

## Phase II study of nivolumab (anti-PD-1 antibody) for treatment of metastatic adrenocortical carcinoma

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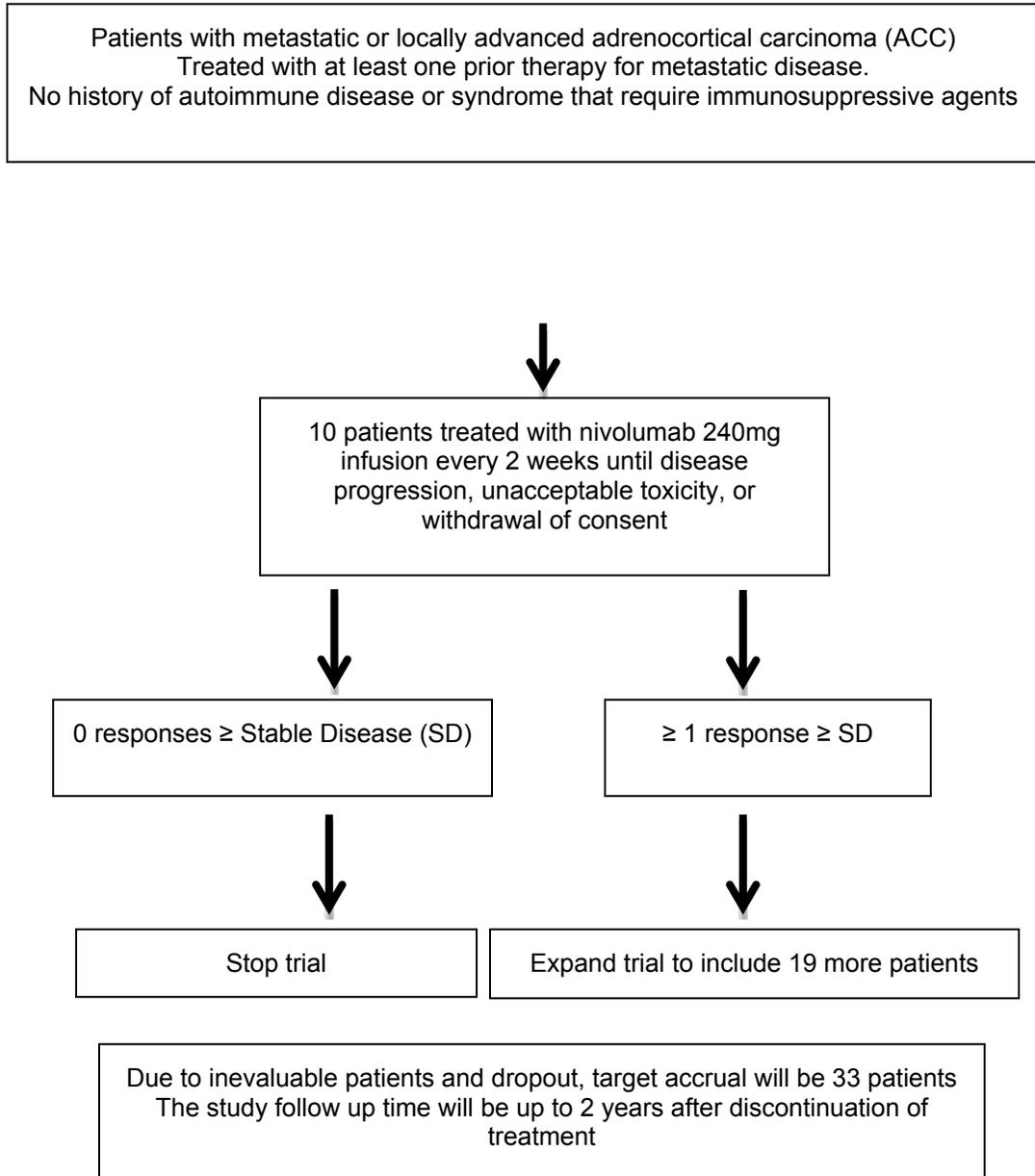
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## LIST OF ABBREVIATIONS

