However, because the combination with radiation has not been previously studied, the first 6 patients of this study will represent the initial run-in phase of the triplet combination of nivolumab, ipilimumab and palliative radiation. The initial doses of ipilimumab and nivolumab will be administered on day 1 of therapy. Stereotactic radiation will be initiated on Week 3 of treatment. SBRT will be delivered to a total dose of 24 Gy, given in 3 fractions of 8Gy every other day. Treatment will be continued according to the study schema unless patient withdraws consent, has confirmed disease progression, and/or develops toxicity that results in treatment discontinuation.

Enrollment will be halted until these first 6 patients complete the first 12 weeks of treatment and acute toxicities will be reviewed. If more than 2 DLTs (to be defined in Section 5.1.2) are noted in this six patient cohort, a dose modification will be implemented (Section 5.1.1) for the remaining 14 patients who will be enrolled in the expansion cohort.

Serum correlative studies will be collected at the following timepoints: at baseline, prior to week 8, and prior to week 16 of treatment. Archived formalin fixed paraffin embedded tissue (obtained in the 12 months prior to trial enrollment) will be collected from patients enrolled. If the patient does not have archived tissue available, a fresh biopsy will be obtained. Tissue requirement will be waived if deemed contraindicated or not clinically available/accessible for resection per the treating physician (PI approval required).

4.3 Efficacy Measurements

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Patients will be evaluated every 8 weeks (± 7 days) with radiographic imaging to assess response to treatment. CT or MRI will be used, per PI discretion, to scan areas of known disease. All imaging will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determination of overall response rate (ORR) and progression-free survival (PFS).

4.4 Inclusion Criteria:

1. Histologically proven salivary gland carcinoma (WHO, 2005) arising from a previous head and neck primary site, and located within the head and neck region, lung or bone, and who are not candidates for curative intent therapy.

2. ≥18 years old at the time of signing informed consent.

3. Demonstrated disease progression during, or after discontinuation, of the most recent line of systemic therapy.

4. Have received any number lines of prior systemic therapy (including systemic therapy in the curative intent setting).

5. Have a target lesion/s deemed suitable by the treating physicians for SBRT with the intent of palliation or prevention of symptoms. This lesion must be:

   a) 1-3 non-overlapping sites in the head and neck region OR

   b) metastatic lesions outside the H&N region in the lung or bone (a minimum of 1 and a maximum 5 lesions will be irradiated), provided there is no significant overlap between the lesions.

   Patients should have RECIST 1.1 criteria measurable disease in addition to the lesion/s treated with SBRT. If the site/s of SBRT were previously radiated to high dose RT (>50Gy), there should be >6 month time interval between the last dose of radiation and the start of SBRT.

6. Have the ability to tolerate required SBRT-related procedures (e.g.: lie flat and hold position for treatment) as determined by the treating physician

7. Be willing and able to provide written informed consent for the trial and comply with the study visit requirements

8. Have measurable disease based on RECIST 1.1. (in addition to the lesion/s that will be treated with stereotactic radiation therapy)

9. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion. Tissue requirement will be waived if deemed contraindicated or not clinically available/accessible for resection per the treating physician (PI approval required).

10. Have a performance status of 0 or 1 on the ECOG Performance Scale.

11. Demonstrate adequate organ function as defined in below, based on screening labs should be performed within 10 days of treatment initiation.

    - Hemoglobin ≥ 9.0 g/dL
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
    - Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
    - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
    - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
    - Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance.

12. Evidence of post-menopausal status OR negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, or hysterectomy).
    - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous

hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

13. Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

14. Female subjects of childbearing potential should be willing to use 1 method of highly effective birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 180 days after the last dose of study medication (Reference Section 8.1). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

15. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 180 days after the last dose of study therapy.

16. Patient is ≥ 5 years free of another primary malignancy, except: a) if the other malignancy is basal cell carcinoma or cervical carcinoma in situ or b) if the other primary malignancy is not considered clinically significant and is requiring no active intervention

4.5 Exclusion Criteria:

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

2. Has a target lesion/s for SBRT that demonstrate any of the following:
   a. located within 2 cm of the proximal bronchial tree
   b. > 5 cm (> 50 cc) in greatest dimension

3. Has a target lesion/s in a region that previously received high dose RT (>50 Gy) demonstrating any of the following:
   a. carotid artery encasement (> 180 degrees)

b. unprotected carotid artery (i.e. skin is directly over the carotid without intervening soft tissue, especially after prior neck dissection without a vascularized free flap) (a&b due to risk of carotid blow out)
c. skin infiltration by tumor (due to risk of fistula)
d. located in the larynx/hypopharynx primaries (due airway threat)
e. treated with high dose radiation therapy (>50 Gy) within 6 months or less of trial enrollment

4. Prior receipt of an anti-PD-1, anti-PDL1 or anti-CTLA4 immune checkpoint inhibitor.

5. Current or prior use of immunosuppressive medication within 14 days before the first dose of nivolumab or ipilimumab. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

6. Has received a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

7. Has received prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

-Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

-Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell

carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

9. Has known brain metastases or spinal cord compression unless the patient is stable (asymptomatic; no evidence of new or emerging brain metastases; and stable and off steroids for at least 14 days prior to start of study treatment). Following radiotherapy and/or surgery of the brain metastases patients must wait 4 weeks following the intervention and before initiating study treatment with imaging to confirm stability.

10. Has an active autoimmune disease requiring systemic treatment within the past 2 years or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement will not be excluded from the study.

11. Has a history of or evidence of active interstitial lung disease or non-infectious pneumonitis.

12. Has an active infection requiring systemic therapy.

13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 180 days after the last dose of trial treatment.

