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Phase II study of nivolumab and ipilimumab for treatment of metastatic/recurrent adenoid cystic carcinoma of all anatomic sites of origin and non-adenoid cystic carcinoma malignant tumors of the salivary gland

Principal Investigator: Young Chae, MD, MPH, MBA
Co-Director, Early Phase Clinical Trials Unit
Developmental Therapeutics - Lurie Cancer Center
Associate Professor of Hematology and Oncology
Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University
645 N. Michigan Ave, Suite 1006
Chicago Illinois 60611
Fax: (312) 472 0564
Phone: (312) 926-4248
Email: ychae@nm.org

Biostatistician: Borko Jovanovic, PhD

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Coordinating Center: **Clinical Research Office**
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
676 N. St. Clair, Suite 1200
Chicago, IL 60611
http://cancer.northwestern.edu/CRO/index.cfm

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LIST OF ABBREVIATIONS

ACC	Adenoid Cystic Carcinoma
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTAs	Cancer/Testis Antigens
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T Lymphocyte Associated Antigen-4
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
GI	Gastrointestinal
H&PE	History & Physical Exam
HunMab	Human Monoclonal Antibody
IFN-γ	Interferon-γ
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL-2	Interleukin-2
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IV (or iv)	Intravenously
LAK	Lymphocyte-Activated Killer
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed Death Receptor-1
PD-L1	PD Ligand-1
PFS	Progression Free Survival
PFSR	Progression Free Survival Rate
PO (or p.o.)	Per os/by mouth/orally

PPK	Population Pharmacokinetics
PR	Partial Response
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TNF-α	Tumor Necrosis Factor-α
WBC	White Blood Cells
WT1	Wilm's Tumor 1

STUDY SCHEMA

Up to 43 patients will be enrolled with metastatic/recurrent ACC of any site of origin with evidence of disease progression who are not candidates for curative surgical or radiation therapy. An exploratory cohort of 20 patients with non-ACC of major or minor salivary glands will be enrolled concurrently.

Tumor tissue collection if available

1 cycle = 12 weeks / 84 days

Nivolumab will be given as follows:
240mg IV every 14 days for 8 doses (Cycle 1 + Cycle 2 Days 1 & 15),
480mg IV every 28 days starting with Cycle 2 Day 29 (Day 1, 29, and 57 of each cycle thereafter)

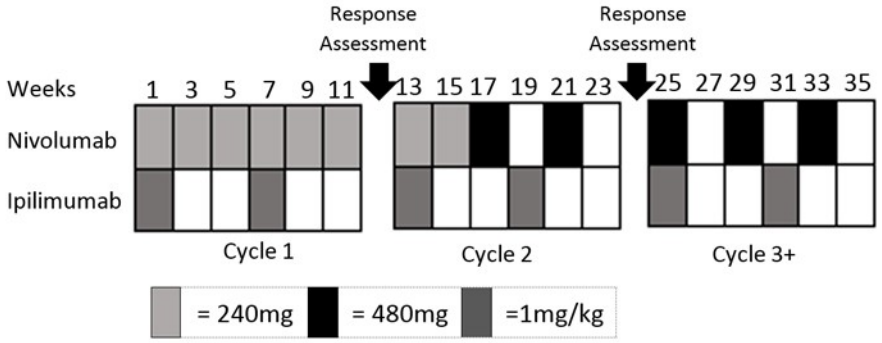
Ipilimumab will be given at 1mg/Kg IV every 42 days (Day 1 and 43 of each cycle)

Response Assessment every 12 weeks (Day 1 of each cycle, ±7 days)

Treat until disease progression, intolerable toxicity, or withdrawal of consent

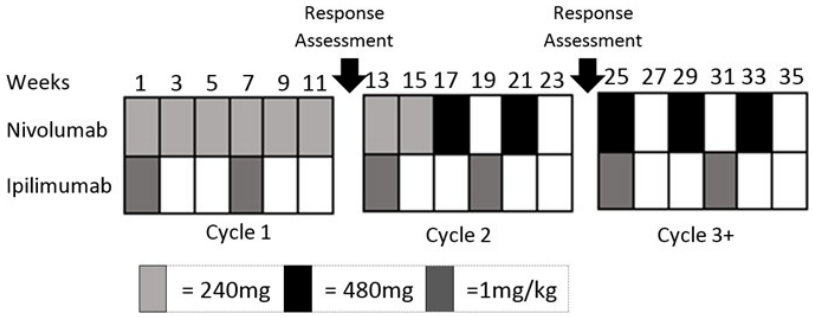
Treatment discontinuation (unless patient meets criteria for treatment beyond progression, listed in section 4.4)

**The first 15 ACC patients will be assessed for safety, and ACC accrual will be terminated if ≥ 7 patients are withdrawn after <24 weeks of treatment for any reason other than withdrawal of consent. Otherwise, enrollment will continue for a total of 43 ACC patients. The exploratory cohort of 20 non-ACC MSGT's will follow an independent accrual process to ACC and will also be assessed for safety; if >2 of the first 10 non-ACC patients are withdrawn after <24 weeks of treatment, the non-ACC cohort will be closed to accrual.



STUDY SUMMARY

Title	Phase II study of nivolumab and ipilimumab for treatment of metastatic/recurrent adenoid cystic carcinoma of all anatomic sites of origin and non-adenoid cystic carcinoma malignant tumors of the salivary gland
Version	October 6, 2022, Amendment 8
Study Design	Simon two-stage single arm multi-center phase II clinical trial
Study Center(s)	Northwestern University
Objectives	Primary: (1) To assess median progression-free survival (PFS) as well as PFS at 6 and 12 months in patients with recurrent or metastatic adenoid cystic carcinoma treated with a combination of nivolumab and ipilimumab. Secondary: (1) To assess the efficacy of nivolumab and ipilimumab according to response rate (RR), disease control rate (DCR) or clinical benefit rate (CBR) at 6 and 12 months- defined as sum of CR, PR, and SD, overall survival (OS) and progression free survival (PFS) in the above population using RECIST criteria. (2) To assess the efficacy of nivolumab and ipilimumab according to ORR, DCR, PFS, and OS in the above population using immune-related RECIST (irRECIST) criteria. (3) To assess the safety and tolerability profile of nivolumab and ipilimumab therapy in the above population using CTCAE version 4.03 Exploratory: (1) To assess the immune-related biomarkers and their association with treatment response (2) To assess activity of nivolumab and ipilimumab in non-ACC malignant salivary gland tumors (MSGTs) using OS, PFS, CBR, and ORR
Sample Size	63 [43 patients with ACC plus 20 patients with non-ACC MSGT(exploratory group)]
Diagnosis & Key Eligibility Criteria	Study population will consist of patients age 18 or older, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, with metastatic/recurrent adenoid cystic carcinoma (ACC) of salivary and non-salivary gland origin, as well as non-adenoid cystic carcinomas (non-ACC) of major or minor salivary glands who are not surgical or radiation candidates with evidence of disease progression. Disease progression is defined as one of the following occurring within the 6 months prior to study entry: (1)At least a 20% increase in radiologically or clinically measurable lesions (2)Appearance of any new lesions or (3)Symptomatic and/or deterioration in clinical status Patients cannot have a history of clinically significant autoimmune diseases or a syndrome that requires systemic steroids or immunosuppressive agents. Patients on treatment with prednisone > 10mg daily or equivalent corticosteroid will be excluded.

Treatment Plan	Eligible patients will be started on nivolumab 240mg IV every 14 days for the first 8 doses and 480mg IV every 28 days starting with Cycle 2 Day 29 (1 cycle = 12 weeks / 84 days). Ipilimumab 1mg/kg IV will be given q 6 weeks starting at Cycle 1 Day 1 until disease progression, unacceptable toxicity or withdrawal of consent. Patients will have response assessments every 12 weeks (each cycle). 
Statistical Methodology	The main outcome is median Progression Free Survival (PFS) as well as PFS at 6 and 12 months. The optimal two-stage design to test the null hypothesis that P<=0.450 versus the alternative that P>=0.650 has an expected sample size of 24.70 and a probability of early termination of 0.654. If the drug is actually not effective, there is a 0.048 probability of concluding that it is (the target for this value was 0.050). If the drug is actually effective, there is a 0.196 probability of concluding that it is not (the target for this value was 0.200). After testing the drug on 15 ACC patients in the first stage, ACC accrual will be terminated if 7 or more patients are withdrawn from the study after <24 weeks of treatment for any reason other than withdrawal of consent (this includes PD, toxicity, intolerance etc.). If the trial goes on to the second stage, a total of 43 patients will be studied. If the total number responding (where response is defined as stable disease or better) is less than or equal to 24, the drug is rejected. An additional exploratory group of 20 patients with non-ACC MSGT will be added concurrently with ACC patients for a total samples size of 63 patients. An additional safety analysis will take place for non-ACC patients; if >2 of 10 non-ACC patients are withdrawn after <24 weeks of treatment, accrual of non-ACC patients will discontinue. Response rates and 95% confidence intervals will be calculated using exact binomial probability distributions for discrete outcomes. Progression-free survival and overall survival will be graphically depicted using Kaplan-Meier curves. Adverse events will be summarized descriptively using frequencies and percentages. Statistics will be given on type, severity, frequency and attribution of adverse events. Sample size considerations are described above.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

Adenoid cystic carcinoma (ACC) is a rare cancer most often occurring in the salivary glands. The cancer can also arise in other locations including the breast, skin, respiratory system, and reproductive organs.[1] ACC has a tendency for delayed recurrence and metastasis after initial treatment.[2] Five, ten, and fifteen year survival rates after surgical resection have been reported as 77.3%, 59.6%, and 44.9%, respectively, with close to half of the patients dying from ACC, as opposed to other causes, at long-term follow-up.[3] Because of its rarity and distinctive clinical features, the pathophysiology of ACC remains understudied, resulting in fewer evidence based therapies compared to other cancers.

Currently there is no standard of care systemic treatment for ACC other than repeated surgical resection for locoregional control for early stage disease. In advanced stage, conventional chemotherapy can be considered as first-line therapy with only modest benefit as is the case with cisplatin and 5-FU. ACC is one of the rare cancers with significantly high unmet need that awaits breakthrough in its treatment methodology. Due to its rarity, there are no disease specific agents specifically designed for the treatment of ACC. When we performed comprehensive analysis of the clinical trials that enrolled ACC, only 5.5% (22 out of 397 total patients enrolled) objective response rate was found.[4]

The newest armamentaria in cancer treatment are cancer immunotherapies. In ACC, cancer vaccination and adoptive immunotherapy using LAK/cytokines have been tried in a small number of clinical trials that showed encouraging results. An *in vitro* study of adoptive immunotherapy for the ACC cell line was performed in 1996 by a Chinese group.[5] This group investigated the susceptibility of ACC cells to lymphocyte-activated killer (LAK) cells under the influence of cytokines, Tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). It was confirmed that LAK cells showed cytotoxicity against ACC cells. Also, they concluded both TNF-α and IFN-γ could enhance this cytotoxic process. Previously, it was reported that these cytokines induced tumor differentiation and apoptosis.[6,7]

In line with this, a clinical trial using adoptive immunotherapy with chemoradiation was performed on 2 maxillary ACC patients in Japan.[8] Both patients were given radiation, 5-FU and peplomycin followed by intra-arterial injection of LAK cells, interleukin-2 (IL-2) and IFN-γ on day 7. Two weeks after the initiation of the treatment, significant tumor regression was observed. 3 weeks after finishing the treatment, a CT scan revealed tumor reduction with new bone formation of the sinus walls in both patients. Furthermore, those patients showed a good quality of life according to the report, meaning that this regimen was well tolerated. Even though the mechanism was not fully understood, it could be assumed that cytokine-induced cell apoptosis and cytotoxic effect of LAK cells contributed to tumor regression. This study result necessitates further trials to confirm the effect of immunotherapy in ACC.

Cancer vaccination, another immunologic approach targeting the specific cancer antigens, has also been attempted in ACC.[9,10] A hypothesis regarding Cancer/testis antigens (CTAs) as a potential target of immunotherapy was suggested based on the finding that CTAs were highly expressed in a subset of ACC cells, but not in normal cells. Similar to CTAs, WT1 (Wilm's tumor 1) antibodies and WT1-specific cytotoxic T cells were observed in many cancer patients, suggesting WT1 protein could be a target of cancer vaccination.[9] In a phase I clinical trial performed in Japan, WT1 peptide vaccination was used on ACC patients with pulmonary metastasis. A significant suppression of the tumor growth was shown during treatment (1 year), while rapid tumor growth and new metastases occurred after the withdrawal of therapy. This trial implicated the role of immune system in the treatment of ACC.[11]

The recent whole exome and genome sequencing of ACC has led to new compelling discoveries. Ho *et al.* analyzed sequences of 60 ACC tumors paired with normal DNA

samples. The study revealed genomic alterations in the pathways associated with *MYB/MYC*, chromatin remodeling, tyrosine kinase signaling, and DNA damage/check point signaling.[12] Errors in the DNA repair system cause genomic instability, which may be associated with malignant transformation of cells. Some of these mutations have also been noted in ACC.[13] The whole genome sequencing revealed more mutated genes involved in DNA damage signaling pathway, in a 27% prevalence of the sample cohort. Those include *BRCA1, ATM, TXNIP, PRKDC* and *TP53*.[12] *TP53* is a tumor suppressor gene, which regulates cell death and DNA repair. It is the most frequently mutated gene in cancers, occurring in up to 75% of invasive cancers.[14] Somatic mutations in *TP53* as well as related genes (e.g. *UHRF1*) were identified in ACC.[12,15] In addition, a recent study demonstrated that down-regulation of p53 induced increased perineural invasion activity of ACC *in vitro* [16]. Recent evidence showed DNA repair pathway defect suggesting higher somatic mutation burden translates into better immune checkpoint inhibitor response.[17] Frequent mutations in DNA damage repair genes and chromatin remodeling genes and a wide array of somatic alterations may results in a significant number of neoepitope peptides derived from these altered genes, eliciting the generation of specific cytotoxic T cells.[18,19]

Building upon this scientific rationale supporting the potential for immunotherapies in ACC (arising in any anatomic site) and the immeasurable clinical need for novel treatments in this population, we hypothesize that immune checkpoint blockade can be a powerful potential therapeutic strategy for patients with ACC that require active clinical investigation. Effective disease control with immune checkpoint inhibitors as monotherapy or in combination (i.e., CTLA4 and PD-1/PD-L1 inhibitors) was observed in several types of cancer in including cutaneous melanoma, squamous cell carcinoma of head and neck.[20-23]. The encouraging results from these trials should pave the way for other malignancies such as ACC[24]. **Therefore, we suggest the use of nivolumab and ipilimumab in ACC with high unmet need and potential for response with these agents.**