ACC	Adrenocortical Carcinoma
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&PE	History & Physical Exam
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NSCLC	Non-small cell lung cancer
NCI	National Cancer Institute
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
RCC	Renal cell carcinoma
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

## STUDY SCHEMA



## STUDY SUMMARY

<b>Title</b>	Phase II study of nivolumab (anti-PD-1 antibody) for treatment of metastatic adrenocortical carcinoma
<b>Short Title</b>	Nivolumab for treatment of metastatic adrenocortical carcinoma
<b>Version</b>	July 5 <sup>th</sup> , 2016
<b>Study Design</b>	Simon two stage optimum Phase II clinical trial
<b>Study Center(s)</b>	Northwestern Medicine Developmental Therapeutics Institute Robert H. Lurie Comprehensive Cancer Center
<b>Objectives</b>	<p><b>Primary:</b> To assess efficacy of nivolumab monotherapy according to objective response rate (ORR) as assessed by RECIST 1.1 in patients with advanced adrenocortical carcinoma</p> <p><b>Secondary:</b> To assess the efficacy of nivolumab according to progression-free survival (PFS), overall survival (OS)</p>
<b>Sample Size</b>	33 study participants
<b>Diagnosis &amp; Key Eligibility Criteria</b>	Patients with metastatic or locally advanced adrenocortical carcinoma with disease progression after treatment with at least one line of therapy including mitotane and/or chemotherapy.
<b>Treatment Plan</b>	Patients will be treated with nivolumab 240mg as in intravenous infusion over 30 minutes every 2 weeks until confirmed disease progression, unacceptable toxicity, or withdrawal of consent.
<b>Statistical Methodology</b>	Up to 33 patients will enroll in the two stage phase II clinical trial. In the first stage, up to 12 patients will be entered to achieve 10 evaluable. If no patients show a response, then the trial will be terminated due to inactivity of the treatment. If 1 or more of 10 show a response, then up to an additional 21 patients will be added to achieve 19 evaluable. If 3 or fewer of 29 show a response, then the trial will conclude that the response rate could be as low as 5%. If 4 or more respond, then the trial will conclude that the response rate is at least 20%. This design has a 20% chance of falsely concluding the rate is 5% (false negative Type II error rate = 20%, or power = 80%), and a 5% chance of falsely concluding that the rate is 20% (false positive Type I error rate = 5%). Taking into account dropout and patients not evaluable, target accrual will be up to 33 patients.

## 1.0 INTRODUCTION – BACKGROUND & RATIONALE

### 1.1 Disease Background

Adrenocortical carcinoma (ACC) is an exceedingly rare malignancy with no effective standard treatment options. ACC is responsible for 0.2% of all cancer deaths in the United States and has an estimated incidence of 0.7 cases per million per year [1, 2]. The disease incidence has a bimodal distribution with peaks in first and fourth decades with a female to male ratio 1.5-2.5:1 [3, 4]. While a growing number of patients are diagnosed with early stage and indolent disease incidentally after having abdominal CT scans, the majority of patients (40-60%) present with symptoms related to excessive hormonal production (i.e. hypercortisolism or hyperandrogenism)[3, 5]. Surgery is the treatment of choice for patients presenting with localized disease and is often followed by adjuvant chemotherapy with mitotane to mitigate the risk of disease recurrence in high-risk patients [6-8]. The group of approximately 30-70% of patients presenting with metastatic disease carry an extremely poor prognosis related to the aggressive biological behavior and lack of effective therapeutic options [3, 5]. The 5-year survival rate for this patient population is estimated at less than 15% [9].