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

17. Has evidence of acute or chronic hepatitis B, or hepatitis C

18. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

19. Has a history of primary immunodeficiency or an allogeneic organ transplant

20. Known history of previous clinical diagnosis of tuberculosis

21. Uncontrolled intercurrent illness including, but not limited to symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, seizures

5. TREATMENT

5.1 Systemic Therapy

5.1.1 Dosage and Administration

The treatment to be used in the run-in phase (initial 6 patients) of this trial is outlined in the table below. If ≤ 1 DLT is observed in the run-in phase, then the remaining 14 patients will be provided treatment per the following:

Drugs	**Dose/Potency**	**Dose Frequency**	**Route of Administration**	**Regimen/Treatment Period**
Weeks 1-24				
1. Nivolumab	3 mg/kg	Q2 weeks	IV infusion	Maximum of 12 doses
2. Ipilimumab	1mg/kg	Q6 weeks	IV infusion	Maximum of 4 doses
Weeks 25-52				
1. Nivolumab	480mg IV flat dose	Q4 weeks	IV infusion	Maximum of 8 doses

If 2 or more DLTs (defined in Section 5.1.2) are observed in the run-in phase, the following treatment will be used for the remaining 14 patients to be treated on the clinical trial protocol:

Drugs	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Weeks 1-24				
1. Nivolumab	3 mg/kg	Q4 weeks	IV infusion	Maximum of 6 doses
2. Ipilimumab	1mg/kg	Q8 weeks	IV infusion	Maximum of 3 doses
Weeks 25-52				
1. Nivolumab	480mg IV flat dose	Q6 weeks	IV infusion	Maximum of 4 doses

Patients who experience a DLT in the run-in phase, will have dose interruptions/reductions as outlined in Section 5.1.3.

5.1.2 Definition of DLT

Dose-limiting toxicities (DLTs) will be evaluated during the run-in phase consisting of the first 6 patients enrolled in this trial. The period for evaluating DLTs will be from the time of first administration of nivolumab and ipilumumab until 12 weeks. Adverse event monitoring will continue for these subjects throughout the course of their treatment as outlined in the Schedule of Study Assessments, these adverse events will include potential XRT related toxicities. Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

- Any Grade 4 irAE
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration

- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below
  - Grade 3 fatigue lasting ≤ 7 days
  - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
  - Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)
  - Concurrent vitiligo or alopecia of any AE grade
  - Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
  - Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
  - Grade 3 or 4 lymphopenia
  - Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
  - Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days
- Grade 4 hematologic toxicity, not described in exclusions above
- Prolonged delay (>2 weeks) in initiating second dose of nivolumab or ipilimumab due to treatment-related toxicity
- Grade 5 toxicity, i.e., death

Dose modification/delays according to Section 5.1.3 will apply to the patients who experience DLTs in the run-in phase.

Immune-related AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

During this DLT period, patients who received <90% of the nivolumab OR ipilimumab infusion on day 1 (e.g., because the infusion of either drug had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the phase I run-in cohort and will be replaced.

5.1.3 Dose Delays/Modifications

Toxicity will be graded using Common Terminology Criteria for Adverse Events (CTCAE version 5.0). The protocol will change to CTCAE version 6.0 if is published within the course of the trial.

Because the toxicities of both nivolumab and ipilimumab overlap, a patient meeting dose delay criteria within weeks 1- 24 will have ***both nivolumab and ipilimumab held until improvement of the adverse event to Grade 1 or baseline and retreatment criteria are met.***

Nivolumab may be delayed until the next planned ipilimumab if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab or ipilimumab-placebo dosing to be synchronized with nivolumab dosing.

Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab-may be adjusted within the permitted -2/+3 day window, as long as **consecutive nivolumab doses are given at least 12 days apart**. Ipilimumab may be delayed beyond the -2/+3 day window if needed to synchronize with the next nivolumab dose

5.1.3.1 Dose Delay Criteria

Doses of both nivolumab and ipilimumab (during study weeks 1-24) or nivolumab alone (during study weeks 25-52) should be held if any of the following are observed:

- Any Grade ≥3 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities

- Any Grade ≥3 drug-related laboratory abnormality with the following exceptions for lymphopenia, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or asymptomatic amylase or lipase:

  – Grade 3 lymphopenia does not require a dose delay
  – If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade 2 toxicity
  – If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥3 toxicity
  – Any Grade ≥3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.

- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

5.1.3.2 Criteria for Resuming Treatment

Subjects may resume treatment with nivolumab and ipilimumab (weeks 1-24) or nivolumab (weeks 2-52) when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.

- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.

- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.

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

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

During weeks 1-24, ipilimumab may not be resumed sooner than 6 weeks (-2/+3 days) after the prior dose. In general, it should be feasible to synchronize dosing of both nivolumab and ipilimumab drugs when resuming treatment. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted -2/+3day window, **as long as consecutive nivolumab doses are given at least 12 days apart**.

If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should be rescheduled to maintain the 6 week interval between consecutive ipilimumab.

5.1.3.3 Criteria for permanent discontinuation of nivolumab and ipilimumab

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with nivolumab and ipilimumab
- Dosing delays lasting 12 weeks or more
- Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen
- Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk

- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed all doses of study drug
- Grade ≥ 3 infusion reaction

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

5.2 Radiation Therapy

All subjects will be immobilized in a custom designed device in the appropriate position to isolate the index lesion. Radiotherapy treatment planning CT scans (with contrast, unless contraindicated) will be required to define the gross target volume (GTV) and planning target volume (PTV). PET-CT and/or MRI imaging are preferred to delineate volumes as accurately as possible. The treatment planning CT scan should be acquired with the subject in the same position and immobilization device, as for the treatment. Treatment planning will be done using a 3D based CT treatment planning system. All tissues to be irradiated must be included in the CT scan. Planning CT scan will be done at 1.25 mm intervals from encompassing the region of interest with sufficient margin for treatment planning.