In addition, malignant salivary gland tumors (MSGTs), including ACC and non-ACC account for less than 1% of all cancers, and 6% to 7% of cancers of the head and neck.[25-27] Unlike ACC, non-ACC MSGTs are a heterogeneous group with distinct histologies and variable biologic behavior. Patients with recurrent or metastatic non-ACC MSGTs may achieve objective response rates ranging from 10-30% with single agent chemotherapy, mostly first line, and 29-50% ORR with combination chemotherapy in the same setting. Duration of response is typically limited between 3 to 9 months. [28,29]

There are no standard of care therapeutic options for non- ACC MSGT following progression of disease on first line therapy. Given this, patients with progressive non-ACC MSGT are in need for novel therapies and make good candidates for trials of investigational new drugs. Therefore, we propose the use of **Nivolumab and ipilimumab combination therapy in non-ACC malignant salivary gland tumors (MSGTs) as an exploratory objective.**

1.2 Intervention Background & Overview

1.2.1 Nivolumab, ipilimumab and nivolumab/ipilimumab combination

Nivolumab (BMS-936558, MDX-1106) is a fully human monoclonal immunoglobulin G4 (lgG4) antibody (HunMab) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [cd279]) cell surface membrane receptor (Investigator brochure version 2014). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an “exhausted” phenotype. Nivolumab anti-tumor activity has been investigated in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC).[22,30,31] The

combination of nivolumab and ipilimumab (anticytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in phase 1/2 trial showed markedly enhanced clinical activity with acceptable safety profile in melanoma patients.[32] Nivolumab is currently FDA approved for BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent in unresectable or metastatic melanoma, in combination with ipilimumab, metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy and advanced renal cell carcinoma who have received prior anti-angiogenic therapy, the treatment of patients with advanced stage non-small cell lung cancer after progression on platinum based chemotherapy and patients with metastatic renal cell carcinoma. Nivolumab is well tolerated when compared to chemotherapy with rare grade 3 or 4 toxicities. Nonetheless is has been associated with immune related adverse events such as pneumonitis, colitis, which have frequency of less than 5%.[30]

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody. Several preclinical studies demonstrated that CTLA-4 blockade could augment T cell-mediated immune responses against tumors.[33,34] This let to the development of ipilimumab, a fully humanized IgG1 monoclonal antibody to CTLA-4. Two phase 3 trials demonstrated a durable clinical benefit for approximately 20-25% of metastatic melanoma patients with ipilimumab resulting in FDA approval of this compound as a first and second-line agent in metastatic melanoma.[35,36] Ipilimumab has been associated with immune mediated toxicities such as diarrhea, colitis, rash, pruritus, hypothyroidism. The risk of grade 3 and 4 immune-related adverse is estimated at approximately 14%.[35]

Preclinical data show that the combination blockade of the PD-1/PD-L1- and CTLA-4-negative costimulatory pathways allows tumor-specific T cells that would otherwise be inactivated to continue to expand and carry out effector functions, thereby shifting the tumor microenvironment from suppressive to inflammatory.[37] A recently published phase III on patients with untreated metastatic melanoma showed significant PFS in patients treated with the combination of nivolumab and ipilimumab when compared to either agent along.[38] The combination of ipilimumab and nivolumab is now a standard first line option in the treatment of metastatic melanoma patients. Grade 3 and 5 treatment-related toxicities were described in 55% of patients treated with diarrhea, fatigue, and elevation of liver enzymes happening in less than 10% of the patients.[38]

1.2.2 Clinical development

Nivolumab in combination with ipilimumab is being evaluated in completed and ongoing BMS-sponsored clinical trials in melanoma, renal cell carcinomas, glioblastomas, lung cancer and gastrointestinal (GI) malignancies including colorectal cancer with microsatellite instability (MSI), and triple-negative breast cancer (TNBC) with an expanding group of indications (Investigator Brochure version 2015). On September 30, 2015, the U. S. Food and Drug Administration granted accelerated approval to nivolumab (Opdivo Injection, Bristol-Myers Squibb Company) in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma.

1.2.3 Clinical efficacy

Nivolumab and ipilimumab have demonstrated clinical activity as monotherapy and as combination therapy in several tumor types. The majority of responses was durable and exceeded 6 months (Investigator Brochure version 2015).

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in

NSCLC, melanoma, and RCC. ORs were observed at all doses. Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Heavily pretreated patients with NSCLC treated with nivolumab (1, 3, or 10mg/kg) achieved median OS across all dose cohorts of 9.9 months with response rates of 17% and median duration of response 17 months [39]. In addition, responses were similar between both squamous and non-squamous carcinoma cohorts in this study. A subsequent phase 3 study compared nivolumab to docetaxel in second-line treatment setting of advanced squamous cell carcinoma among 272 patients. Nivolumab arm demonstrated superior median OS (9 vs. 6 months), 1 year survival rate (42 vs. 24%), response rates (20 vs. 9%), and significantly lower rates of grade 3-4 treatment related adverse events (7 vs. 55%) [30]. These results supported the FDA approval of nivolumab for second-line treatment of advanced squamous cell carcinoma following treatment with platinum-based chemotherapy.

Nivolumab has also clinically meaningful activity in RCC. A phase II study treated 168 patients with advanced clear cell RCC with progression after agents targeting VEGF pathway at three doses of nivolumab (0.3, 2 and 10mg/kg) [40]. Median overall survival was 18, 25, and 24 months for the three dose cohorts, respectively. More recently 821 patients previously treated with anti-angiogenic therapy were randomized to either nivolumab (3mg/Kg every 2 weeks) or everolimus (10mg daily).[41] The median overall survival was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The hazard ratio for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; P=0.002), which met the prespecified criterion for superiority (P≤0.0148). Response rates were in average 20% with only 11% incidence of grade 3-4 treatment-related adverse events.

The clinical efficacy of ipilimumab monotherapy was assessed in phase 3 trial among 676 patients with metastatic progressive melanoma.[35] total of 676 HLA-A*0201-positive patients with unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease, were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus gp100 (403 patients), ipilimumab alone (137), or gp100 alone (136). Ipilimumab, at a dose of 3 mg per kilogram of body weight, was administered with or without gp100 every 3 weeks for up to four treatments (induction). Eligible patients could receive reinduction therapy. The primary end point was overall survival. The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio for death, 0.68; P<0.001). The median overall survival with ipilimumab alone was 10.1 months (hazard ratio for death in the comparison with gp100 alone, 0.66; P=0.003). No difference in overall survival was detected between the ipilimumab groups (hazard ratio with ipilimumab plus gp100, 1.04; P=0.76). Ipilimumab is now FDA approved for the treatment of patients with metastatic unresectable melanoma.

In an advanced melanoma phase 1 study, nivolumab and ipilimumab combination was administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) [32]. The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses of 1 mg/kg nivolumab and 3 mg/kg of ipilimumab, with tumor reduction of 80% or more (modified World Health Organization criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%. These results demonstrate significant

clinical activity of nivolumab across multiple histologies with favorable toxicity profile.

In a phase 2 study of nivolumab in combination with ipilimumab vs. ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma, the combination of nivolumab with ipilimumab demonstrated clear evidence of clinical activity over ipilimumab monotherapy, as measured by statistically significant improvements in ORR and PFS, and a higher proportion of subjects with complete responses.[22] A phase 3 study of nivolumab monotherapy or nivolumab in combination with ipilimumab vs. ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma, the combination of nivolumab with ipilimumab demonstrated clear evidence of clinical activity over ipilimumab monotherapy, as measured by statistically significant improvements in median PFS in the combination arm (11.5 vs. 6.87 vs. 2.89 months).[38] Based on descriptive analyses, the combination of nivolumab with ipilimumab demonstrated improved PFS nivolumab and ipilimumab monotherapies.

Most recently, nivolumab at 3mg/Kg every 2 weeks combined with ipilimumab at 1mg/KG every 6 weeks was evaluated in patients with advanced NSCLC in the first line setting(CheckMate 012 trial).[23] In this trial 4 different combinations of nivolumab were compared (nivolumab 1mg/Kg every 3 weeks x 4+ ipilimumab 1mg/Kg every 3 weeks x 4 followed nivolumab 3mg/Kg every 2 weeks (N=31), nivolumab 1mg/Kg every 2 weeks + ipilimumab 1mg/kg every 6 weeks (N=40), nivolumab 3mg/Kg every 2 weeks + ipilimumab 1mg/Kg every 12 weeks (n=38) and finally nivolumab 3mg/Kg every 2 weeks combined with ipilimumab 1mg/Kg every 6 weeks until disease progression (n=46). The efficacy data showed response rates of 13, 25, 39 and 31% respectively. These results suggest that continuation of dual CTLA4 and PD-1 inhibition can improve clinical outcomes when compared to currently used regimen.

1.2.4 Clinical Safety

For nivolumab monotherapy, the safety profile is similar across tumor types (investigator brochure v 2015). The only exception is pulmonary inflammation adverse events (AEs), which may be numerically greater in subjects with NSCLC, because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Safety data for subjects with previously treated advanced or metastatic NSCLC treated with nivolumab monotherapy in CA209017 (131 subjects), CA209057 (287 subjects), and CA209063 (117 subjects) were pooled and safety analyses were performed for these pooled subjects who receiving nivolumab monotherapy (a total of 535 subjects)(investigator brochure v 2015). Based on the pooled analyses, nivolumab monotherapy at a dose of 3 mg/kg administered IV Q2W has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation. The most common adverse events were fatigue (19.6%), decreased appetite (12.3%), nausea (12.0%), and asthenia (10.5%). The majority of drug-related AEs were of Grade 1-2 in severity.

The toxicity profile of ipilimumab at the dose of 3mg/Kg for 4 doses in previously treated patients with metastatic melanoma was assessed in phase 3 trial. One hundred and thirty one patients with received ipilimumab as monotherapy, 380 received it with gp100 peptide, and 132 received gp100 peptide vaccine alone. Patients in the study received a median of 4 doses. Ipilimumab was discontinued

for adverse events in 10% of patients. The most common adverse events in patients who received ipilimumab at 3mg/Kg were fatigue (31%), pruritus (23%) and rash (22%)(package insert v 2013). The majority of drug-related AEs were of Grade 1-2 in severity.

In several ongoing clinical trials, the safety of nivolumab in combination with ipilimumab is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab + ipilimumab in subjects with melanoma. Thus far, the combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases with a greater frequency.[32]

Safety data for subjects with previously untreated unresectable or metastatic melanoma treated with nivolumab in combination with ipilimumab in phase III (313 subjects) and phase II (94subjects) trials were pooled and safety analyses were performed for these pooled subjects receiving nivolumab in combination with ipilimumab (a total of 407 subjects) as described in the investigator brochure BMS-936558/MDX1106 Version No14, 30-Jun-2015.[22,38] Based on the pooled analyses, nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg administered IV Q3W for 4 doses followed by nivolumab 3 mg/kg IV Q2W has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation. The most frequently reported drug-related AEs of any grade were diarrhea (43.0%), fatigue (35.4%), pruritus (33.4%), rash (31.0%), nausea (24.8%), pyrexia (18.7%), ALT increased (18.2%), AST increased (16.7%) and decreased appetite (16.2%). The most frequently reported drug-related Grade 3-4 AEs (≥ 5% of subjects) were colitis (9.6%), diarrhea (8.80%), ALT increased (8.4%), lipase increased (8.4%), and AST increased (5.9%). Study drug toxicity was considered responsible for 2 deaths; 1 subject died of ventricular arrhythmia within 30 days of the last dose and the other died of pneumonitis between 31 and 100 days of the last dose.

Most recently, nivolumab at 3mg/Kg every 2 weeks combined with ipilimumab at 1mg/KG every 6 weeks was administered in patients with advanced NSCLC in the first line setting (CheckMate 012 trial).[23] In this trial 4 different combinations of nivolumab were compared (nivolumab 1mg/Kg every 3 weeks x 4+ ipilimumab 1mg/Kg every 3 weeks x 4 followed nivolumab 3mg/Kg every 2 weeks (N=31), nivolumab 1mg/Kg every 2 weeks + ipilimumab 1mg/kg every 6 weeks (N=40), nivolumab 3mg/Kg every 2 weeks + ipilimumab 1mg/Kg every 12 weeks (n=38) and finally nivolumab 3mg/Kg every 2 weeks combined with ipilimumab 1mg/Kg every 6 weeks until disease progression (n=46). Toxicity data favored the latter group with estimates of grade 3 and 4 treatment related adverse events 29, 35, 29 and 28%, respectively. These results indicate that the nivolumab dose of 3mg/Kg administered every 2 weeks combined with ipilimumab 1mg/Kg every 6 weeks until disease progression has favorable disease profile and should be further explored in future clinical trials.

1.2.5 Biomarkers

Significant efforts continue to explore potential tumor cells and microenvironment-related biomarkers that could predict response to nivolumab and other checkpoint inhibitors. For instance, tumor cell expression of PD-L1 was characterized with the use of immunohistochemistry (IHC) staining and pharmacodynamics changes in the peripheral blood absolute lymphocyte count in the study investigating the combination of nivolumab and ipilimumab in melanoma.[32] PD-L1 positivity was defined as expression in at least 5% of tumor cells. Among patients treated with the concurrent regimen of nivolumab and

ipilimumab, ORs were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22). In the sequenced regimen cohorts, a higher number of overall responses were seen among patients with PD-L1–positive tumor samples (4 of 8 patients) than among patients with PD-L1–negative tumor samples (1 of 13) suggesting the possibility that these tumors have higher response rates to the combination. Other biomarkers such as tissue expression of PDL-2, interferon-γ (IFN- γ), IDO (indoleamine-pyrrole 2,3-dioxygenase), and T cell CD8+ infiltration are also being investigated. However, there is no definitive date to support the use of any of these biomarkers to select patients for treatment at this time.