Mitotane, the only FDA-approved drug for ACC, displays single-agent activity (10-30% tumor response rates) based on its adrenolytic activity but its broad clinical use is challenged by an unfavorable toxicity profile [10-12]. Chemotherapy has also limited efficacy in advanced disease with retrospective studies showing response rates of 10-20% [13-15]. The only phase 3 randomized clinical trial ever conducted in advanced ACC showed that mitotane combined with etoposide, doxorubicin and cisplatin (EDPM) provided additional clinical benefit compared to mitotane plus streptozocin [16]. In spite of higher tumor response rates with EDPM (23% vs. 9%) and prolongation of progression-free survival (PFS; 5 vs. 2 months), there was no significant benefit in median overall survival (OS; 14 vs. 12 months) and up to 58% of patients receiving EDPM had serious adverse events. In fact, as a clear statement to the unmet need for effective treatments, the National Comprehensive Cancer Network recommendations for first line treatment of metastatic ACC include consideration of systemic therapies in clinical trials.

Advances in the molecular understanding of pathogenesis revealed novel therapeutics targets but no definitive efficacy with targeted therapies have been demonstrated. The role of the insulin growth factor (IGF) pathway in adrenal gland development coupled with results showing that overexpression of IGF2 in 80% of ACC tumors correlates with worse outcome provided the rationale for investigating inhibitors of the IGF-1R [17-20]. Nevertheless, a placebo-controlled phase III trial evaluating the IGF1-R inhibitor linsitinib among 139 patients with recurrent or metastatic ACC following first or second line treatments showed no improvement in PFS or OS (10.8 vs. 11.8 months) [21]. Disappointing results were also seen with agents blocking the VEGF pathway including bevacizumab, sorafenib, and sunitinib despite preclinical data supporting angiogenesis as a relevant therapeutic target [6, 22-24]. Even though results of comprehensive genetic profiling revealed promising therapeutic targets, strategies beyond interfering with disrupted cancer cell signaling are urgently needed [25]. Hence, immunotherapy approaches emerge as potential treatment options clinically feasible with novel checkpoint inhibitors. We propose to investigate the safety and efficacy of the monoclonal antibody against programmed death-1 (PD-1) nivolumab for the treatment of metastatic ACC.

## 1.2 Intervention Overview & Background

### 1.2.1 Overview

Nivolumab (BMS-936558, MDX-1106) is a fully human monoclonal immunoglobulin G4 (IgG4) 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). 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 [26].

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure version 2014). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of “exhausted” T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2, 3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-

modulate the activated T-cell immune response through SHP-1 phosphatase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment [27]. Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma, renal, esophageal, gastric, ovarian, pancreatic, lung, and other cancers (Investigator Brochure version 2014) [28-34]. No published data is available evaluating PD-L1 expression in adrenocortical carcinoma.

### **1.2.2 Clinical development of nivolumab**

Nivolumab is being evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), 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 2014). Nivolumab is currently FDA approved for the treatment of patients with: (i) unresectable or metastatic melanoma and disease progression after ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor; (ii) patients with metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy.

### **1.2.3 Clinical efficacy**

Nivolumab has demonstrated clinical activity as monotherapy and as combination therapy with ipilimumab in several tumor types, including RCC, melanoma, NSCLC, and some lymphomas. The majority of responses was durable and exceeded 6 months (Investigator Brochure version 2014). Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

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 [35]. 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%) [36]. 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) [37]. Median overall survival was 18, 25, and 24 months for the three dose cohorts, respectively. Response rates were in average 20% with only 11% incidence of grade 3-4 treatment-related adverse events. In an advanced melanoma phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) [26]. 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 1 mg/kg nivolumab and 3 mg/kg 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.

#### **1.2.4 Clinical safety**

The overall safety experience with nivolumab, as monotherapy or in combination with other therapeutics, is based on experience in approximately 4,000 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. 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.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced 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 [26].

#### **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 IHC staining and pharmacodynamics changes in the peripheral blood absolute lymphocyte count in the study investigating the combination of nivolumab and

ipilimumab in melanoma [26]. 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- $\gamma$  (IFN- $\gamma$ ), IDO (indoleamine-pyrrole 2,3-dioxygenase), and T cell CD8+ infiltration are also being investigated. However, there is no definitive data to support the use of any of these biomarkers to select patients for treatment at this time.