5.2.1 Stereotactic Targeting and Treatment

SBRT has now been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic Radiology and Oncology (Potters, 2004). This protocol will respect that guideline. The term stereotactic, for the purposes of this protocol, implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable "fiducial" markers. This differs from conventional radiation therapy, in which therapy is directed toward less-than-reliable skin marks or bony landmarks that are indirectly referenced to the tumor (surrogates). This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation-producing device in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward a target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radiopaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (e.g., acquiring tomographic views of the tumor simultaneously with the treatment). Metallic "seeds" placed within the tumor will be allowed to constitute a fiducial so long as the methods are validated and a plan is in place to identify seed migration (e.g., redundant seeds placed).

5.2.2 Target Contouring

Gross Tumor Volume (GTV) is defined as all known gross disease encompassing the selected index lesion. The GTV will consist of the index lesion as visualized on CT +/- PET/CT, and/or MRI. Image fusion is encouraged when using multiple modalities to define the GTV.

Clinical Target Volume (CTV) will be the same as GTV for most cases. In case of uncertainty, GTV could be expanded to CTV by 2-3mm per clinician discretion.

Internal Gross Tumor Volume (IGTV) is defined for mobile index lesions at the discretion of the treating physician. For mobile index lesions, a 4-D CT scan will be acquired in order to account for the motion of the lesion during treatment. The IGTV will be defined as the union of the visualized index lesion on all gated CT data sets.

Planning Target Volume (PTV) will be defined as per convention for photon beam radiotherapy. A 3-dimensional margin of 3-5mm will be created on the CTV or IGTV (if available) to allow for daily set-up variance. For Proton beam radiotherapy, an additional range uncertainty is added during planning.

Organ at Risk volume (OAR) is contoured as visualized on the planning CT or MR scan.

Planning organ at Risk Volume (PRV) is the OAR expanded for setup uncertainty or organ motion. The physician will contour the OAR. The dosimetrist will create the PRV by expanding the OAR by 1-3 mm, depending on the situation.

Pertinent Organs at Risk (OARs) in the index region are contoured as applicable:

Spinal cord, Brain stem, Brachial plexus (roots & trunks)
Optic pathways – optic nerves, optic chiasm, Retina, Cornea
Carotid artery (Internal & common),
Cochlea & vestibular apparatus
Skin (3-5 mm of body outline)
Larynx (infrahyoid supraglottis to bottom of cricoid. Only include the endolarynx within the cartilaginous framework
Other uninvolved mucosal structures e.g.: oral cavity & pharynx
Facial Bones: Mandible, Maxilla, temporal bone that pertain to index region
Esophagus
Heart and Pericardium
Lungs
Ribs
Trachea and Large/Central Bronchi
Bronchii – smaller airways

5.2.3 Treatment planning, dose fractionation and specification

Computer based planning & QA will be performed using our standard institutional SBRT guidelines, including corrections for tissue heterogeneity, and robustness analysis (for Proton therapy). Treatment planning may be done with IMRT, VMAT, Proton beam RT (Pencil beam RT or Uniform scanning).

The dose prescription will be as follows: 24 Gy given in 3 fractions to PTV (80-95% IDL) delivered at 8 Gy per fraction every other day.

Dose rate: For the purpose of this study, dose rate utilized will be that which is commissioned by the manufacturer and the medical physics group for external beam radiotherapy delivery by the treating institution. There will be no special dose rate modifications required for this study.

The following PRV dose constraints will be used: (adopted from Timmerman RD. An overview of hypofractionation. Seminars of Radiation Oncology 2008 Oct;18(4):215-222).

Spinal cord max 21Gy, 18Gy (< 0.35cc), 12 Gy (<1cc)

Brain stem max 23 Gy, 18 Gy (< 0.5cc)

Optic chiasm max 15 Gy, 12 Gy (< 0.2cc) (for bilateral blindness risk)

Ipsilateral Optic nerve max 18 Gy, 15 Gy (< 0.2cc)

Contralateral optic nerve max 12 Gy, 10 Gy (< 0.5cc)

Carotid artery max 15 Gy, (V12 Gy to < 30% of carotid volume)

Brachial plexus max 24 Gy, 20 Gy (< 3cc)

Esophagus* max 24 Gy, 17 Gy (< 5cc)

Heart/Pericardium max 24 Gy, 20 Gy (< 15cc)

Trachea* max 24 Gy, 15 Gy (< 4cc)

Bronchus max 23 Gy, 18 Gy (< 1cc)

Ribs max 24 Gy, 20 Gy (< 5cc)

Skin 24 Gy (< 10cc), 20 Gy (<10cc)

Lung (Right & Left) – Volume to spare > 1000cc to </= 12 Gy and
> 1500 cc to </= 11.5 Gy, V15 Gy < 35%

Liver – spare >700cc to </=19 Gy

Stomach – max 22 Gy, 16 Gy to < 10cc

Rest of OARS = ALARA

* avoid circumferential radiation

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, noncoplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used with roughly equal weighting for photon planning. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of 7 non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized.

Proton beam planning is performed with 2-4 beams. In order to obtain acceptable coverage, field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception should be when observing the minimum field dimension of 3.5 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 60-90% line (where the maximum dose is 100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The treatment isocenter or setup point in stereotactic coordinates will be determined from system fiducials (and can be adjusted pretreatment depending on the results from localization imaging studies) and translated to the treatment record.