1.3 Rationale for the Current Study

Monoclonal antibodies immune checkpoint inhibitors have shown evidence of antitumor efficacy among various solid tumors as discussed below. Recent evidence showed significant correlation between higher somatic mutation burden and better immune checkpoint inhibitor response.[17] Frequent mutations in DNA damage repair genes and chromatin remodeling genes and a wide array of somatic alterations found from the recent genomic sequencing studies in ACC may result in a significant number of neoepitope peptides derived from these altered genes, eliciting the generation of specific cytotoxic T cells.[18,19] Also results from early phase clinical trial support that activation of the immune system through vaccination may indeed results suppression of the adenoid cystic tumor growth.[11]

1.3.1 Study design

The rationale for use of a phase II study is based on the fact that it allows for evaluation of anti-tumor efficacy of nivolumab combined with ipilimumab in patients with recurrent/metastatic adenoid cystic carcinomas. Patients with non-ACC who also have recurrent/metastatic disease will be studied as part of an exploratory objective but will not be included in our statistical analysis. To our knowledge this is the first study to address this question.

1.3.2 Nivolumab flat dose regimen

The safety and efficacy of 240 mg (monotherapy) Q2W flat dose of nivolumab has recently received FDA approval and is expected to be similar to the 3 mg/kg Q2W dosing regimen. Using the population PK (PPK) model, exposure of nivolumab at 240 mg flat doses is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight in nivolumab clinical trials. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat doses compared to 1mg/kg and 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

In addition, nivolumab 480 mg administered once every 4 weeks (Q4W) is currently under investigation. The less frequent dosing regimen is designed to afford more convenience to the target patient populations. The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) to provide an approximately equivalent dose of nivolumab 3 mg/kg Q2W. Exposures following nivolumab 480 mg Q4W regimen are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are

not considered to put participants at increased risk. Hence, the flat doses of 240mg and 480mg nivolumab are under investigation.

1.3.3 Ipilimumab dose regimen

Ipilimumab will be administered at 1mg/Kg every 6 weeks until disease progression in combination with nivolumab 240mg every 2 weeks. As discussed above, this drug combination regimen has been compared with the current FDA approved combination regimen of nivolumab 1mg/Kg every 3 weeks x 4 and ipilimumab 3mg/Kg every 3 weeks x 4 followed by nivolumab 3mg/Kg every 2 weeks until disease progression and showed favorable toxicity profile with maintained efficacy among patients with advanced lung cancer.[23]

1.4 Exploratory Studies

In the era of personalized therapy appropriate patient selection to immune-check point inhibitors remains an elusive goal. There are conflicting data on the predictive value of PD-L1 expression on PD-1 directed therapy in solid tumors.[30,42] Herbst et al. showed that patients with solid tumors including non-small cell lung cancer and melanoma treated with humanized PD-L1 antibody had higher ORR when immunohistochemistry showed intense staining for PD-L1 in the tumor [43]. The same correlation was not observed on stratified analysis according to tumor cell membrane PD-L1 expression of non-small cell lung cancer patients treated with nivolumab therapy in the second line setting.[30]

All subjects will be asked to provide consent to supply a sample of their archival tumor blocks if a sample is available. Archival tumor samples, when available, may be evaluated for the immunosuppressive biomarker PD-L1 protein on tumor cells and the expression level and localization of other markers of inflammatory/immune signature that may include but not be limited to PD-1, OX40, CD73, CD39, T cell immunoglobulin and mucin domain containing protein 3 (TIM3), GITRL, CTLA-4, CD3, CD4, CD8, protein tyrosine phosphatase receptor type C (CD45RO), forkhead box P3 (FOXP3), and granzyme by immunohistochemistry analysis and/or flow cytometry and comprehensive genomic profiling.

The association between treatment response and the above biomarker status will be investigated.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

To assess median progression-free survival (PFS) as well as PFS at 6 and 12 months in patients with recurrent or metastatic adenoid cystic carcinoma (ACC) treated with a combination of nivolumab and ipilimumab.[44] Patients will have scans every 12 weeks. Efficacy will be evaluated in all patients who receive at least one dose of study treatment and have had their disease re-evaluated.

2.2 Secondary Objectives & Endpoints

2.2.1 To assess the efficacy of nivolumab and ipilimumab according to response rate (RR), disease control rate (DCR; CR, PR, and SD at 6 and 12 months), overall survival (OS) and progression free survival (PFS) using RECIST criteria in patients with recurrent or metastatic ACC. [44]

The time in months from start of treatment to progression or death will be measured for all patients who receive at least one dose of study drug. Patients will be followed up to 2 years after completion of treatment. Efficacy will be evaluated in all patients who receive at least one cycle of study treatment.

2.2.2 To assess the efficacy of nivolumab and ipilimumab according to ORR, DCR, PFS, and OS in patients with recurrent or metastatic ACC using irRECIST criteria.[45]. Efficacy will be evaluated in all patients who receive at least one dose of study treatment and have had their disease re-evaluated.

2.2.3 To assess the safety and tolerability profile of nivolumab and ipilimumab therapy in patients with recurrent or metastatic ACC using CTCAE version 4.03. The number, frequency, and severity of adverse events will be collected from time of consent until 30 days after study treatment for all patients who receive at least one dose of study drug.

2.3 Exploratory Objectives & Endpoints

2.3.1 Assess safety, tolerability and activity of nivolumab and ipilimumab in non-ACC malignant salivary gland tumors (MSGT's) using CBR, ORR, PFS, OS.

2.3.2 To assess the predictive value of genomic aberrations observed upon comprehensive genomic profiling of the tumor DNA derived from archival tumor tissue, if available, or blood from patients with recurrent or metastatic ACC and non-ACC MSGTs.

2.3.3 Correlation between expression of PD-L1 and response to treatment will be explored in all patients enrolled in the study.

2.3.4 Correlations between other markers of inflammatory/immune signature will be performed that may include but not be limited to PD-1, OX40, CD73, CD39, T cell immunoglobulin and mucin domain containing protein 3 (TIM3), GITRL, CTLA-4, CD3, CD4, CD8, protein tyrosine phosphatase receptor type C (CD45RO), forkhead box P3 (FOXP3), and granzyme by immunohistochemistry analysis and/or flow cytometry.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with metastatic/recurrent adenoid cystic carcinoma (ACC) and non-adenoid cystic carcinomas (non-ACC) of major or minor salivary glands who are not surgical or radiation candidates with evidence of disease progression. This study will be led by Northwestern University. At Northwestern University, there is no competing trial.

A total of 63 [43 patients with ACC plus 20 patients with non-ACC MSGT (exploratory group)] subjects will be needed for this trial. Approximately 2 potentially eligible patients are seen per month, and it is anticipated that at least 2 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed metastatic/recurrent adenoid cystic carcinoma (ACC) of any anatomic site of origin or non-adenoid cystic carcinomas (non-ACC) of major or minor salivary glands

3.1.2 Patients must have evidence of disease progression and cannot be a candidate for curative surgical or radiation therapy.
NOTE: Disease progression is defined as one of the following occurring at least 6 months prior to study entry:

- At least a 20% increase in radiologically or clinically measurable lesions
- Appearance of any new lesions or
- Symptomatic and/or deterioration in clinical status

NOTE: Palliative radiotherapy is permitted.

3.1.3 Patients may or may not have received prior therapy for their recurrent/metastatic disease.
NOTE: There is no limit to the number of prior systemic therapies for stage IV disease.
NOTE: Patients should not be a candidate for curative surgical or radiation therapy (palliative radiotherapy is permitted).

3.1.4 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension in accordance with RECIST criteria v1.1.
NOTE: Scans must be ≤28 days prior to study treatment.

3.1.5 Patients must be ≥ 18 years old.

3.1.6 Patients must exhibit an ECOG status of 0-2.
NOTE: ECOG performance status 3 will be allowed only if thought to be directly secondary to adenoid cystic carcinoma disease by treating physician.

3.1.7 Patients must have adequate organ and bone marrow function within 14days prior to registration, as defined below:

- leukocytes ≥ 2,000/mcL
- absolute neutrophil count ≥ 1,500/mcL, regardless of transfusion or growth factor support
- platelets ≥ 100,000/mcl, regardless of transfusion or growth factor support
- total bilirubin total bilirubin ≤1.5× institutional upper limit of normal (ULN) (except patients with Gilbert Syndrome or liver metastasis, who can have total bilirubin ≤3.0 x ULN)
- AST(SGOT)/ALT(SPGT) ≤ 2.5 X institutional upper limit of normal (ULN) (or ≤5 times ULN in case of liver metastasis)
- creatinine Serum creatinine of ≤ 3.0 X ULN (upper limit of normal) or creatinine clearance ≥ 30 mL/minute (using Cockcroft/Gault formula below):

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

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

3.1.8 Patients with history of central nervous system (CNS) metastases are eligible if CNS disease has been stable for at least 6 weeks prior to study registration in the opinion of the investigator and does not require corticosteroids (of any dose) for symptomatic management.
NOTE: Only patients with a known history or indication of CNS disease are required to have CNS imaging prior to study entry.

3.1.9 Females of childbearing potential (FOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) ≤14 days prior to registration.

NOTE: A FOCBP is *any woman* (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not* undergone a hysterectomy or bilateral oophorectomy
- *Has had* menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)

3.1.10 FOCBP and men who are sexually active with FOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment and the designated post-treatment period (see Appendix C for details on appropriate contraception methods)

3.1.11 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.2 Exclusion Criteria

3.2.1 Patients must not have had chemotherapy ≤ 28 days or radiotherapy ≤ 7 days prior to study treatment.
NOTE: See section 4.6.1 for further clarification on palliative radiotherapy.

3.2.2 Patients who have not recovered to ≤ Grade 1 or tolerable Grade 2 from adverse events due to agents administered ≥ 28 days earlier are not eligible.

3.2.3 Patient must not be a candidate for curative surgical or radiation therapy.
NOTE: Palliative radiotherapy is permitted.

3.2.4 Patients may not be receiving any other investigational agents ≤ 28 days prior to study treatment.

3.2.5 Patients who have had prior exposure to immune checkpoint inhibitors are not eligible. Please contact principal investigator, for specific questions on potential interactions.
NOTE: Immune checkpoint inhibitors working through OX40 are an exception (for example, MEDI6383, MEDI6469, MEDI0562, oxelumab, and PF-04518600) and are permitted ≥ 28 days prior to study registration.

3.2.6 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including chronic prolonged systemic corticosteroids (defined as corticosteroid use of duration one month or greater), should be excluded. These include but are not limited to patients with a history of:

- immune related neurologic disease
- multiple sclerosis
- autoimmune (demyelinating) neuropathy
- Guillain-Barre syndrome
- myasthenia gravis
- systemic autoimmune disease such as SLE
- connective tissue diseases
- scleroderma
- inflammatory bowel disease (IBD)
- Crohn's
- ulcerative colitis
- patients with a history of toxic epidermal necrolysis (TEN)
- Stevens-Johnson syndrome
- anti-phospholipid syndrome

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

3.2.7 Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible:

- Ongoing or active infection (including minor localized infections) requiring oral or IV treatment
- Symptomatic class 3 or 4 congestive heart failure, defined as a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
- Unstable angina pectoris
- Cardiac arrhythmia
- Psychiatric illness/social situations that would limit compliance with study requirements
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

3.2.8 Patients should not have any condition requiring systemic treatment with corticosteroids (>10mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug.

NOTE: Inhaled or topical steroids and adrenal replacement steroids at any dose are permitted in the absence of active autoimmune disease. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

3.2.9 Female patients who are pregnant or nursing are not eligible.

3.2.10. No other prior malignancy is allowed except for the following:

- adequately treated basal cell or squamous cell skin cancer,
- in situ cervical cancer,
- or any other cancer from which the patient has been disease free for at least three years.

3.2.11. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) is not permitted.

3.2.12. Any known positive test for Hepatitis B or Hepatitis C virus indicating acute infection is not permitted.

3.2.13. Patients who received a live, attenuated vaccine ≤ 30 days before study treatment or are anticipated to require such a live attenuated vaccine are not eligible.

NOTE: Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist) ≤ 30 days prior to study registration or at any time during the study.

4.0 TREATMENT PLAN

4.1 Overview

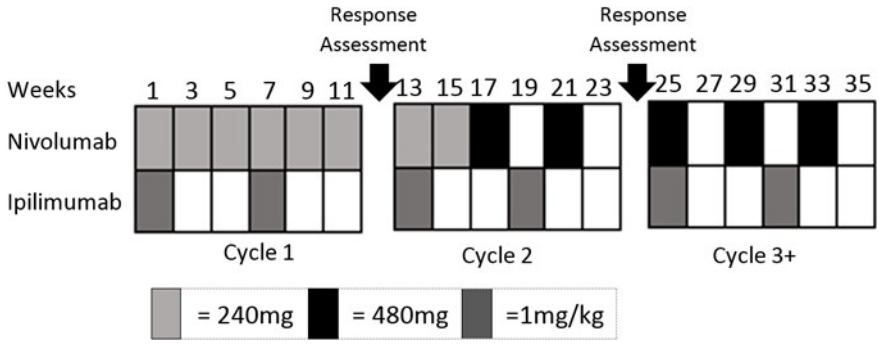
Nivolumab and ipilimumab combination will be administered intravenously until disease progression or intolerable toxicity. Nivolumab will be given at 240mg over 30 minutes (-5 / +15 minutes) every 2 weeks starting with Cycle 1 Day 1 for the first 16 weeks (1 cycle = 12 weeks). Starting with Cycle 2 Day 29, nivolumab will be given at 480mg IV over 60 minutes (-10 / +15 minutes) every 4 weeks. Ipilimumab will be given at 1mg/Kg every 6 weeks starting with Cycle 1 Day 1 over approximately 90 minutes (-5 / +15 minutes). On days when both nivolumab and ipilimumab are administered, nivolumab should be given first, followed by ipilimumab about 30 minutes after completion of nivolumab. Patients will be assessed for response every 12 weeks (±7 days). Note: Please refer to section 4.4 for patients who may continue treatment after initial progression.