### **1.3 Rationale for the Current Study**

Studies investigating immunotherapy strategies in ACC provide preliminary evidence that anti-tumor immune response can be promoted in this disease. Based on the wide expression of the steroidogenic acute regulatory protein (StAR) in ACC tumors, a specific immune response against this antigen was elicited using an immunization protocol with DNA plasmids and recombinant vaccinia virus vector that resulted in an anti-tumor effect in a xenograft model utilizing tumor cell line expressing StAR [38, 39]. Another study describing vaccination of two patients with metastatic ACC using autologous dendritic cells pulsed with autologous tumor lysate showed tumor-specific immune response in spite of tumor excess production of glucocorticoids [40]. Furthermore, results from molecular studies show that ACC is a heterogeneous disease defined by a wide array of somatic alterations and differential transcriptional patterns. The characteristic genetic instability of ACC with high rate of chromosomal alterations and somatic mutations certainly results in a significant number of neoepitope peptides derived from these altered genes [25]. These neoepitopes can elicit the generation of specific CD4+ T cells capable of killing cancer cells directly [41, 42].

Hence, the proposed association between mutational burden of tumors and clinical benefit from immunotherapy strategies (i.e. checkpoint inhibitors anti-CTLA-4 and anti-PD-1 antibodies), with remarkable anti-tumor effects seen with tumors displaying the highest rates of mutations such as melanoma [43, 44]. This is also illustrated by the anti-tumoral immunologic response to anti-PD-1 antibody in patients with colorectal cancer with increased mutational burden secondary to mismatch repair deficiency [45]. Building upon this scientific rationale supporting the potential for immunotherapies in ACC and the immeasurable clinical need for novel treatments, we propose to investigate the safety and efficacy of nivolumab for the treatment of metastatic ACC. In light of the afore mentioned antitumor activity in solid tumors, well studied pharmacokinetics and toxicity profile a phase II trial is appropriate at this juncture to assess the antitumor activity of nivolumab in these patients at current standard approved dose of 240mg intravenously every 2 weeks.

#### **1.3.1 Rationale for nivolumab dose and schedule**

The dose and schedule of nivolumab in this study will be 240mg every 2 weeks, based upon safety, efficacy, and exposure-response data from ongoing BMS studies. The Phase 1 study, CA209003. Anti-tumor activity was observed in study CA209003 at dose levels ranging from 1 to 10 mg/kg in RCC. The antitumor activity of nivolumab tended to increase with dose, as did the incidence of SAEs. The anti-tumor activity of

nivolumab in RCC was investigated at dose levels 1 and 10 mg/kg, with the higher activity observed at 10 mg/kg. The observed anti-tumor activity in melanoma, and NSCLC was highest at 3 mg/kg, suggesting that anti-tumor activity approaches a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of the exposure-response analyses for these tumor types, show that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 and 10 mg/kg every 2 week dosing. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose (MTD) was identified. Although the spectrum, frequency, and severity of nivolumab-related AEs were generally similar across the dose levels tested, the 10 mg/kg doses level had numerically higher Grade 3/4 drug-related SAEs and AEs leading to discontinuation. Based on the totality of the safety, efficacy, and exposure-response data, a dose of 3 mg/kg every two weeks was selected as the dose anticipated achieving an appropriate balance of benefit and risk.

### 1.3.2 Flat Dose Regimen

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to 3 mg/kg Q2W dosing regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose 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 dose compared to 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. Hence, a flat dose of 240 mg nivolumab is under investigation.

## 1.4 Exploratory Studies

### **To explore the correlation between PD-1, PD-L1 and PD-L2 expression and CD4+ and CD8+ tumor infiltrating lymphocytes and PFS, OS and response to treatment.**

PD-1 is a key immune checkpoint receptor expressed by activated T cells and mediates immunosuppression. PD-1 functions primarily in peripheral tissues, where T cells may encounter the immunosuppressive PD-1 ligands PD-L1 and PDL-2, which are expressed by tumor cells, stromal cells or both [46-48]. PD-L1 and PD-L2 are overexpressed in a variety of solid tumors however no data exists in ACC [46].

There are conflicting data on the predictive value of PD-L1 expression on PD-1 directed therapy in solid tumors [36, 46]. 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 [49]. 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 [36].