Dose specifications

Successful treatment planning will require accomplishment of all of the following criteria:

1. Maximum dose: The treatment plan should be created such that 100% corresponds to the maximum dose delivered to the patient. This point must exist within the PTV.
2. Prescription isodose: The prescription isodose surface must be ≥ 60% and < 90% of the maximum dose.
3. Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV V95%RX = 100%) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (PTV V90%RX > 99%).
4. High Dose Spillage: The cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should be no more than 15% of the PTV volume. Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1 through 4 to the volume of the PTV is ideally <

1.2 (see table below). These criteria will not be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3.5 cm results in the inability to meet a conformality ratio of 1.2. The "None" and "Minor" entries in this table define the Per Protocol, Variation Acceptable and Deviation Unacceptable Compliance Criteria.

5. Intermediate Dose Spillage: The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:

a. Location: The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D2CM where D2CM is given by the table below.

b. Volume: The ratio of the volume of the 34 or 12 Gy isodose volume to the volume of the PTV must be no greater than R50% where R50% is given by the table below (adapted from RTOG 0915). This table is used for all prescription requirements irrespective of calculation algorithm and total treatment dose.

Table 1: Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (Gy)	
	Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0

Image guided RT (IGRT) is required with physician review per institutional QA requirements before each treatment is delivered. Cone beam CT will be matched to target volume to be treated and bony anatomy or other defined fixed fiducials. If CBCT is unavailable, orthogonal pair KV imaging matched to bony anatomy closest to PTV is acceptable.

6. STUDY DRUGS

The following investigational drugs will be provided. Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

Product Description	**Potency**	**Packaging/Appearance**	**Storage Conditions (per label)**
(Nivolumab) Solution for Injection	100 mg (10 mg/mL)	10 mL/vial (5 or 10 vials/carton)	Store at 2° - 8°C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL/vial (4 vials/carton)	Store at 2°- 8°C. Protect from light and freezing.

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from the official study site by authorized personnel according to local regulations.

6.1 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns

regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert. Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets). Infusion-related supplies (e.g., IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab and ipilimumab.

6.2 Concomitant medications

Permitted concomitant medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed under Excluded Concomitant Medications.

Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy other than the protocol specified therapies.

2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of

steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).

4. Live attenuated vaccines within 30 days of nivolumab and ipilimumab dosing (i.e., 30 days prior to the first dose, during treatment with nivolumab and ipilimumab for 30 days post discontinuation of nivolumab and ipilimumab). Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

Table 2. Prohibited and Rescue Medications

Prohibited medication/class of drug:	**Usage:**
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given whilst the patient is on IP treatment
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given whilst the patient is on IP treatment through 90 days after the last dose of IP
Any concurrent chemotherapy, local therapy (except palliative radiotherapy for non-target lesions, e.g., radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given whilst the patient is on IP treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable.)
Immunosuppressive medications, including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumor necrosis factor α blockers	Should not be given whilst the patient is on IP treatment. (Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP during the study
VEGF inhibitors such as sunitinib, sorafenib and bevacizumab	Should not be given 90 days prior to first dose of investigational drug and with 30 days after last dose of investigational drug

Rescue/supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (e.g,, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc.])	Should be used when necessary for all patients

7. SCHEDULE OF ASSESSMENTS

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject	Screening	all assessments to be performed pre-infusion unless stated otherwise								
		Weeks 1-6			Weeks 7-24	Weeks 25-52	End of treatment	Safety Follow-Up[n]	Long-Term Follow-Up[o]	Survival Follow-Up[p]
Day	**- 28 to - 1**	**Day 1 of the Week (-2/+3)**			**-2/+3**	**-2/+3**		**-30**	**±14**	**±14**
Week	**-4 to -1**	**Week1**	**Week3**	**Week5**					**Q8 wks**	**Q12 wks**
Written informed consent	X									
Demography and history of tobacco and alcohol use	X									
Previous treatments for head and neck cancer	X									
Tumor tissue sample	X									
Formal verification of eligibility criteria	X									
Medical and surgical history	X									
Urine hCG or serum βhCG[a]	X									
Physical examination[b]	X	X	X	X	X	X	X	X		
Vital signs[c]	X	X	X	X	X	X	X	X		
Weight[c]	X	X	X	X	X	X	X	X		

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject	**Screening**	**all assessments to be performed pre-infusion unless stated otherwise**								
		Weeks 1-6			**Weeks 7-24**	**Weeks 25-52**	**End of treatment**	**Safety Follow-Up[n]**	**Long-Term Follow-Up[o]**	**Survival Follow-Up[p]**
Day	**- 28 to - 1**	**Day 1 of the Week (-2/+3)**			**-2/+3**	**-2/+3**		**-30**	**±14**	**±14**
Week	**-4 to -1**	**Week1**	**Week3**	**Week5**					**Q8 wks**	**Q12 wks**
Nivolumab administration		X[d]	X[d]	X[d]	X[d]	X[e]				
Ipilimumab administration		X			X[f]					
Adverse event/serious adverse event assessment and concomitant medications [c]	X	X	X	X	X	X	X	X	X	X
Radiation therapy evaluation and radiation planning/simulation	X									
Palliative hyporfractionated Radiation therapy			X[g]							
ECOG performance status[c]	X	X	X	X	X	X	X	X	X	
TSH with reflexive free T4[h]	X	Repeat every 12 weeks								
Complete blood count[i]	X	X	X	X	X	X				
Serum chemistry[i]	X	X	X	X	X	X				
Urinalysis[j]	X	Additional testing as clinically indicated								
Coagulation parameters[k]	X	Additional testing as clinically indicated								
Correlative blood samples[l]	X				X					
Tumor assessments[m]	X				X	X			X	
Survival Status										X

[a] Pre-menopausal female subjects of childbearing potential only

[b] Full physical examination at screening and baseline; targeted physical examination prior to each administration of investigational drug, discontinuation of treatment and safety follow-up

[c] To be done on each visit prior to administration of investigational drug. Concomitant medication collected up to the Safety Follow (-30 days post last dose of study treatment) or initiation of new anti-cancer treatment. AEs will be collected up to 100 days post last dose of study treatment or initiation of new anti-cancer treatment.