4.2 Treatment Administration

Table 1 - Treatment Administration Summary

Agent	Pre-meds	Dose	Route	Schedule**	Cycle Length	Supportive Therapies
Nivolumab	None	240mg	IV infusion over ~30 minutes (-5 / +15 minutes, **before** ipilimumab)	C1: q2weeks C2D1 & C2D15	12 weeks (84 days)	As needed
Nivolumab	None	480mg	IV infusion over 60minutes (-10 / +15 minutes, before ipilimumab)	C2D29 & C2D57 C3+: D1, 29, 57		
Ipilimumab	None	1mg/Kg	IV infusion over ~90 minutes (-5 / +15 minutes) (30 min **after** completion of nivolumab)	Day1 & 43 of each cycle		

**See Table 2 for a simplified summary of the treatment schedule



4.2.1 Nivolumab

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described below. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

For the first 8 doses (Cycle 1 + C2D1 + C2D15) nivolumab will be administered at a dose 240mg as an intravenous infusion over 30 minutes (-5 / + 15 minutes)

every 14 days. Starting with C2D29, nivolumab will be administered at 480mg IV over 60 minutes (-10 / +15 minutes) every 28 days until disease progression, unacceptable toxicity, or withdrawal of consent.

There will be no dose escalations or reductions of nivolumab allowed. Patients may be dosed no less than 12 days or 24 days from the previous dose (for 240mg and 480mg doses respectively). There are no pre-medications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.3.3.

Nivolumab is to be administered as a 30-minute (-5 / +15 minutes) or 60-minute (-10 / +15 minutes) IV infusion (for 240mg and 480mg doses respectively), using a volumetric pump with a 0.2- 1.2 micron low-protein binding in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% Sodium Chloride or 5% Dextrose for delivery but the total drug concentration of the solution cannot be below 0.35 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Subjects will be monitored continuously for AEs while on study. Treatment delay or discontinuation will be based on specific laboratory and adverse event criteria.

4.2.2 Ipilimumab

Ipilimumab will be administered at a dose of 1mg/Kg as an intravenous infusion over approximately 90 minutes every 6 weeks until disease progression or unacceptable toxicity. Dosing will be based on weight at baseline, however if there is a weight change ≥10%, the dose should be adjusted accordingly. It should be administered approximately 30 minutes after nivolumab infusion.

There will be no dose escalations or reductions of ipilimumab allowed. There are no pre-medications recommended for ipilimumab on the first cycle. If an acute infusion reaction is noted subjects should be managed according to Section 4.3.3.

Ipilimumab is to be administered as a 90-minute IV infusion (a window of -5 / +15 minutes is allowed), using a volumetric pump with a 0.2/1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution must be 1-2 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Subjects will be monitored continuously for AEs while on study. Treatment delays or discontinuation will be based on specific laboratory and adverse event criteria.

4.3 Toxicity Management & Dose Delays/Modifications

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table). Toxicity will be assessed according to the NCI CTCAE v. 4.03.

4.3.1 Dose delays: Ipilimumab and/or nivolumab

Ipilimumab and/or nivolumab administration should be delayed for the following until resolution to ≤ Grade 1 or baseline:

- Any Grade 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities
- Any Grade ≥ 3 skin drug-related AE
- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
    - Grade 3 lymphopenia does not require a dose delay
    - If a participant has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade 2 toxicity
    - If a participant 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.

Participants that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab and nivolumab for Grade ≥ 3 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab alone.)

4.3.2 Treatment discontinuation: Ipilimumab and/or nivolumab

Should the treating physician decide to discontinue treatment given suspicion for a drug-related side effect, the side effect should be attributed to one study drug to the best of the physician's ability. Either ipilimumab or nivolumab should be discontinued based on this attribution, or both if a definite attribution is not possible.

Ipilimumab and/or nivolumab should be discontinued permanently for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction **of any duration** (can be < 7 days) requires discontinuation
    - Grade 3 drug endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding (aside from minor bleeds ≤ Grade 1) requires discontinuation

        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
            - AST or ALT > 5-10 x ULN for > 2 weeks
            - AST or ALT > 10 xUL
            - Total bilirubin > 5 x ULN
            - Concurrent AST or ALT > 3 xULN and total bilirubin > 2 x ULN
    - Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
        - Grade 4 neutropenia < 7 days
        - Grade 4 lymphopenia or leukopenia
        - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. PI and Data Safety and Monitoring Committee (DSMC) should be consulted for Grade 4 amylase or lipase abnormalities.
        - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
        - Grade 4 drug related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation.
    - Any event that leads to interruption in dosing lasting > 6 weeks (42 days) from the previously required dose requires discontinuation, with the following exceptions:
        - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruptions lasting > 6 weeks from the previous dose, the PI and DSMC must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 4 weeks or more frequently if clinically indicated during such dosing interruptions.
        - Dosing interruptions lasting > 6 weeks from the previous dose that occur for non-drug- related reasons may be allowed if approved by the PI and DSMC. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the PI and DSMC must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 4 weeks or more frequently if clinically indicated during such dosing interrupted.
        - Any adverse event, laboratory abnormality, or intercurrent illness, which in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.
        - If the patient is still receiving clinical benefit, he or she can hold drug for a maximum of 42 days (6 weeks), or 60 days with approval from the DSMC, and subsequently continue therapy following the original treatment schedule.

4.3.3 Treatment of Nivolumab or Ipilimumab-related infusion reactions

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

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Remain at bedside and monitor subject until recovery from symptoms.	The following prophylactic pre-medications are recommended for future infusions: • Diphenhydramine 50 mg (or equivalent) and/or • Acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab administrations
Grade 2 Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for < 24 hours	Stop the nivolumab/ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; Remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.	For future infusions, the following prophylactic pre-medications are recommended: • Diphenhydramine 50 mg (or equivalent) and/or • Acetaminophen 325 to 1000 mg should be administered at least 30 minutes before nivolumab or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
Grades 3 or 4 Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life-threatening; pressor or ventilatory support indicated	Immediately discontinue infusion of nivolumab/ipilimumab infusion. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids	

4.4 Treatment with ipilimumab and or nivolumab beyond progression

In the event of an initial assessment of PD (based on RECIST Version 1.1), a subject may continue to receive the assigned study treatment as long as none of the criteria listed below are met.

a. Confirmed PD: a subsequent scan obtained no sooner than 4 weeks from prior scan is suggestive of PD by RECIST 1.1 (see section 6.6), and the patient has clinical decline. NOTE: If PD is confirmed but the patient continues to have clinical benefit (e.g. improvement of symptoms and is tolerating treatment), the patient can continue treatment beyond PD per clinician's discretion.
b. Meets any of the other investigational product discontinuation criteria (Section 4.3.2)
c. Clinical symptoms or signs indicating significant PD, for example the benefit-risk ratio of continuing therapy is no longer justified.
d. Decline in ECOG performance status.
e. Threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention, and continuation of study therapy would prevent institution of such intervention.

If the lesions included in the tumor burden subsequently regress to the extent that the criteria for PD are no longer met, then treatment may continue according to the treatment schedule.

4.5 Interim Safety Analyses

Enrollment will be paused for a safety analysis after the first 15 evaluable ACC patients have been enrolled and treated. If ≥ 7 patients have been discontinued after <24 weeks of treatment for any reason (including toxicity, progression, intolerance etc.) accrual of ACC patients will be terminated. Otherwise, the study may continue enrollment until a total of up to 43 ACC subjects are treated.

An additional 20 patients with non-ACC MSGT's will be treated as an exploratory cohort. They can be enrolled at any point throughout the study and will not count toward the 15-patient safety analysis. A separate safety analysis will take place to analyze the first 10 non-ACC patients who are enrolled and treated. If >2 patients discontinue treatment prior

to 24 weeks (for reasons other than withdrawal of consent), accrual of non-ACC patients will discontinue.

4.6 Concomitant Medications/Treatments

4.6.1 Permitted Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care and the protocol's prohibited medications in 4.5.2. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
Inhaled or topical steroids are permitted at any dose in the absence of active autoimmune disease. Adrenal replacement steroid doses are permitted as long as < 10mg prednisone (or equivalent) per day.

Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed if initiated prior to first dose of study therapy.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered past 30 days of treatment should be recorded if associated with an SAE.

4.6.1.1 Palliative Radiation Therapy or Surgery

Non-target Lesion

During study treatment, palliative radiation therapy or surgery to **non-target lesions** is permitted for symptom control. Study treatment must be held for the duration of the palliative treatment.

Target Lesion

If radiotherapy or surgery is needed for a **target lesion**, the patient is permitted to continue study treatment if another target lesion can be identified. Study treatment must be held for the duration of the palliative treatment. The newly selected target lesion will then be included for future scan assessments. In addition, previous scan assessments will be reevaluated to include the newly selected target lesion. If another target lesion cannot be identified, it will be per physician's discretion if treatment may continue after discussion with the PI and study QAM.

4.6.2 Prohibited Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy ≤ 28 days prior to starting study treatment
- Immunotherapy not specified in this protocol ≤ 28 days prior to starting study treatment

- Chemotherapy not specified in this protocol ≤ 28 days prior to starting study treatment
- Investigational agents other than nivolumab or ipilimumab ≤ 28 days prior to starting study treatment
- Radiation therapy
- NOTE: Palliative radiation on study is permitted. Refer to Section 4.6.1.1 for details.
- Live attenuated vaccines ≤ 30 days prior to starting study treatment NOTE: Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist) ≤ 30 days prior to study treatment or at any time during the study.
- Corticosteroids are not permitted ≤ 14 days prior to study treatment unless they fall under the criteria listed in 4.6.1

4.7 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (please refer to 4.4 for guidance regarding treatment beyond progression),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) as already described in session.
- Patient holds drug for ≥6 weeks (42 days) for reasons of toxicity (or 60 days with approval from the DSMC)

4.8 Duration of Follow Up

All patients will be followed for adverse events for 30 days after last dose of nivolumab and or ipilimumab (100 days for SAEs), or until the patient starts a new treatment, whichever occurs first. Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event (i.e. the grade is not changing). If a patient stops treatment due to unacceptable adverse event(s) but has not demonstrated disease progression, then the patient will be followed with imaging studies every 12 weeks until the time of progression radiographically according to RECIST 1.1 criteria. In the event that a radiographic response is detected, then this event will be included as a response in the final analysis, and the time of progression used in calculation of the survival analysis. Patients will be seen in clinic every 4 weeks for the first 12 weeks after treatment discontinuation. Thereafter, patients will be followed for survival (by clinic visit or phone call) every 12 weeks for 2 years from treatment discontinuation or until death, whichever occurs first.

4.9 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements (follow-up permitted)
- Patient demonstrates disease progression (per parameters above, follow-up permitted)
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest

- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

4.10 Patient Replacement

Any patient who signs consent but does not receive study treatment may be replaced.

5.0 STUDY PROCEDURES

	Screening[1]	On Treatment[15,16] (1 cycle = 12 weeks / 84 days)																		Off Treatment	
		Cycle 1 (Each visit -2/+4 days)						Cycle 2 (Each visit -2/+4 days)						Cycle 3+ (Each visit -2/+4 days)						End of Treatment[17] (±7 days)	Follow-Up
Day of each cycle		1	15	29	43	57	71	1	15	29	43	57	71	1	15	29	43	57	71		
Weeks on study		1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35+		
Informed Consent	X																				
Medical history	X																				
Physical exam[2]	X	X			X			X			X			X			X			X	
ECOG status	X	X			X			X			X			X			X			X	
Adverse Events & ConMeds	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X		X	X[17]
Scans (C/A/P/N) [3,4,5]	X[3]							X[4,5]						X[4.5]						X[5]	
CBC with diff [6]	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X		X	
Chemistry panel [7]	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X		X	
Amylase/Lipase[8]	X	X			X			X			X			X			X			X	
TSH with reflex[9]	X	X			X			X			X			X			X			X	
Echo/ECG[19]	X[19]																				
Tissue for NGS[20]	X[20]	X[20]																			
Liquid biopsy[21]	X[21]	X[21]							X[21]					X[21]						X[21]	
Pregnancy test[10]	X	X																			
Nivolumab administration[11]		T	T	T	T	T	T	T	T	F		F		F		F		F			
Ipilimumab administration[12]		X			X			X			X			X			X				
Study Labs[13]		X						X[13]												X	
Tissue collection[14]	X							X[14]													
Survival status																					X[18]

T = 240mg nivolumab
F = 480mg nivolumab

1 Screening procedures must take place within 28 days of registration unless otherwise specified (CBC with diff and Chemistry panel should be within 14 days of registration; scans should be within 28 days prior to starting treatment);

2 Includes vital signs (pulse, blood pressure) and height (baseline only) and weight.

3 Imaging scans must include recurrent and/or metastatic disease, and must be within 28 days prior to starting study treatment. If a patient is scheduled to start treatment >28 days after the last scan, imaging must be repeated. Per treating investigator's discretion, images may include Neck, Chest, Abdomen, and Pelvis (or any combination to perform tumor assessment). Scans may be by CT, PET/CT or MRI (per treating investigator's

discretion) with contrast unless strictly contraindicated; the same modality used at baseline should be used throughout. Brain MRI should be performed at baseline if clinically indicated, ≤ 6 weeks prior to registration. Tumor assessment (incorporating both RECIST and clinical criteria) should be done Day 1 of every cycle, i.e. every 12 weeks (± 7 days) starting with Cycle 2, until progression or treatment discontinuation whichever occurs first.

[4] Earlier scans may be performed at the discretion of the treating physician.

[5] If PD is confirmed at any time, see section **4.4** on how to determine whether patient can be considered for further treatment. If patient continues, scans should be obtained every 8 weeks until PD is confirmed by 2 consecutive scans.

[6] CBC with differential will be collected within 14 days of registration and at each treatment visit, pre-treatment. It will include WBC, ANC, ALC, Platelets, and Hemoglobin.

[7] Chemistry panel will be collected within 14 days of registration and at each treatment visit, pre-treatment. It will include glucose, calcium, albumin, ALT, AST, sodium, potassium, total bilirubin, alk phos, and creatinine.

[8] Amylase and lipase will be assessed at screening and every 6 weeks (Day 1 and 43 of each cycle) pre-treatment.

[9] TSH will be tested at screening and every 6 weeks (Day 1 and 43 of each cycle), pre-treatment. If TSH is abnormal, free T4 should be tested

[10] Serum or urine test for females of child-bearing potential (FOCBP) ≤14 days prior to registration. FOCBP are also required to have a negative pregnancy test within 24 hours of starting nivolumab.

[11] Nivolumab will be administered in combination with ipilimumab as follows:
First 8 doses (Cycle 1, C2D1, & C2D15): 240mg IV q2weeks
Starting with C2D29: 480mg IV q4weeks until disease progression, intolerable toxicity or withdrawal of consent.

[12] Ipilimumab will be administered IV at 1mg/kg over 90 minutes every six weeks in combination with nivolumab. Dosing will be based on weight at baseline unless there is a change ≥10%. Nivolumab will be given before ipilimumab.