Pathological slides from tumor archival tissue will be stained using a monoclonal antibody against PD-L1 and defined as PD-L1 positive if equal or greater than 5% of the tumor cells membrane analyzed. We hypothesize that tumor cell membrane expression of PD-L1 or PD-L2 can have an impact on treatment responses.

#### **Peripheral blood lymphocyte phenotypes**

Lymphocyte subsets (CD3, CD4, CD8, CD19, and CD56) will be analyzed according to absolute cell numbers per microliter of whole blood, percent representation among all lymphocytes, and coexpression of the activation markers CD25, HLA-DR, and CD45RO using automated flow cytometric techniques at the Flow Cytometry Core Laboratory, Robert H Lurie Cancer Center of Northwestern University under the supervision of Suchitra Swaminathan, PhD.

**To measure humoral and cellular responses to tumor antigens on serum samples by measuring the levels of cytokines (ie, IL-2, IL-6, IL-8, IL-10, IL-18, IFN $\gamma$  and TNF- $\alpha$ ) and peripheral blood lymphocyte phenotype.** Measures of immunologic response correlate with lack or presence of response to treatment with nivolumab.

## **2.0 OBJECTIVES & ENDPOINTS**

### **2.1 Primary Objective & Endpoint**

The primary objective will be to assess overall response rate of nivolumab in patients with metastatic or locally advanced adrenocortical carcinoma. Overall response rate will be measured according to RECIST criteria 1.1 at every 8 weeks interval by using CT scans.

### **2.2 Secondary Objectives & Endpoints**

- 2.2.1 To assess the progression free survival defined as time from date of first nivolumab infusion until date of death or evidence of progression of disease as assessed by CT imaging every 8 weeks according to RECIST criteria 1.1.
- 2.2.2 To assess the overall survival defined as time from date of first nivolumab infusion until death of patients with metastatic or locally advanced ACC. The patients will be assessed for survival (either by routine clinic visit or by phone) every 2 weeks while on treatment and every 3 months for up to 2 years after completion of trial to document survival and disease progression,
- 2.2.3 To assess the safety and tolerability profile of nivolumab described by number, frequency, and severity of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3 assessed every 2 weeks while patients are on therapy.

### 2.3 Exploratory Objectives & Endpoints

- 2.3.1 To assess the overall response rate, progression free survival and overall survival according to tumor PD-L1 and PD-L2 expression,
- 2.3.2 To assess the overall response rate, progression free survival and overall survival according to serum interleukin levels and peripheral T cell profile levels,
- 2.3.3 To measure humoral and cellular responses to tumor antigens on serum samples by measuring the levels of cytokines (ie, IL-2, IL-6, IL-8, IL-10, IL-18, IFN $\gamma$  and TNF- $\alpha$ ) and peripheral blood lymphocyte phenotype. We will explore potential correlations between differential measures of response and the toxicity and efficacy of nivolumab,

### 3.0 PATIENT ELIGIBILITY

The target population for this study is patients with metastatic or locally advanced ACC who have been treated with mitotane and/or one line of chemotherapy. This will be a multicenter trial conducted at Northwestern University. Northwestern University will serve as the lead site and coordinating center for this study. Participating sites will include Ohio State University, Moffitt Cancer Center, and Johns Hopkins University.

A total of up to 33 subjects will be needed for this trial. Given that this is an NIH rare disease, approximately 5 patients can be enrolled per year. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Devalingam Mahalingam at (312) 472-1234.

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.

#### 3.1 Inclusion Criteria

- 3.1.1 Patients must have a histologically confirmed stage IV or unresectable locally advanced adrenocortical carcinoma,
- 3.1.2 Patients must have disease progressing after treatment with at least one line of therapy including mitotane and/or chemotherapy.

Note: Patients who are deemed ineligible to receive first line treatment with mitotane and/or chemotherapy or who decline first line treatment may be eligible for this study after discussion with the PI.