[d] On weeks 1-24, see Section 5.1.1 for Nivolumab administration (-2/+3days), **nivolumab doses are given at least 12 days apart**

[e] On weeks 25-52, see Section 5.1.1 for Nivolumab administration(-2/+3days) at a flat dose of 480mg, **nivolumab doses are given at least 12 days apart**

[f] On weeks 1-24, see Section 5.1.1 for Ipilimumab administration(-2/+3 days) for 3 doses

[g] XRT to begin 2 weeks after the first dose of Nivolumab and Ipilimumab and to be completed in 2 weeks

[h] Add free T4 if TSH is abnormal. Repeat at least every 12 weeks.

[i] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety blood test must be available and reviewed before commencing an infusion. **During weeks 7-24**: CBC and serum chemistries will be done every 2 weeks prior to the nivolumab or nivolumab/ipilimumab infusions. **During weeks 25-52**: CBC and serum chemistries will be performed every 4 weeks prior to each nivolumab infusion.

[j] Urinalysis performed at Screening and then as clinically indicated.

[k] Coagulation tests: prothrombin time, aPTT and INR – only performed at Screening and then as clinically indicated.

[l] Correlative blood samples will be collected on 3 occasions, prior to week 1, prior to week 8 and prior to week 16.

[m] Timing of CT scans for tumor assessments will be every 8 weeks (+/- 7 days).

[n] If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

[o] Follow-up phase for patients that discontinue treatment for reasons other than disease progression (see Section 7.1.4.5).

[p] Patients that have documented disease progression or starts treatment on new anti-cancer therapy will move into the survival follow-up phase.

7.1 Trial Procedures

7.1.1 Administrative

The Schedule of Assessments chart- Section 7 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator and/or Sponsor.

7.1.1.1 Informed Consent

The approved informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki. Investigator obtaining consent must 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. Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial. The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use.

The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

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

7.1.1.5 Disease Detail, Treatments and Subsequent Anti-Cancer Therapy

The investigator or qualified designee will obtain prior and current details regarding disease status. The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Assessments (Section 7) and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Sections: 5.1.2, 8.2, 8.3). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. AE collection will start once the subject signs consent and up to 100 days after the last dose of study treatment.

7.1.2.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening/baseline period. Clinically significant abnormal findings should be recorded as medical history. For cycles that do not require a full physical exam per the Schedule of Assessments (Section 7), the investigator or qualified designee will perform a targeted physical exam as clinically indicated prior to trial treatment administration, treatment discontinuation and during the safety follow-up.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, at treatment discontinuation and during the safety follow-up as specified in the Schedule of Assessments (Section 7). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment, discontinuation of trial treatment, and during the safety and long-term follow-up visits as specified in the Schedule of Assessments (Section 7).

7.1.2.5 Tumor Imaging and Assessment of Disease

See Section 4.3 for efficacy assessments.

7.1.2.6 Correlative Blood Collection

Blood will be collected for research purposes on three occasions: prior to week 1, prior to week 8 and prior to week 16. Blood will be separated into cellular and serum components for preservation and batch analysis. Flow cytometric evaluation of CD3, CD4, CD8, CD14, PD-1, PD-L1, PD-L2 on peripheral blood mononuclear cells.
Specimen Requirements: Submission for flow cytometry

- A 5-10 mL specimen of peripheral blood in a lavender- (EDTA) or green- (sodium heparin) tube is acceptable for each draw.
- Storage/Transport Temperature: Specimens can be transported with a cold pack or wet ice, but do not fix or freeze specimens.
- Unacceptable Conditions: Frozen specimens, specimens greater than 48 hours old, specimens fixed in formalin for flow cytometry

Address for shipping specimens:
Attn: Jenny Mao Zhengwei, Hematopathology
Seattle Cancer Care Alliance
Hematopathology Laboratory G7800
825 Eastlake Ave E.
Seattle, WA 98109

7.1.2.7 Tumor Tissue Collection

All patients will be required, unless waived by treating physician, to submit archival tissue as part of study participation. In patients who do not have archival tissue, a pretreatment tumor biopsy will be performed, unless deemed contraindicated by the treating physician. These samples will be submitted centrally for immunohistochemical expression studies involving proteins in the PD-1 family as well as CD3, CD69 and FOXP3. Acceptable archival tissue for correlative studies include formalin fixed paraffin embedded tissue collected within 12 months of study enrollment. Patients who do not have acceptable FFPE tissue will be required to undergo a study related biopsy to obtain fresh tissue. In cases where biopsies yield insufficient tissue for both tumor slice culture (TSC) and PDL1 testing, TSC testing will take priority. Any tissue not used for tumor slice culture will be submitted for PDL1 testing.

PD-L1 Testing

To ensure comparability of data across all studies of nivolumab and ipilimumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the Ventana SP263 assay. Testing should be restricted to the Ventana SP263 assay and should be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

The Ventana SP263 assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully reproducibility data package supporting cut-off and scoring algorithm. Following completion of ATLANTIC and HAWK clinical trials, the assay will be associated with clinical utility. In other cancer types (bladder, pancreatic, gastric, hepatocellular, triple negative breast, ovarian, esophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma, cholangiocarcinoma, small cell lung, melanoma and cervical HPV+ cancers), the Ventana SP263 assay has only limited clinical performance data.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a patient's PD-L1 status is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current PD-L1 status of the tumor and considered clinically most relevant.
- Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e., >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.
- When the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen it is not older than12 months. When archival samples are used to assess PD-L1 status, the age of the sample / date of collection should be captured.
- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis.