[13] A correlative blood sample (3x 8mL heparin tubes) will be drawn at baseline (C1D1, pre-dose), at the first scheduled study visit after response is confirmed (PR or CR), and at the end of treatment visit. Please see separate lab manual for details.

[14] Archival tissue will be collected at baseline for all patients (if available).Additional tissue may be collected (if feasible) during biopsies performed as standard of care during study participation. Please see separate lab manual for details.

[15] Treatment will start within 7 days after registration, and continue until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. See section 4.4 for conditions to continue treatment beyond initial progression.

[16] Study procedures may take place within 24 hours prior to study treatment.

[17] End of Treatment visit will occur 30 days (± 7 days) after stopping nivolumab or combination treatment, or before the patient starts new treatment, whichever occurs first. Adverse events will be recorded for up to 30 days after stopping treatment (SAE's for 100 days).

[18] Patients will be followed every 4 weeks (±7 days) by routine clinic visit for the first 12 weeks after treatment. Thereafter, patients will be followed (either by routine clinic visit or by phone) every 3 months for up to 2 years to document survival and disease progression. SAE's will be recorded for the first 100 days after treatment discontinuation.

[19] Echocardiogram and/or ECG should be performed at screening as clinically indicated for patients with a history of congestive heart failure or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs. Cardiac toxicities should be closely monitored throughout treatment.

[20] Tissue will be collected for Next Generation Sequencing any time prior to study treatment (we will accept archival tissue from the lesion demonstrating progression of recurrent/metastatic disease, as long as the patient has not received other treatment since that biopsy). Tissue will also be collected with any SOC biopsies throughout study treatment. If a patient has not had NGS performed from the lesion demonstrating PD, and the lesion is amenable to biopsy, the patient may agree to provide a fresh biopsy for standard-of-care NGS. If a biopsy is not feasible, is a high-risk procedure for patient, or the patient is not willing, he or she will be required to provide blood for ct DNA and will not be excluded from the study.

21 A liquid biopsy (blood sample for ctDNA) will be collected at baseline (any time prior to study treatment). If a patient already had this test, we will accept that, as long as the patient has not received other treatment since that liquid biopsy was obtained. During the course of treatment, patients will be asked to have repeat ctDNA testing, as per standard of care procedures, progression of disease, and as clinically indicated.

6.0 ENDPOINT ASSESSMENT

6.1 Definitions

For the purposes of this study, patients should be re-evaluated for response every 12 weeks (±7 days). In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response greater than Stable Disease (SD). Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [44]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

High resolution CT with oral/intravenous contrast or contrast-enhanced MRI is the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 28 days of registration. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is only required during screening for patients who have a known history of CNS disease. All known or suspected sites of disease (including CNS if history of CNS metastases) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

6.2 Primary Endpoint

Median progression-free survival (PFS) as well as PFS at 6 and 12 months [defined the absence of death and of progression of disease. The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment.[44]

- Clinical and radiological assessments will be performed every 12 weeks (+/- 7 days) while on treatment. All patients who receive at least one dose of nivolumab and have had their disease re-evaluated will be included in the primary analysis of PFS.

6.3 Secondary Endpoints

- Progression free survival defined as time in months from the date of first study treatment to the date of disease progression or death from any cause, whichever comes first. Overall survival (OS) is defined as time in months from the date of first study treatment to the date of death. All patients who receive at least one dose of nivolumab and have had their disease re-evaluated will be included in the secondary analyses of PFS and OS.
- Clinical Benefit Rate at 6 and 12 months (CBR, defined as CR + PR + Stable Disease (SD)) in patients with advanced progressive adenoid cystic carcinoma treated with nivolumab and ipilimumab using RECIST v1.1.
- To assess the efficacy of the regimen according to ORR, CBR, PFS, and in the above population using immune-related response criteria (irRECIST) criteria.[45]

- The number, frequency, and severity of adverse events will be collected from the time of consent until 12 weeks after study treatment to evaluate safety of nivolumab in patients with advanced progressive adenoid cystic carcinoma. Adverse events will follow National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03
- Overall survival defined as time in months from the date of first study treatment to the date of death.

6.4 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with nivolumab and or ipilimumab.

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

6.5 Disease parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam (such measurements must be clearly documented). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly should be selected. A sum of the diameters (longest for non- nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used

as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.6 Response Criteria – RECIST v1.1

6.6.1 Evaluation of target lesions

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

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.6.2 Evaluation of Non-Target Lesion

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.6.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Responses will be assessed using CT scans or magnetic resonance imaging according to standard RECIST 1.1 criteria in order to assess disease progression. These criteria will also allow for patients who experience an initial disease flare, and as some patients who will have a delayed response may experience an initial disease flare, we will allow patients to continue receiving nivolumab beyond progression (see section 4.4).

6.6.4 Duration of response

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

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

6.7 Immune-related RECIST (irRECIST)

Immune-related complete Response (irCR): complete disappearance of all lesions (whether measurable or not, and no new lesions)

Immune-related partial Response (irPR): decrease in tumor burden ≥30% relative to baseline.

Immune-related progressive Disease (irPD): increase in tumor burden ≥20% relative to nadir (minimum recorded tumor burden)
Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

Immune-related stable Disease (irSD): not meeting criteria for irCR or irPR, in absence of irPD

6.8 Evaluable patients

All patients who receive at least one dose of nivolumab will be considered evaluable for the toxicity endpoints.
All patients who receive at least one dose of nivolumab and have a radiologic evaluation of disease are evaluable for efficacy endpoints.

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to NOTIS for additional information). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations, which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html
If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 100 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is *life-threatening*.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- **Results in *persistent or significant disability or incapacity*.**
- **Is a *congenital anomaly/birth defect.***
- Is associated with an overdose.
  For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for nivolumab or ipilimumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of nivolumab or ipilimumab. In the event of overdose, nivolumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
  If an adverse event(s) is associated with ("results from") the overdose of a BMS product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
  If a dose of BMS's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."
  All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to BMS Global Safety.

- **Is an *important medical event*.**

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

All grade 3 or 4 infusion reactions should be reported within 24 hours to the study QAM and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others (UPIRSO)

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Reporting of pregnancy and lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner, that occurs during the trial or within 5 months after the last dose of study drug for FOCBP or 7 months for males with FOCBP partners. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

7.4 Adverse Event Reporting

7.4.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine AEs will be reviewed by the Data Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

7.4.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol

- the drug package insert
- the current Investigator's Brochure

7.4.3 Expedited Reporting of SAEs/Other Events

7.4.3.1 Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DSMC at their next meeting.

7.4.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment) will be promptly reported to the NU IRB within 24 hours of notification, per Lurie Cancer Center policy.
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.4.3.3 Reporting to BMS

All SAE reports (including death by any cause), regardless of attribution will be reported within 24 hours to BMS Global Safety (using the NU CRO SAE Form and referencing the BMS study number, CA 209-802). The assigned study coordinator will facilitate all reporting to BMS Global Safety and email QA a copy of the report upon completion. BMS Global Safety can be notified at:

Email Address: Worldwide.Safety@BMS.com
Facsimile Number: 609-818-3804

8.0 DRUG INFORMATION

8.1 Nivolumab

8.1.1 Other names

ONO-4538, BMS-936558, or MDX1106, Opdivo

8.1.2 Classification - type of agent

Human IgG4 anti-PD-1 monoclonal antibody

8.1.3 Mode of action

Nivolumab acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells anti-PD1.

8.1.4 Storage and stability

Nivolumab solution for infusion is a sterile, non-pyrogenic single-use, isotonic aqueous solution. Vials must be stored in a secure, limited-access location at 2 to 8 degrees C (36 to 46 degrees F) and protected from light, freezing, and shaking. The product is a clear to opalescent solution, which may contain proteinaceous and extraneous particulates. The product is intended for IV administration. The drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Opened or accessed vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered.

After preparation, store the Nivolumab infusion either:

- at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.
- Do not freeze.

8.1.5 Protocol dose specifics

240mg q2weeks and 480mg q4weeks

8.1.6 Preparation

Nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.
Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles.
Note: Mix by gently inverting several times. Do not shake.
Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. Do not enter into each vial more than once.
Do not administer study drug as an IV push or bolus injection.
Nivolumab injection can be infused undiluted (10 mg/mL) or diluted so as not to exceed a total infusion volume of 120mL.

8.1.7 Route of administration for this study

Intravenous infusion. Do not administer as an IV push or bolus injection.
Administer nivolumab 240 mg as an intravenous infusion over 30 (-5/+15)

minutes and 480mg as an intravenous infusion over 60 (-10/+15) minutes through a 0.2 micron to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

8.1.8 Incompatibilities

No incompatibilities between nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed. Nivolumab should not be infused concomitantly in the same intravenous line with other medicinal products.

8.1.9 Availability & Supply

Nivolumab will be supplied by the study as 100 mg/Vial (10 mg/mL) clear to opalescent, colorless to pale yellow liquid in 10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals. May contain particles.

A supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS. The first request may take place upon screening of the first patient. The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is imperative that only drug product designated for this protocol number be used for this study.

Drug re-supply request form should be submitted electronically 10 business days before the expected delivery date. Deliveries will be made Tuesday through Friday. When assessing need for resupply, keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific.

8.1.10 Side effects

Related side effects reported in subjects receiving nivolumab alone were:

Very Frequent – Expected to occur in more than 20% of people (more than 20 out of 100 people): Fatigue (50%), Dyspnea (38%), Musculoskeletal pain (36%), Rash (21%), Increased AST (28%), Increase alkaline phosphatase (22%), Hyponatremia (25-38%)

Frequent - Expected to occur in 10% to 20% of people (10 to 20 out of 100 people): Pruritus (19%), Cough (17%), URI (11%), Peripheral edema (10%), Increased ALT (16%), Hyperkalemia (15%)

Not Frequent – Expected to occur in less than 10% of people (less than 10 out of 100 people): ventricular arrhythmia, iridocyclitis, infusion-related reactions, increased amylase, increased lipase, dizziness, peripheral and sensory neuropathy, exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis

Deaths thought to be related to nivolumab when given alone were reported in approximately 0.5% of subjects treated (approximately 1 out 200 people).

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.1.11 Safety and monitoring plan

All participants will be carefully followed for safety. Participants are seen by their study doctor and research nurse before each dose of nivolumab every 2 or 4 weeks. Safety evaluations at this time include a physical exam, vital signs, performance status assessment, and safety laboratory tests. The study team will continuously monitor participants for treatment side effects. Participants are instructed to inform their study doctor right away if they notice or feel anything different so the study doctor can check for side effects. The study doctor may be able to provide treatment for side effects. The study doctor may temporarily hold the study drug to reduce side effects. The study doctor will permanently stop the study drug if side effects are too severe and/or long lasting. All participants will be followed for side effects for 30 days from their last dose of nivolumab. Participants with ongoing side effects will continue to be followed until resolution or stabilization of the side effects. Because it is not known if nivolumab will be effective against this type of cancer, enrollment will stop after 12 participants are treated with nivolumab if none of them have their tumors shrink..

8.1.12 Return and Retention of Study Drug

The clinical study team will be responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and not used by the subjects and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. Inform BMS on all drug destructions pertaining to both nivolumab and ipilimumab.

Table 8.1 – Nivolumab Product Information

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection	100 mg (10 mg/mL)	10 mL vial	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8ºC. Protect form light and freezing

8.2 Ipilimumab

8.2.1 Other names

MDX-CTLA-4, MDX-010, Yervoy

8.2.2 Classification and type agent

Human IgG1 Kappa anti-CTLA-4monoclonal antibody

8.2.3 Mode of action

Ipilimumab acts as an immunomodulator by blocking the interaction between of the CTLA-4 receptor and its ligands CD80/CD86. CTLA-4 has been shown augment T-cell proliferation and activation.

8.2.4 Storage and stability

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Ipilimumab injection is a sterile, nonpyrogenic, clear to slightly opalescent, colorless to pale yellow solution, single-use, preservative-free, isotonic aqueous solution that may contain particles. It is formulated at a concentration of 5 mg/mL ipilimumab in TRIS hydrochloride

(also known as 2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride), sodium chloride, mannitol, pentetic acid (also known as diethylenetriaminepentaacetic acid or DTPA), polysorbate 80, and water at pH 7.0. Sodium hydroxide and/or hydrochloric acid may be used to adjust the pH of the solution.
Ipilimumab Injection 50 mg/10 mL (5 mg/mL) is packaged in a 10-cc Type I flint tubing glass vials, stoppered with 20-mm gray butyl rubber stoppers, and sealed with 20-mm aluminum flip-off seals. Each vial includes a 0.7-mL overfill for vial, needle, and syringe (VNS) holdup

Ipilimumab injection, 50 mg/10 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% sodium chloride injection or 5% dextrose injection in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

8.2.5 Protocol dose specifics
1mg/Kg

8.2.6 Preparation
Ipilimumab injection, 50 mg/10 mL (5 mg/mL), can be used for intravenous (IV) administration without dilution after transferring to a polyvinyl chloride (PVC), non-PVC/non-di(2-ethylhexyl)phthalate (DEHP), or glass container and is stable for 24 hours at 2°C to 8°C or room temperature/room light. Ipilimumab injection may be diluted in 0.9% sodium chloride injection or 5% dextrose injection to concentrations between 1 mg/mL and 4 mg/mL and stored in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm). Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

8.2.7 Route of administration for this study
Intravenous infusion. Do not administer using IV push or bolus. Administer through a volumetric pump with a 0.2 to 1.2 micron in-line filter (non- pyrogenic and low-protein binding). At the end of the infusion, flush the line with a sufficient quantity of approved diluents.

8.2.8 Incompatibilities
No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab

8.2.9 Availability & Supply
The supply for this study will be investigational – not commercially available. Supply will be provided by BMS free of charge. Ipilimumab will be supplied as 50mg /vial (5mg/mL) packaged in cartons of 6 vials. Drug is protocol specific, but not patient specific.

Drug can be ordered using the Drug Request Form provided by BMS. The form is provided as a separate document and should be submitted electronically at least 7 business days for initial order and at least 14 days for re-supply before the expected delivery date. Contact and submission details can be found directly on the Drug Request Form.
Deliveries will be made Tuesday through Friday.

Starting January 2023, Ipilimumab will be supplied in 50mg vials. Each carton will contain 6 x 50mg vials.