- 3.1.3 Patients must have measurable disease according to the standard RECIST version 1.1. CT scans or MRIs used to assess the measurable disease must have been completed within 28 days prior to registration.
- 3.1.4 Patients must be of age  $\geq 18$  years at the time of study registration.
- 3.1.5 Patients must exhibit an ECOG performance status of 0-3.
- 3.1.6 Patients must have adequate organ and bone marrow functions:
  - leukocytes  $\geq 2,000/\text{mcl}$

- absolute neutrophil count  $\geq 1,500/\text{mcl}$
- hemoglobin  $\geq 9 \text{ g/dL}$
- platelets  $\geq 75,000/\text{mcl}$
- total bilirubin  $\leq 1.5 \times$  institutional upper limit of normal (ULN)  
(except patients with Gilbert Syndrome, who can have total bilirubin  $< 3.0 \text{ mg/dL}$ )
- AST(SGOT)/ALT(SGPT)  $\leq 3 \times$  ULN  
*NOTE: If liver metastases are present, AST/ALT  $\leq 5 \times$  ULN is permitted*
- Serum creatinine of  $< 3.0 \times$  ULN (upper limit of normal) or creatinine clearance  $> 30 \text{ mL/minute}$  (using Cockcroft/Gault formula below):  
Female CrCl =  $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$   
Male CrCl =  $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$

3.1.7 Patients with history of central nervous system (CNS) metastases are eligible if CNS disease has been radiographically and neurologically stable for at least 6 weeks prior to study registrations and do not require corticosteroids (of any dose) for symptomatic management

3.1.8 Females of childbearing potential (FOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

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)

3.1.9 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 B for details on appropriate contraception methods)

3.1.10 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 who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study are not eligible.

3.2.2. Patients who have not recovered to  $\leq$  Grade 1 from adverse events due to agents administered more than 4 weeks earlier are not eligible.

3.2.3. Patients may not be receiving any other investigational agents.

3.2.4. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab are not eligible.

- 3.2.5. Patients should be excluded if they have had prior treatment with an anti-PD1 or anti-PD-L1. Please contact principal investigator, Devalingam Mahalingam, for specific questions on potential interactions.
- 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 are ineligible who 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 steroids and adrenal replacement steroid doses >10mg daily prednisone equivalents 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 (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.*

- 3.2.8. Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible:
- Uncontrolled hypertension – blood pressure  $\geq$  150/90 mmHg despite medical therapy
  - Ongoing or active infection requiring systemic treatment
  - Symptomatic congestive heart failure
  - 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

3.2.9. 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, adequately treated Stage I or II cancer from which the patient is currently in complete remission, 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 or chronic infection is not permitted.

## **4.0 TREATMENT PLAN**

This will be a single-center phase II trial with patients with metastatic or locally advanced ACC who have been treated with at least one line of therapy including mitotane and/or chemotherapy. Patients will be treated with nivolumab 240mg as an intravenous infusion over 30 minutes every 2 weeks until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Note: Please refer to section 4.2.3 for patients who may continue treatment after initial progression.

### **4.1 Treatment Administration**

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.

Nivolumab will be administered at a dose of 240mg as an intravenous infusion over 30 minutes every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose. 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 4.2.4.

Nivolumab is to be administered as a 30-minute IV infusion (a window of +/- 5 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 cannot be below 1 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 modifications (e.g., dose delay or discontinuation) will be based on specific laboratory and adverse event criteria.

Early recognition and management may mitigate severe toxicity. Evaluation and Management Guidelines were developed to assist investigators and can be found in the Investigator Brochure:

- Suspected Pulmonary Toxicity
- Diarrhea and Colitis
- Suspected Hepatotoxicity (including asymptomatic liver function tests [LFT] elevations)
- Suspected Endocrinopathy
- Nephrotoxicity

#### **4.2 Dosing delays, support care, and discontinuation of therapy**

There will be no dose modifications allowed for management of toxicities.

Nivolumab administration should be delayed for the following until resolution to  $\leq$  Grade 1:

- Any Grade  $\geq 2$  non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
  - Any Grade 3 skin, drug-related adverse event
  - Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
    - Grade 3 lymphopenia or leukopenia does not require dose delay
    - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade  $\geq 2$  toxicity
    - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade  $\geq 3$  toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure and appendix D of this protocol.