Sample data collection for PD-L1 testing

The following fields of data should be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (ecode or unique identifier)
- Specimen identifier (written on the specimen)
- Site identifier
- Specimen collection date
- Type of specimen submitted

- Quantity of specimen
- Date of sectioning
- Archival of fresh tumor
- Tumor type
- Primary tumor location
- Metastatic tumor location (if applicable)
- Fixative

The following fields of data should be collected from PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

The Ventana SP263 assay to measure PD-L1 in tumors is experimental. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

Sample processing and if indicated submission process for PD-L1 testing

Preparing Stored samples for testing

- Where samples already exist, they should be retrieved from the Bio-Bank storage location. These blocks should undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for PD-L1 testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 status. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 2 cores is advised in order to provide sufficient tissue for PD-L1 assessment.
- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. To fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate

volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature.

- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for PD-L1 testing

- An overnight processing schedule into paraffin wax is recommended
- Below is the suggested routine overnight processing schedule:

Storage of tumor blocks for PD-L1 testing

- FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

Quality control of samples to be used for PD-L1 testing

- Tissue should be assessed by the site pathologist prior to PD-L1 testing.
- Each sample should be reviewed for:
    - Adequate fixation
    - Good preservation of morphology
    - Presence of tumor tissue
    - Histopathology consistent with indication
    - Greater than 100 tumor cells are required to determine PD-L1 status – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.

If indicated, shipping samples to a PD-L1 testing laboratory

- When submitting sample to for PD-L1 testing the recommendation is to ship the block in order for sectioning to occur at the laboratory. Blocks should be shipped - containing enough material to be provided to allow a minimum of 5, and preferably 10, sections to be cut (each 4 micron thick) to be used for PD-L1 testing.

Sectioning instructions

- Where it is not possible or indicated to ship the block to laboratory for PD-L1 testing, unstained slides should be prepared from the paraffin-embedded tumor sample block as described below:

    - A minimum of 5-10 x 4 micron (μm) thick, unstained sections should be provided for PD-L1 testing
    - A new disposable microtome blade must be used for each block to prevent contamination between Slides are stable under these conditions for 6 months.
    - patient samples
    - Apply one section per slide to positively-charged Superfrost glass slides

- The sections should be dried overnight between room temperature and 37°C. Do not dry sections at temperatures above 37°C.

Sections should be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 status

Fresh tumor biopsies for tumor slice culture

Patients who do not have suitable archival tissue will be consented for fresh tissue biopsies. Dr. Venu Pillarisetty's lab will oversee the collection of fresh tissue during this biopsy. Tissue will be collected for tumor slice culture (TSC) preparation as described below. In cases where biopsies yield insufficient tissue for both TSC and PDL1 testing, TSC testing will take priority. Any tissue not used for tumor slice culture will be submitted for PDL1 testing.

TSC Preparation

Fresh treatment biopsy tissue in excess of that required for central IHC will be mounted and sliced (250 μm) using a Leica vibrating microtome. This tissue will be placed in 24-well plates in an air-liquid interface culture system using media optimized by our group for TSC.
Experiment #1 – Immune cell populations
TSC will be cultured for 1 to 6 days with control antibody, DMSO control, nivolumab (dose to be determined) alone, ipilimumab (1 μM) alone, or a combination of both drugs.

IHC for CD4, CD8, FOXP3, CD68

When adequate tissue is available for replicates, we will perform flow cytometry on enzyme-digested, disaggregated slices to measure:
Macrophage phenotype (CD68, HLA-DR, CD163, CD115, CD206)
T cell phenotype (general): CD3, CD4, CD8, CD25
T cell memory phenotype (CD45RO, CD127, CD28, CD27, CD62L, CCR7)
T cell inhibitor phenotype (PD-1, CTLA-4, LAG3, TIM3)
Tumor immune related markers (PD-L1, class I MHC, HLA-DR)

Experiment #2 – Induction of CD8+ T cell function

Upon completion of each culture period after drug treatment, slices will be treated with SR-FLICA caspase 3/7 assay reagent (Immunochemistry Technologies) for 1 hr, fixed, and then stained with DAPI prior to imaging by confocal microscopy to measure apoptosis. Fixed tumor slices will then be paraffin embedded and sectioned. IHC will be performed for CD8 and Ki67 (to measure proliferation) or granzyme B (to measure cytotoxic activity) or cleaved caspase 3 (to measure apoptosis). Number of positive cells for each marker will be determined.

Experiment #3 – Correlation of induction of cytotoxic T cell function with PD-L1 expression

We hope to have access to the centrally determined PD-L1 expression so that we will be able to correlate our CD8+ T cell functional data with induction of CD8+ T cell function.

Experiment #4 – Correlation of induction of cytotoxic T cell function with clinical response
We will use multivariate statistics to test the hypothesis that the degree of immune checkpoint inhibition-triggered CD8+ T cell activation and carcinoma cell death in TSC predicts response in our ongoing clinical trial.

Experiment #5 – Rescue of drug-refractory CD8+ T cell activation
Biopsies from patients with lack of clinical response will be placed in TSC and treated with combinations of nivolumab and ipilimumab and monoclonal antibodies designed to block additional immune checkpoints (GITR, LAG-3, TIM-3, CTLA-4), as this strategy may overcome T cell exhaustion.(Lu et al., 2014)

Experiment #6 – Correlation between T cell infiltrate and immunosuppressive signals
IHC of tumor tissue for cellular subtypes (CD3, CD4, CD8, FOXP3, CD68) and immunosuppressive molecules (PD-1, PD-L1, TIM-3, LAG-3, CTLA-4, IL-10, TGF-beta1, IDO, FASL). We will use multivariate statistics to correlate T cell infiltrate density and level of immunosuppressive signaling. Furthermore, we will be able to confirm whether the tumors fall into their expected category of level of T cell infiltration, as we believe that the immunophenotype is more important than traditional histology in determining response to immune checkpoint inhibition.