Ipilimumab product supply			
Container description	Type: Single-use vials of 50 mg/10 mL	*Material:* clear glass	*Size:* 10 mL vials
Active ingredient content	*Mass/Weight:* 50 mg	*Volume:* 10 mL	*Concentration:* 5 mg/mL

Table 8.2 – Ipilimumab Product Information

Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Ipilimumab Solution for Injection	50 mg (5 mg/mL)	10 mL vial	6 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

8.2.10 Side effects

Immune-related adverse events have been associated with ipilimumab is administered intravenously.

Since its first approval for advanced melanoma in the US on 25-Mar-2011, followed by European Medicines Agency approval in the EU on 13-Jul-2011, ipilimumab has been approved for market use in 47 countries worldwide. Based on information published in the ipilimumab Periodic Benefit-risk Evaluation Report (PBRER) #5, cumulatively through 24-Mar-2015 (the cutoff date for the last PBRER), approximately 30,540 patients have been exposed to ipilimumab through marketed drug worldwide (excluding investigator-sponsored trials/research exposure). In addition, 5,877 subjects have been cumulatively exposed to ipilimumab through clinical trials, and 10,486 patients have been exposed to ipilimumab through EAPs. During the reporting period of PBRER #5, 13 clinical trials (including EAPs, CA184045 and CA184089) met the inclusion criteria as ongoing studies, and 1 clinical trial (Study CA184202, Phase 1 to 3) in melanoma was completed. During that reporting period, the Company Core Data Sheet was updated once, on 21-Jan-2015. One new safety signal was identified: drug reaction with eosinophilia and systemic symptoms. For toxic epidermal necrolysis, a known, labeled AE, a cautionary note was added for the specific context when ipilimumab treatment is considered for a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune-stimulatory therapy.

Based on package insert below are safety data from 131 patients with metastatic melanoma who received ipilimumab as monotherapy in a phase 3 trial.

Very Frequent – Expected to occur in more than 20% of people (more than 20 out of 100 people):Fatigue (42%), Pruritus (24.4%), Decreased appetite (26.7%) Diarrhea (32.8%), Nausea (35.1%),Constipation (20.6%), Vomiting (23.7%),

Frequent - Expected to occur in 10% to 20% of people (10 to 20 out of 100 people): Abdominal pain (15.3%), pyrexia(12.2%), headache (14.5%), Cough (16%), dyspnea (14.5%), anemia (11.5%), rash (19.1)

Not Frequent – Expected to occur in less than 10% of people (less than 10 out of 100 people): vitiligo, colitis, hypothyroidism, hypopituitarism and adrenal insufficiency, increased aspartate aminotransferase and alanine aminotransferase

Deaths thought to be related to ipilimumab when given alone were reported in approximately 3 % of subjects treated (approximately 4 out 131 people).

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.2.11 Safety and monitoring plan

All participants will be carefully followed for safety. Participants are seen by their study team before each dose of ipilimumab (every 2 weeks). Safety evaluations at this time include a physical exam, vital signs, performance status assessment, and safety laboratory tests. The study team will continuously monitor participants for treatment side effects. Participants are instructed to inform their study doctor right away if they notice or feel anything different so the study doctor can check for side effects. The study doctor may be able to provide treatment for side

effects. The study doctor may temporarily hold the study drug to reduce side effects. The study doctor will permanently stop the study drug if side effects are too severe and/or long lasting. All participants will be followed for side effects for 30 days from their last dose of ipilimumab. Participants with ongoing side effects will continue to be followed until resolution or stabilization of the side effects. Because it is not known if ipilimumab will be effective against anal cancer, to enrollment will stop after 12 participants are treated with ipilimumab if none of them have their tumors shrink. Study team conferences will be held monthly or more frequently if needed.

8.2.12 Return and Retention of Study Drug

The clinical study team will be responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and not used by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. Inform BMS on all drug destructions pertaining to both nivolumab and ipilimumab.

Container description	Type: Single-use vials of 50 mg/10 mL	*Material:* clear glass	*Size:* 10 mL vials
Active ingredient content	*Mass/Weight:* 50 mg	*Volume:* 10 mL	*Concentration:* 5 mg/mL

9.0 CORRELATIVES/SPECIAL STUDIES

Archival tumor samples, when available, and any tissue that may feasibly be collected from SOC biopsies throughout the study, may be evaluated for the immunosuppressive biomarker PD-L1 protein on tumor cells and the expression level and localization of other markers of inflammatory/immune signature that may include but not be limited to PD-1, OX40, CD73, CD39, T cell immunoglobulin and mucin domain containing protein 3 (TIM3), GITRL, CTLA-4, CD3, CD4, CD8, protein tyrosine phosphatase receptor type C (CD45RO), forkhead box P3 (FOXP3), and granzyme by immunohistochemistry analysis and/or flow cytometry. Comprehensive genomic profiling of the tumor samples will also be performed.

A baseline whole blood sample and serum sample will also be collected for future biomarker analysis that may include tumor and immune cell, poreosome, and exosome analysis at partnering laboratories. Collection and processing instructions are available in a separate lab manual, available on the NOTIS protocol page.

Repeated blood samples will be collected at the time of disease progression and partial or complete response (± 2 weeks of confirmation). Details on sample collection, shipping, and processing are available in a separate lab manual.

9.1 Specimen Banking

Patient samples collected for this study will be retained at Robert H Lurie Cancer Center of Northwestern University Pathology Core Facility. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

The PI will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of Northwestern University. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of Northwestern University for publication and any licensing agreement will be strictly adhered to.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a single arm open label phase II clinical trial which will assess the anti-tumor efficacy of nivolumab in combination with ipilimumab in ACC. As these two monoclonal anti-bodies already have been studied and approved as monotherapy or combination in other histological tumor types we believe that a phase II study is appropriate for development of these drugs in metastatic/recurrent adenoid cystic carcinoma (ACC). The non-adenoid cystic carcinomas (non-ACC) of major or minor salivary glands are for exploratory purposes for signal finding and will not be included in our statistical plan.

10.1.1 Primary:

To assess the median progression-free survival (PFS) as well as PFS at 6 and 12 months [defined as the absence of death and of progression of disease] in patients with metastatic/recurrent and progressive ACC. The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment

10.1.2 Secondary:

(1) To assess the efficacy of nivolumab and ipilimumab according to response rate (RR), disease control rate (DCR; CR, PR, and SD at 24 weeks), overall survival (OS) and progression free survival (PFS) in the above population using RECIST criteria.
(2) To assess the efficacy of nivolumab and ipilimumab according to ORR, DCR, PFS, and OS in the above population using irRECIST criteria.
(3) To assess the safety and tolerability profile of nivolumab and ipilimumab therapy in the above population using CTCAE version 4.03
(4) To assess the immune-related biomarkers and their association with treatment response
(5) Assess activity of nivolumab and ipilimumab in non-ACC malignant salivary gland tumors (MSGTs)

10.1.3 Exploratory endpoints:

- To assess the predictive value of baseline immunosuppressive biomarker PD-L1 protein on tumor cells and the expression level and localization of

other markers of inflammatory/immune signature. Correlations between cell free tumor DNA and tumor tissue genomic aberrations with anti-tumor efficacy of nivolumab/ipilimumab combination will be explored.

10.2 Sample Size and Accrual

A Simon two stage optimum Phase II design will be used [46]. The main outcome is median Progression Free Survival (PFS) as well as PFS at 6 and 12 months. The optimal two-stage design to test the null hypothesis that P<=0.450 versus the alternative that P>=0.650 has an expected sample size of 24.70 and a probability of early termination of 0.654. If the drug is actually not effective, there is a 0.048 probability of concluding that it is (the target for this value was 0.050). If the drug is actually effective, there is a 0.196 probability of concluding that it is not (the target for this value was 0.200). After testing the drug on 15 patients in the first stage, ACC accrual will be terminated if 7 or more patients are withdrawn from the study after <24 weeks of treatment for any reason other than withdrawal of consent (this includes toxicity, PD, intolerance etc.) If the trial goes on to the second stage, a total of 43 patients will be studied. If the total number responding (defined as stable disease or better) is less than or equal to 24, the drug is rejected. An exploratory group of 20 patients with MSGTs will be included in the study, in addition to the 43 patients mentioned above. They can be enrolled in any order within the total accrual of 63 patients and will not participate in statistical analysis. A separate safety analysis will take place; if >2 of the first 10 non-ACC patients are withdrawn after <24 weeks of treatment, non-ACC accrual will discontinue.

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10.3 Data Analyses Plans

Response rates and 95% confidence intervals will be calculated using exact binomial probability distributions for discrete outcomes. Progression-free survival and overall survival will be graphically depicted using Kaplan-Meier curves. Adverse events will be summarized descriptively using frequencies and percentages. Statistics will be given on type, severity, frequency and attribution of adverse events. Sample size considerations are described above.

An intention to treat analysis will be done. In a single group Phase II study, intention to treat means that all patients who are evaluated and registered for the study are followed and analyzed regardless of (a) whether they were subsequently found to be protocol ineligible and (b) the amount of study treatment (nivolumab/ipilimumab) they received. To calculate progression-free and overall survival in patients who received nivolumab/ipilimumab, times will be taken from the time of study registration. This definition parallels the definition of intention to treat in randomized clinical trials.

11.0 STUDY MANAGEMENT REFERENCES

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the

implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by BMS. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system. Training on eCRF completion will be provided at the time of site activation.

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document). Generally, all data are due at the end of each cycle.

11.5 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.
- Draft informed consent form should for review/approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent.

- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

11.6 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to NOTIS for additional information). The level of risk attributed to this study requires high monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level.

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to NOTIS for additional information). The level of risk attributed to this study requires High Intensity Monitoring as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level.

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document).

11.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.8 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.9 Publication Policy

This section should be removed if the trial is not rated as a high intensity trial.
All potential publications and/or data for potential publications (e.g. manuscripts, articles, data, text, diagrams, abstracts, posters, charts, slides, pictures, or clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. For trials that require high intensity monitoring, the assigned QAM will prepare a preliminary data summary (to be approved by the DSMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DSMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DSMC at their next available meeting, and a final, DSMC-approved dataset will be released along with any DSMC decisions regarding publication. The investigators are expected to use only DSMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DSMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

NU shall provide BMS with a copy of each Publication at the earliest practicable time, but in any event not less than thirty (30) days prior to its submission to a journal, publisher or meeting or fifteen (15) days prior to any public disclosure of any manuscript or other public disclosure (e.g., presentations). To the extent applicable, BMS personnel shall be acknowledged (including authorship where applicable) in accordance with customary scientific practice.

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APPENDICES

Appendix A.
Common Terminology Criteria for Adverse Events V4.0.3 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix B – ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) performance status scale	
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self- care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982*. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Appendix C – Contraception Requirements

Investigators shall counsel FOCBP and male subjects who are sexually active with FOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise FOCBP and male subjects who are sexually active with FOCBP on the use of highly effective methods of contraception from the time of treatment initiation to 5 months (for FOCBP) or 7 months (for males with FOCBP partners) after the last dose of nivolumab. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

a) Male condoms with spermicide
b) Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by FOCBP subject or male subject's FOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.
c) Nonhormonal IUDs, such as ParaGard®
d) Tubal ligation
e) Vasectomy.
f) Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

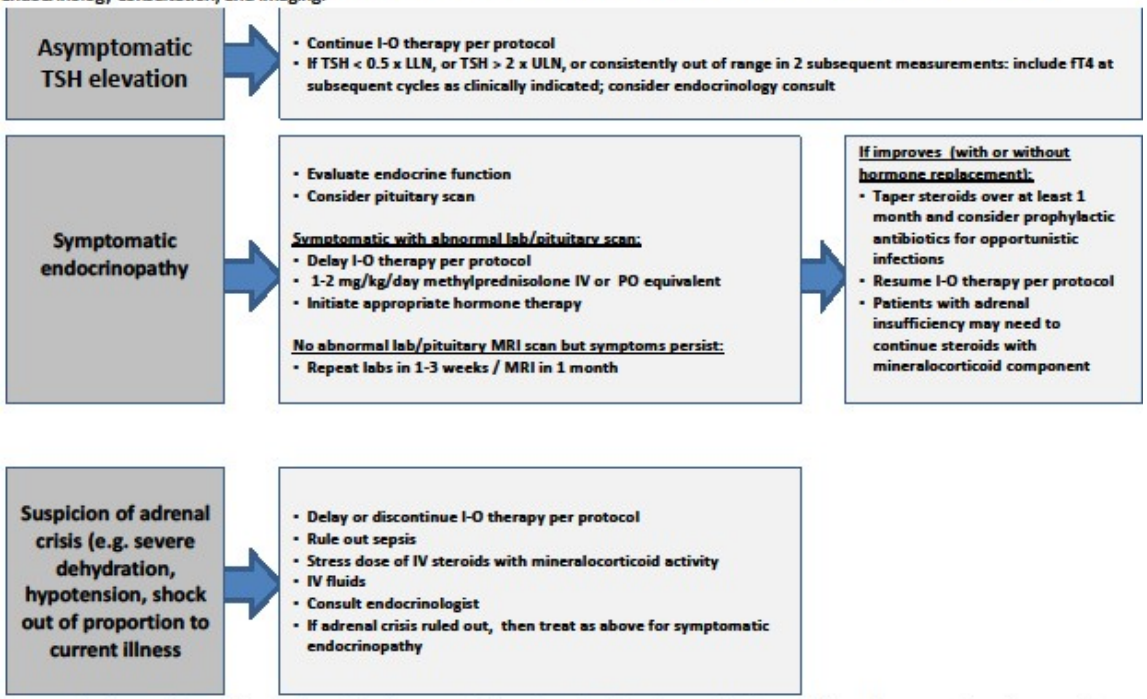
a) Diaphragm with spermicide
b) Cervical cap with spermicide
c) Vaginal sponge
d) Male Condom without spermicide*
e) Progestin only pills by FOCBP subject or male subject's FOCBP partner
f) Female Condom*

*A male and female condom must not be used together

Appendix D– Adverse Event Algorithms
Recommended management algorithms for suspected nivolumab related endocrinopathy, gastrointestinal toxicity, hepatotoxicity, neurologic toxicity, pulmonary toxicity, renal toxicity and skin toxicity