Experiment #7 – CD8+ T cell suppression
The proliferation of CD8+ TIL from TSC (cultured with or without exogenous IL-2 +/- CD3/CD28 beads) will be measured in two ways: directly by Ki67 staining, and indirectly by treating the TSC with BrdU and then subsequently staining for it. In both cases TSC will be fixed, embedded and double stained after 1 to 6 days in culture to determine what percentage of CD8+ T cells are cycling. Duplicate slices will be digested with collagenase-DNAse-hyaluronidase cocktail in rotating flasks to obtain a single-cell suspension. CD8+ T cell proliferation and activation state, as well as macrophage polarization, will be tested using a multi-color flow cytometry panel. We will correlate these data with those from Experiment #1 to determine if high-level expression of multiple immunosuppressive signals has functional consequences in the TSC.

Experiment #8 – Combination immune checkpoint inhibition
TSC will be cultured for 1 to 6 days with control antibody or nivolumab and ipilimumab (dose to be determined).
Upon completion of each culture period, slices will be treated with SR-FLICA caspase 3/7 assay reagent (Immunochemistry Technologies) for 1 hr, fixed, and then stained with DAPI prior to

imaging by confocal microscopy to measure apoptosis. Fixed tumor slices will then be paraffin embedded and sectioned. IHC will be performed for CD8 and Ki67 (to measure proliferation) or granzyme B (to measure cytotoxic activity) or cleaved caspase 3 (to measure apoptosis).

To determine whether immune checkpoints in fact inhibit the proliferation of T cells in the TSC, each of the known checkpoint molecules will be inhibited, either by antibody (PD-1, TIM-3, LAG-3, CTLA-4, IL-10, TGF-beta1, FASL) or using a small molecule (IDO) in the organotypic cultures. If the checkpoint is suppressing cytotoxic T cell proliferation, we would expect to see increased Ki-67 staining, and increased BrdU uptake by CD8+ T cells in the TSC. In tumors that express multiple checkpoint molecules, inhibition of several pathways may be required to overcome T cell functional exhaustion; in these cases, the effects of combination of checkpoint inhibitors on T cell proliferation will be investigated. Assessment of T-cell exhaustion and rescue will be based on the stimulated expression of IFN□. Single-cell suspensions from tumor slices will be treated with Golgi plug and stimulated with CD3/CD28 beads (for TCR and costimulation) or PMA/ionomycin (bypassing TCR signaling) prior to performing intracellular cytokine staining for flow cytometry. The proportion of IFN□-expressing CD8+ T cells in the TSC will be compared between treatment and control samples. For all immunohistological and flow cytometric analyses, a minimum of 100 cells of interest will be scored for each endpoint. Results between treated and control groups will be analyzed by t-test and ANOVA. Data will be analyzed across tumors with relation to level of T cell infiltration and immunosuppressive signal expression.

Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.
The Principal Investigator:

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject is informed about the sample disposal.

7.1.2.8 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

At baseline and during treatment local laboratory collection and assessments are to include: hematology, chemistry, urinalysis, hepatic panel, pregnancy test (for WOCBP) and correlative blood collection (see Section 7 and Table 3.)

Table 3. Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Collect T4 if TSH abnormal (repeat ≤ every 12 weeks)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Thyroid stimulating hormone (TSH) (repeat ≤ every 12 weeks)
	(CO_2 or bicarbonate)	Urine pregnancy test †	Blood for correlative studies
	Calcium		
	Chloride		
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

7.1.3 Other Procedures

7.1.3.1 Withdrawal/Discontinuation

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

7.1.4 Visit Requirements

Visit requirements are outlined in Section 7 –Schedule of Assessments. Specific procedure-related details are provided above in Section 7.1.1-7.1.2 - Trial Procedures.

7.1.4.1 Screening Period

The following assessments will be performed up to 28 days prior to initiation of study treatment:

- Written informed consent
- Verification of eligibility
- Full Physical Examination
- Vital Signs and weight
- ECOG performance status
- Demographic and history of tobacco and alcohol use
- Medical and previous treatment history
- Pregnancy test or Serum B-HCG in females of childbearing age (within 72 hours of starting therapy)
- Tumor tissue sample collection
- Correlative blood collection
- Hematology panel (within 3 days of starting therapy repeat on C1D1 not required)
- PT/INR and aPTT (at screening and when clinically indicated)
- Serum Chemistry panel (within 3 days of starting therapy repeat on C1D1 not required)
- Urinalysis (at screening and when clinically indicated)
- TSH and T4 if TSH abnormal (repeat ≤ every 12 weeks)
- Tumor imaging of known sites of disease
- Radiation therapy planning/simulation
- Adverse event/serious adverse event review
- Concomitant medication review

7.1.4.2 Treatment Period

The following assessments will be performed on day 1 of each cycle and must be performed no more than 24 hours prior to treatment unless otherwise specified:

- Targeted physical examination
- Vital Signs and weight
- ECOG performance status
- Hematology panel
- PT/INR and aPTT (as clinically indicated)

- Serum chemistry panel
- Urinalysis (as clinically indicated)
- TSH and T4 if TSH abnormal (repeat ≤ every 12 weeks)
- Correlative blood collection as indicated in Section 7
- Radiation therapy as outlined in Sections 5.1.1. and 7
- Nivolumab and Ipilimumab therapy as outlined in Section 5.1.1 (-2/+3 days), **nivolumab doses are given at least 12 days apart**
- Tumor imaging of known sites of disease (imaging every 8 weeks ±7 days)
- Adverse event/serious adverse event review
- Concomitant medication review