Endocrinopathy Management Algorithm

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



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

GI Adverse Event Management Algorithm

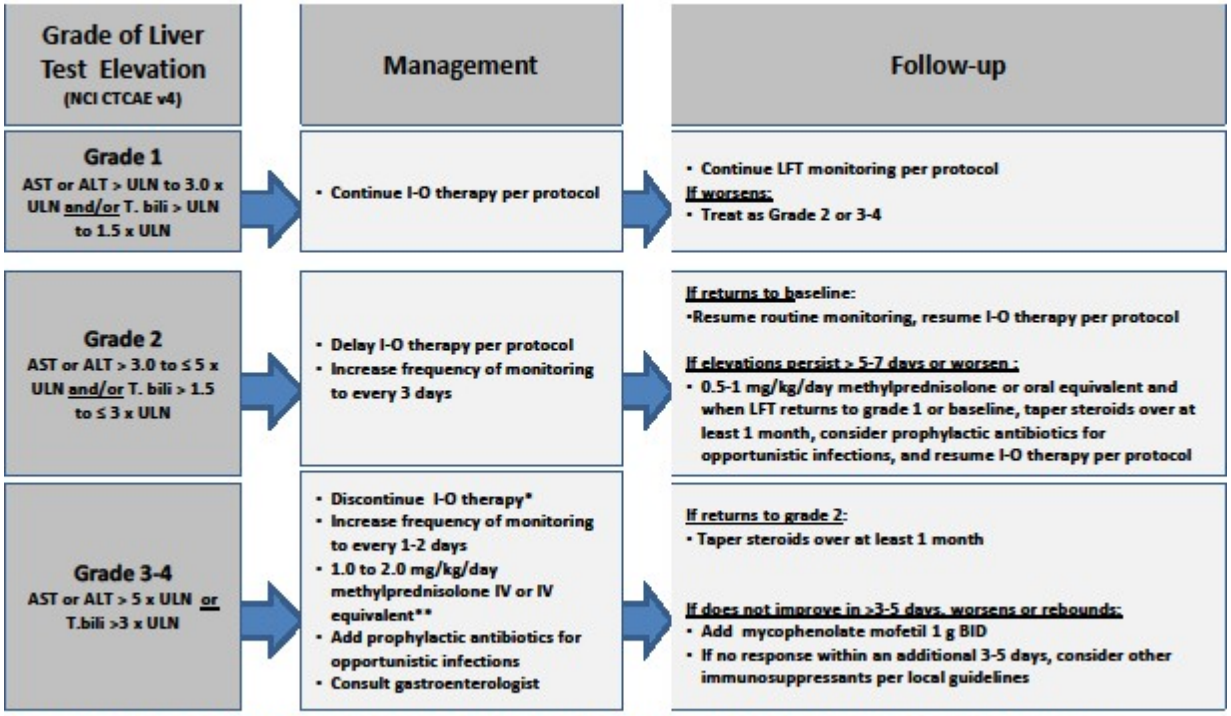
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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

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

Hepatic Adverse Event Management Algorithm

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



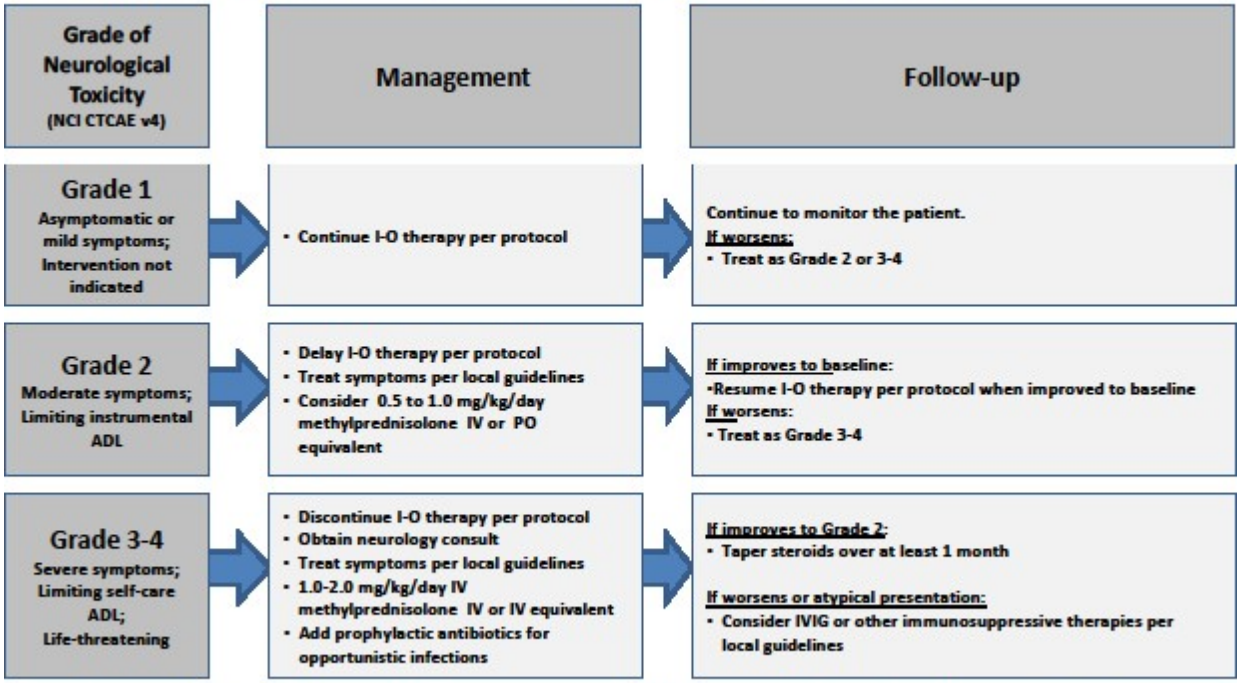
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

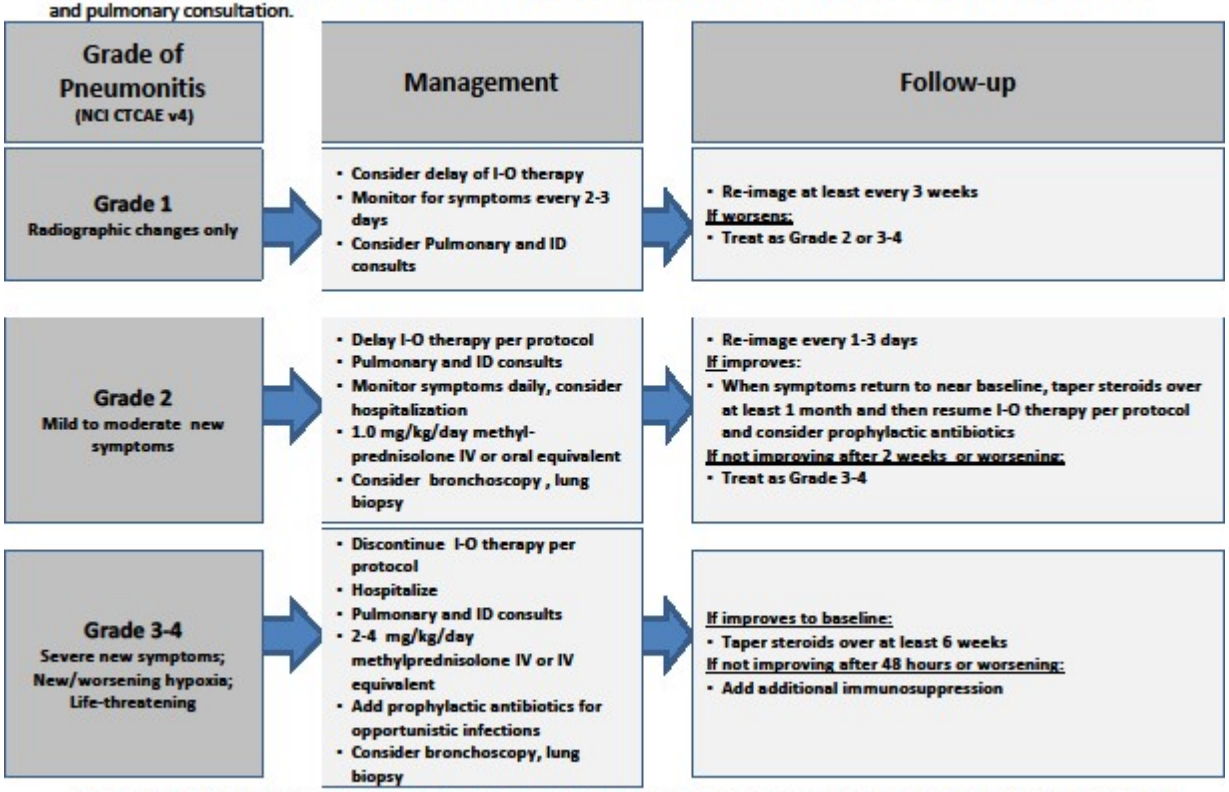
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

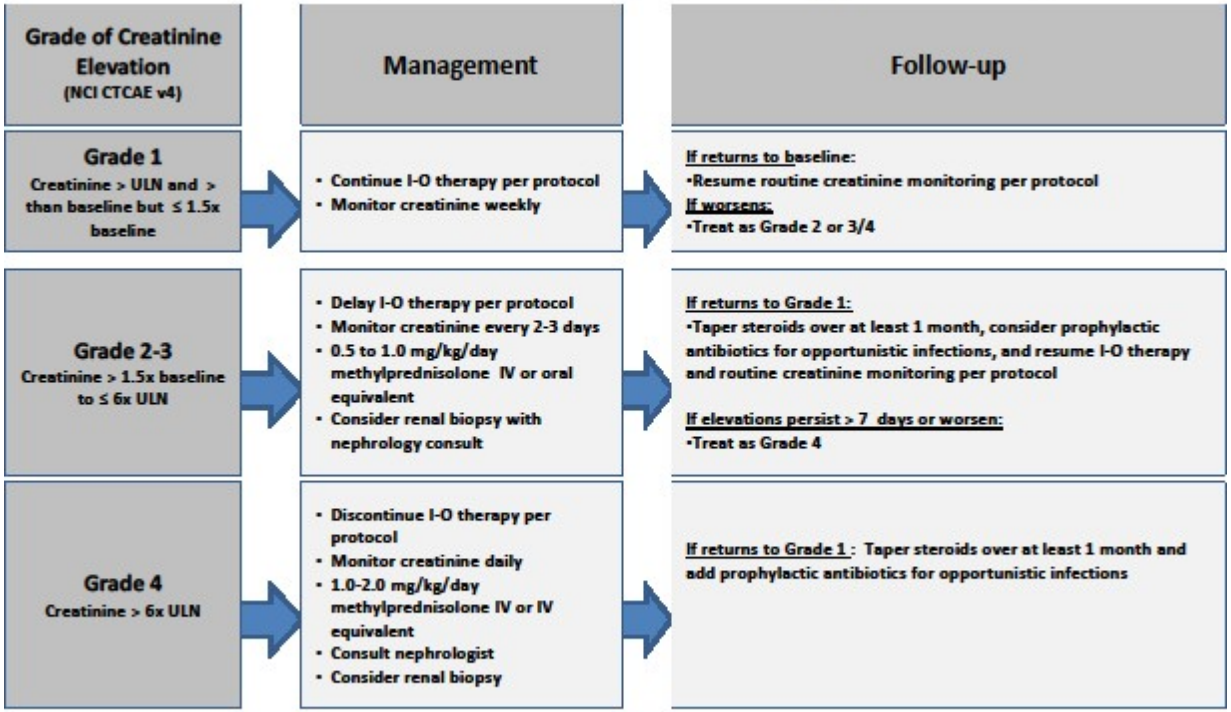
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Renal Adverse Event Management Algorithm

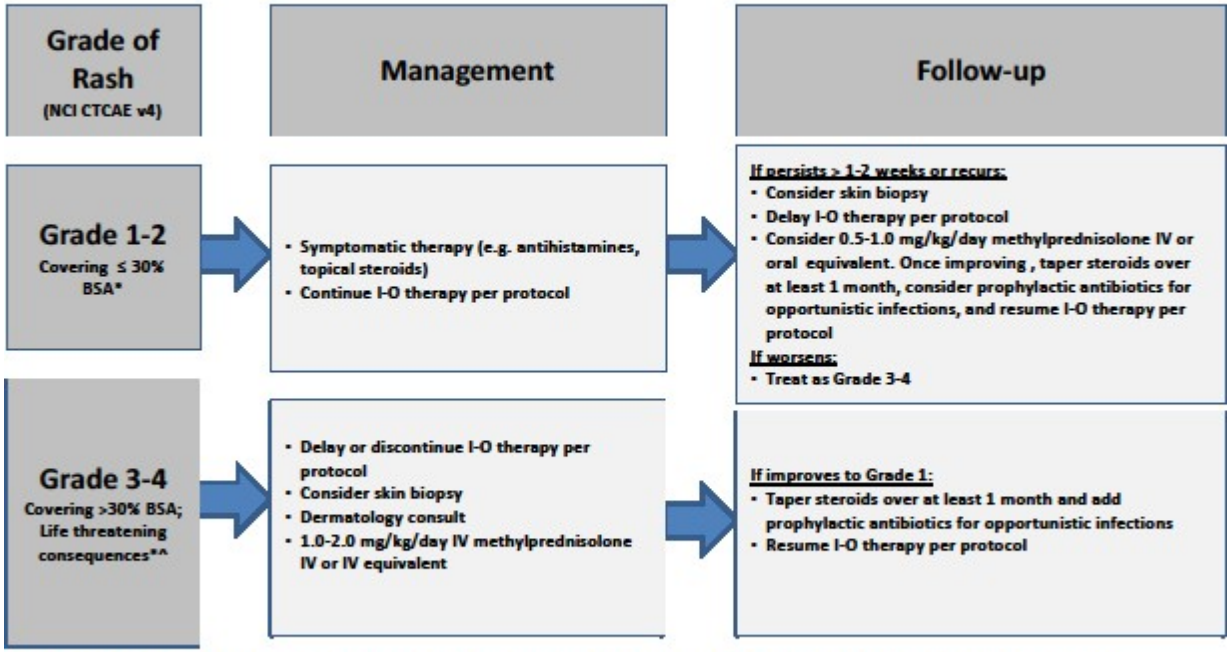
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Skin Adverse Event Management Algorithm

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



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

Appendix D – Protocol Summary of Changes

Amendment 1 – February 16, 2017 *Approved by Scientific Review Committee: March 1, 2017*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover Page; Study Summary	Title referred to treatment of "advanced" ACC and non ACC	Changes title to refer to treatment of "metastatic/recurrent" ACC and non ACC	Revised for consistency with population and eligibility criteria
Study Schema; Study Summary; 3.0 (Patient Eligibility); 3.1.2, 3.1.3 (Inclusion Criteria)	Patients "cannot be a candidate for surgical treatment"	Patients "cannot be a candidate for surgical **or radiation** treatment"	Revised for consistency with 3.2.3
Study Summary; 2.1 (Primary Objective); 6.2 (Primary Endpoint); 10.1.1 (Primary); 10.2 (Sample Size and Accrual)	"To assess progression-free survival rate (PFSR) at 6 months" **or** "To assess median progression-free survival rate (PFSR) as well as PFSR at 6 and 12 months"	To assess median progression-free survival (PFS) as well as PFS at 6 and 12 months	Progression-free survival does not need to be measured as a rate. To correct discrepancies – we will look at median and 12-month PFS as well as 6-month.
3.1.3 (Inclusion Criteria)	"Patients must have received at least one prior line of systemic therapy"	"Patients **may or may not** have received prior therapy **for their recurrent/metastatic disease**"	Disease team requested to expand eligibility to patients who have not received treatment for metastatic/recurrent disease.
4.1 (Overview); 4.2 (Treatment Administration); 4.2.1 (Nivolumab); 4.2.2 (Ipilimumab)	Treatment windows were as follows: Nivolumab over 30 mins **(±5 mins)** / 60 mins **(±10 mins)** Ipilimumab over 90 mins **(±5 mins)**	Changes treatment windows: Nivolumab over 30 mins **(-5 / +15 mins)** / 60 mins **(-10 / +15 mins)** Ipilimumab over 90 mins **(-5 / +15 mins)**	Allows for flexibility of a longer infusion if needed, without compromising safety
11.6.2 (Other Protocol Deviations)	Refers to "Promptly Reportable Non-Compliance (PRNC)"	Changes to "Reportable New Information (RNI)"	Administrative – to align with current internal policies
Amendment 2 – March 13, 2017 *Approved by Scientific Review Committee: March 27, 2017*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
1.4 (Exploratory Studies); 2.3.3 (Exploratory Objectives & Endpoints); 5.0 (Study Procedures); 9.0 (Correlatives / Special Studies)	Included cfDNA exploratory objective and correlative samples, to be performed at Guardant	Removes cfDNA samples and any reference to such analysis at Guardant. Such samples will be collected and sent as part of SOC, and have been added as a separate procedure in 5.0.	Administrative decision to remove samples due to logistical issues with Guardant
5.0 (Study Procedures)	n/a	Adds optional Echo/ECG at baseline for patients with a history of congestive heart failure or at risk because of	Response to CTEP action letter advising for cardiac monitoring as a result of recent myocarditis

		underlying cardiovascular disease	
5.0 (Study Procedures, #12); 9.0 (Correlative/ Special Studies)	Tissue was to be collected from SOC biopsies throughout the study "If the patient agrees", and were not mentioned in 9.0	Removes "If the patient agrees" and adds "if feasible"	Tissue collection from SOC biopsies will be mandatory if feasible, and the patient's overall consent will account for this
5.0 (Study Procedures); 9.0 (Correlative/ Special Studies)	NGS was listed as a correlative sample	Adds NGS as a separate study procedure, which will be performed as part of standard of care (rather than a correlative sample)	Clarification – NGS is performed SOC and is not meant to be processed through Pathcore or as a research charge.
5.0 (Study Procedures, #11)	n/a	Adds blood volume and tube types for correlative samples.	Clarification
Amendment 3 – May 17, 2017 *Approved by Scientific Review Committee: June 2, 2017*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Cover Page	Includes Ricardo Costa as Sub-Investigator	Removes Ricardo Costa as Sub-Investigator	Administrative; Dr. Costa has left the university
Study Summary; 6.3 (Secondary Endpoints)	Secondary objective to look at clinical benefit rate (CBR) at 24 weeks	Changes secondary objective to clinical benefit rate (CBR) and **6 and 12 months**	Revision of discrepancy
Study Summary; 2.2.2 (Secondary Objectives & Endpoints); 6.7 (Immune-related RECIST); 10.1.2 (Secondary)	Secondary objective of efficacy using immune-related response criteria (irRC)	Changes secondary objective to efficacy using **immune-related RECIST** (irRECIST). Updates criteria in 6.7 to align with current definitions of irRECIST	Revision of discrepancy; irRECIST is most current immune-related response criteria
3.1.9 (Inclusion Criteria); 5.0 (Study Procedures, #8)	Pregnancy test was required within 72 hours of Registration	Pregnancy test required **≤14 days** prior to registration	Clarification to allow for greater flexibility in screening
3.2.1, 3.2.4, 3.2.13 (Exclusion Criteria); 4.6.2 (Prohibited Medications)	Windows for prohibited medications were from study registration	Windows for prohibited medications are changed to be measured from start of study treatment	A window from study treatment rather than registration allows for greater flexibility at screening, and is more clinically appropriate, per PI
4.2.2. (Ipilimumab); 5.0 (Study Procedures, #10)	n/a	Adds: "Dosing will be based on weight at baseline, however if there is a weight change ≥10%, the dose should be adjusted accordingly"	Clarification
5.0 (Study Procedures)	TSH	TSH with reflex	Clarification
	#2: Vital signs included pulse, respirations, and blood pressure	#2: Removes respirations from vital signs	Missing respirations are a common source for protocol deviations; they are not clinically necessary
	#11: Correlative blood samples were to be collected in 10mL heparin tubes	#11: Changes correlative tubes to 8mL heparin tubes	Correction
Amendment 4 – August 14, 2017			

Approved by Scientific Review Committee:			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Cover Page; Study Summary	Title: Phase II study of nivolumab and ipilimumab for treatment of metastatic/recurrent adenoid cystic carcinoma and non-adenoid cystic carcinoma	Title: Phase II study of nivolumab and ipilimumab for treatment of metastatic/recurrent adenoid cystic carcinoma **of all anatomic sites of origin** and non-adenoid cystic carcinoma **malignant tumors of the salivary gland**	Clarification to address discrepancies in study population
Study Schema; 3.1.1 (Inclusion Criteria);	Study population was to include ACC patients with evidence of disease progression.	Clarifies that ACC can be of any anatomic site of origin	Clarification of study population to ensure it is inclusive
Study Schema; 3.1.2, 3.1.3 (Inclusion Criteria); 3.2.3 (Exclusion Criteria)	Study population was to include ACC patients who are not surgical or radiation candidates	Clarifies that patients cannot be a candidate for **curative** surgical or radiation therapy	Clarification; distinguishes between surgical/radiation therapy which is palliative or otherwise non-curative, which is permitted
3.1.3 (Inclusion Criteria)	NOTE: There is no limit to the number of prior therapies for stage IV Disease	NOTE: There is no limit to the number of prior **systemic** therapies	Clarification
3.1.4 (Inclusion Criteria)	n/a	Adds note that scans must be ≤28 days prior to study treatment	Clarification
3.1.7 (Inclusion Criteria)	Requirements for bilirubin and creatinine were listed as <3.0 x ULN and > 30 mL/minute	Updates to ≤ and ≥ respectively	Clarification; criteria are meant to be inclusive of the borderline value
3.2.1 (Exclusion Criteria)	Chemotherapy and radiotherapy were not permitted ≤28 days prior to study treatment	Shortens window for radiotherapy; now permitted >7 days prior to study treatment	Allows greater flexibility in the allowance for radiotherapy since it might be clinically indicated to have radiotherapy close to treatment and is lower risk
3.2.5 (Exclusion Criteria)	Included a reference to specific PD-1, PD-L1, and CTLA4 monoclonal antibodies	Removes reference and list of specific monoclonal antibodies	The list is incomplete and potentially misleading. The PI can be contacted for any questions on specific immune checkpoint inhibitors
3.2.12 (Exclusion Criteria)	Patients were excluded with any known positive test for Hepatitis B or C indicating acute or chronic infection	Only acute, and not chronic, Hepatitis B or C infection is considered exclusionary	A controlled chronic condition does not indicate the need to exclusion
4.3.2 (Treatment Discontinuation); 4.7 (Duration of Therapy); 7.4.1	Referred to NU's internal Data Monitoring Committee (DMC)	Changes to Data Safety Monitoring Committee (DSMC)	To align with updated policies

(Routine Reporting); 7.4.3.1 (Reporting to NU QAM/DSMC); 11.9 (Publication Policy)			
5.0 (Study Procedures)	Window for treatment and procedures was ±4 days	Changes treatment and procedure window to -2/+4 days Changes EOT window to ±7 days	Nivolumab cannot be given <12 or 24 days after the previous dose; smaller window prevents overlap Larger EOT window allows flexibility
5.0 (Study Procedures #1,3)	Baseline imaging was to include CT of Neck, Chest, Abdomen and Pelvis within 28 days prior to registration.	Baseline imaging must be within 28 days prior to **starting treatment** and may include Neck, Chest, Abdomen and Pelvis (**or any combination**) at investigator discretion.	Allows more flexibility for investigator to use discretion as to which scans are clinically relevant. The timing of scans from treatment is more important to get the most accurate picture of disease burden.
5.0 (Study Procedures #3,4,5)	One footnote was included with all instructions related to scans on study	Separates into 3 footnotes to clearly delineate instructions for scans at baseline, prior to each cycle, and in the case of PD. Re-numbers subsequent footnotes appropriately.	Simplified for clarity
5.0 (Study Procedures, #20)	NGS was to be performed using Foundation One, “any time prior to study treatment, preferably within 6 weeks”	• Removes Foundation One • NGS can be performed any time prior to study treatment as long as the patient has not received other treatment since the biopsy. • Clarifies that tissue should be taken from the lesion demonstrating progression and that patients may agree to provide a fresh biopsy if not available	• Allows greater flexibility in using different companies for NGS testing • Clarification; it is more important that the biopsy not be intervened by treatment rather than the actual timing • Clarification
5.0 (Study Procedures, #21)	A liquid biopsy was to be performed prior to study treatment, “preferably within 6 weeks, per clinician’s discretion”	Liquid biopsy can be performed any time prior to study treatment “as long as the patient has not received other treatment since the biopsy, per standard of care procedures”	Clarification; it is more important that the sample not be intervened by treatment rather than the actual timing
8.1 (Nivolumab)	Contained outdated language on nivolumab details. Specifically: 8.1.4: Nivolumab could be stored up to 4 hours at room temperature 8.1.6: Listed details on minimum concentration with weight-based dosing	Updates nivolumab details to align with new Investigator’s Brochure and internal template language for nivolumab protocols. Specifically: 8.1.4: Nivolumab can be stored up to 8 hours at room temperature	Updated for simplicity to align with other internal nivolumab protocols

		8.1.6: Removes reference to weight-based dosing preparation	
Amendment 4 continued – September 8th, 2017 *Approved by Scientific Review Committee:*			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes cont.***	***Rationale***
7.3 (Reporting of pregnancy and lactation); Appendix A	Contraception timing post-treatment was not specified; pregnancy was to be monitored up to at least 6 half-lives after product administration	WOCBP will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab.	Updated per BMS to align with new nivolumab IB v16 requirements for pregnancy and contraception.
8.1.9 (Availability and Supply)	Did not specify timing for drug re-supply requests	Drug re-supply should be submitted 10 business days before the delivery date	Updated for accuracy per BMS
8.1.12, 8.2.12 (Return & Retention of Study Drug)	n/a	Adds statement: "Inform BMS on all drug destructions pertaining to both nivolumab and ipilimumab."	BMS request.
Tale 8.1 (Nivolumab Product Description)	5-10 vials per carton were supplied	5 vials per carton are supplied	Updated for accuracy per BMS
8.2.4 (Storage and stability)	n/a	Replaces language with internal ipilimumab template	For consistency among internal IIT protocols using ipilimumab
Table 8.2 (Ipilimumab Product Description)	4 vials per carton were supplied	5 vials per carton are supplied	Updated for accuracy per BMS
Appendix B	Contained outdated AE Management Algorithms. Specific outdated parameters include: Hepatic: • Discontinue for AST/ALT >5xULN **and/or** Tbili >3xULN Pulmonary (G3-4): • Includes example immunosuppression Renal (G2-3): • "Consider renal biopsy" Skin (G3-4): • n/a	Updates AE Management Algorithms to align with nivolumab IB v16. Specific changes to AE management include: Hepatic: • Discontinue for AST/ALT > 5xULN **or** Tbili > 3xULN Pulmonary (G3-4): • Removes examples of immunosuppression Renal (G2-3): • "Consider renal biopsy with nephrology consult" Skin (G3-4): • Adds footnote: "If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed,	Updated per BMS for consistency with new nivolumab IB v16 and additional or clarified safety measures.

		permanently discontinue I-O therapy."	
Amendment 5 – September 11th 2019			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Coverpage 3.0 (Subject Eligibility)	Lists Maria Matsangou as the PI for the study	Changes to list Mark Agulnik as the PI	Change due to original PI leaving Northwestern
Amendment 6 – October 11th 2019			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
4.6.1 (Permitted Medications) 4.6.2 (Prohibited Medications)	n/a	Adds guidelines of permitted palliative radiation or surgery on study	To allow patients to have palliative radiation or surgery when on treatment
Amendment 7– June 26th 2020			
Section(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***
Coverpage	Lists Mark Agulnik as the PI for the study	Changes to list Young Chae as the PI	Change due to PI leaving Northwestern
	Lists Sub-investigators for the study	Removes Sub-investigators from the coverpage	Per new policies, sub-investigator lists will be maintained in DOA and APL only and not on the protocol coverpage
3.0 (Subject Eligibility) 9.1 (Specimen Banking)	Lists the PIs by name and in some places provides contact information	Removed or replaced with "PI"	Removed as PI is leaving Northwestern and to provide consistency throughout the protocol
Amendment 8			
Section(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
8.2.5 Ipilimumab storage and stability	Previous information	Updated with current information	***As mandated by BMS, based on current IB***
8.2.6 Preparation of ipilimumab	Previous information	Updated with current information	***As mandated by BMS, based on current IB***
8.2.9 Availability and supply of Ipilimumab And 8.2.12 Return and retention of drug	Previous information	Updated to state, "Starting January 2023, Ipilimumab will be supplied in 50mg vials. Each carton will contain 6 x 50mg vials." Other associated information updated	***As mandated by BMS, based on current IB***