7.1.4.3 End of Treatment Visit

- Targeted physical examination
- Vital Signs and weight
- ECOG performance status
- Adverse event review/serious adverse event review
- Concomitant medication review

7.1.4.4 30-Day Post Last Treatment Visit

- Targeted physical examination
- Vital Signs and weight
- ECOG performance status
- Adverse event/serious adverse event review
- Concomitant medication review

7.1.4.5 Long-Term Follow-Up Visits every 8 weeks (±7 days) for patients without documented progression/ have not started new anti-cancer therapy

- ECOG performance status
- Adverse event/serious adverse event review collection up to 100 days after last dose of study treatment
- Follow-up will continue until end of study

7.1.4.6 Survival Follow-Up -Every 12 weeks for patients with documented disease progression/have started new anti-cancer therapy

- Medical record confirmation or phone contact confirmation to document survival

- Adverse event/serious adverse event review collection up to 100 days after last dose of study treatment
- Follow-up will continue until end of study.

8. SAFETY AND REPORTING

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of last dose of study treatment must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy). Hospitalizations and/or death related solely to progression of the underlying disease will not be considered an SAE.

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

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

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.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.

  - The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
  - The MedWatch form is available at: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

- Worldwide.Safety@bmsaepbusinessprocess@bms.com
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on either CIOMS or MedWatch form & pregnancies must be reported on a Pregnancy Surveillance Form or can be submitted on the aforementioned SAE form to BMS.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

8.1 DEFINITIONS FOR SERIOUS ADVERSE EVENTS

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

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

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

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported). Hospitalizations and/or death related solely to progression of the underlying disease will not be considered an SAE.

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

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 (e.g., 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

- Hospitalizations and/or death related solely to progression of the underlying disease will not be considered an SAE.

8.2 ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

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

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

8.3 NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) 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.
- Non-serious 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 ***non-serious adverse event*** is an AE not classified as serious.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected

continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

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

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 to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

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

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

Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

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) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

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

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form. A BMS Pregnancy Surveillance Form may be provided upon request.

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. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

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 non-serious or serious AE, as appropriate, and reported accordingly.

8.4 STUDY STOPPING RULE

In keeping with the study primary endpoint, a stopping rule will be implemented in the unlikely event that the combination under study is deemed to have unacceptably high toxicities. Enrollment will be halted if more than 3 patients experience a Grade 4 or higher drug related toxicity (CTCAE v. 5) during the trial treatment period or up to 30 days after the last investigational drug infusion. The likelihood of observing more than 3 Grade 4+ drug-related adverse events is 80% if the true

rate is 20% and the likelihood is 91% if the true rate is 25%. This rule has an 83% chance of prematurely discontinuing trial enrollment after the 1st 10 patients are enrolled if the true rate of Grade 4 drug related toxicity is 40%. The study will be reviewed by the University of Washington/Fred Hutch Cancer Consortium Data and Safety Monitoring Committee (DSMC

STATISTICAL CONSIDERATIONS

All patients enrolled in the study, including those in the run-in phase will be included in the analysis of toxicity and efficacy.

Safety and tolerability is the primary endpoint of this study, and all patients enrolled will be assessed for this endpoint. Adverse events will be recorded and graded based on CTCAE v. 5, and their relationship to the experimental agents reported.

Similarly, all patients enrolled in the study (i.e., the initial 6 patient cohort, and the additional 14 patient expansion) will be included in the efficacy analyses. Clinical responses to the combination of nivolumab, ipiliumumab and hypofractionated radiation will be based on RECIST 1.1 criteria. Oncologic outcome endpoints such as progression free and overall survival will be calculated from the date of study enrollment, until disease progression or death from any cause, respectively. Survival estimates will be calculated using the Kaplan-Meier method.

Exploratory endpoints of this study include correlative work performed on research serum and tissue samples.

Sample size determination

There are multiple ongoing studies in various tumor types exploring the activity of nivolumab and ipilimumab. In a published report of the combination in patients with advanced NSCLC treated on a phase I study (Checkmate, 012), treatment related serious adverse events were observed in 28% of patients (Hellmann Lancet Oncol 2017). This study plans to accrue 20 patients, a sample size that would allow us to estimate grade 3 or higher acute drug related toxicity rate of 30% with a confidence interval of 20% (95% confidence level) or an upper bound of 50%. This would allow us to reasonably exclude a clinically significant increase in toxicity with the addition of radiation therapy to the nivolumab and ipilimumab combination as defined by the upper bound of the confidence interval.

9. STUDY MANAGEMENT

All investigators on the protocol will receive formal training in the ethical conduct of human research. Institutional support of trial monitoring is provided in accordance with the Cancer Consortium's data and safety monitoring plan

Monitoring of the study

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, Fred Hutch Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study. The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state, and federal guidelines.

Data Management

The Protocol Director, or her designees, will prepare and maintain adequate and accurate participant case histories with observations and other data pertinent to the study. Original source documents should be transcribed to Case Report Forms (CRFs) and used to analyze the study data. Source documents include hospital records, clinical charts, laboratory and pharmacy records, and recorded electronic data.

All data required by the trial will be entered onto paper and electronic case report forms. Any corrections to data required into the paper case report forms must be made in such a way that the original entry is not obscured. Only designated study staff will enter data for study participants after study visits. Case report forms will be checked against source document data by study staff. Patient records will be kept in a secure location at the University of Washington accessible only to research authorized personnel. The patient identity will be kept as confidential as possible as required by law. Except as required by law, the patient will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Study subjects will be assigned an ID code. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, the patient identity will not be disclosed. The patient's personal data which may be included in the investigator’s database shall be treated in compliance with all applicable laws and regulations.

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