##### **4.2.1 Treatment discontinuation criteria**

Nivolumab treatment should be permanently discontinued 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
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
    - AST or ALT > 5-10x ULN for > 2 weeks
    - AST or ALT > 10x ULN
    - Total bilirubin > 5x ULN
    - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events:
  - Grade 4 neutropenia  $\leq$  7 days does not require discontinuation
  - Grade 4 lymphopenia or leukopenia does not require discontinuation
  - 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 do not require discontinuation
  - Isolated Grade 4 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. The PI and Data Monitoring Committee (DMC) should be notified of Grade 4 amylase or lipase abnormalities (please do so by sending an email to [croqualityassurance@northwestern.edu](mailto:croqualityassurance@northwestern.edu))
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the PI and DMC should be consulted (by emailing [croqualityassurance@northwestern.edu](mailto:croqualityassurance@northwestern.edu)). Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the PI and DMC. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the PI and DMC designee must be consulted. Tumor assessments should continue as per protocol even if dosing is 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.

**4.2.2 Treatment of nivolumab-related infusion reactions**

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. 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 4.0.3) guidelines.

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
<p><u>Grade 1</u> Mild reaction; infusion interruption not indicated; intervention not indicated</p>	<p>Remain at bedside and monitor subject until recovery from symptoms.</p>	<p>The following prophylactic pre-medications are recommended for future infusions:</p> <ul style="list-style-type: none"> <li>• Diphenhydramine 50 mg (or equivalent) and/or</li> <li>• Acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations</li> </ul>
<p><u>Grade 2</u> 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 &lt; 24 hours</p>	<p>Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg;</p> <p>Remain at bedside and monitor subject until resolution of symptoms.</p> <p>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.</p>	<p>For future infusions, the following prophylactic pre-medications are recommended:</p> <ul style="list-style-type: none"> <li>• Diphenhydramine 50 mg (or equivalent) and/or</li> <li>• Acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.</li> </ul>

	<p>Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.</p>	
<p>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</p>	<p>Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 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.</p> <p>Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms</p> <p>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)</p>	<p>No subsequent dosing</p>

**4.2.3 Treatment with nivolumab beyond progression**

A minority of subjects treated with immunotherapy may derive clinical benefit (either delayed responses, stable disease, or increased overall survival) despite initial evidence of progressive disease (PD) with nivolumab.

Patients may be permitted to continue treatment beyond initial RECIST 1.1-defined PD occurring during the initial treatment period (up to 12 weeks) as long as they meet the following criteria:

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

- No indication for immediate alternative treatment
- Patient [assessed by the investigator] is showing clinical benefit and tolerates study drug. The assessment of clinical benefit should take into account whether the subject is clinically stable or deteriorating and likely or unlikely to receive further benefit from continued treatment.
- The time of progression is noted from the first assessment that exceeds standard criteria

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

Patients are allowed to continue treatment after initial disease progression for 2-3 additional doses (4-6 weeks) only after consulting with the study PI. These patients must be reassessed for response within 8 weeks; the scan initially confirming PD should be used as a new baseline. If two consecutive scans confirm PD, the patient should come off treatment. However, as long as subsequent scans show a response equal to or better than Stable Disease (SD), the patient may continue receiving treatment every 2 weeks, and must have scans every 8 weeks. Treatment may continue up to an additional 30% total single diameter increased over baseline. New measureable lesions are not permitted with this schema

#### **4.3 Concomitant Medications/Treatments**

##### **4.3.1 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. 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.

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 after 30 days after the last dose of trial treatment should be recorded for SAEs.

In general, corticosteroids (>10mg prednisone or equivalent) and other immunosuppressive medications are not permitted. However, 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 (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

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.

#### **4.3.2 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
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than nivolumab
- Radiation therapy
- Systemic corticosteroids (>10mg prednisone or equivalent) or other immunosuppressive medications are not permitted unless they fall under the criteria listed in 4.3.1.

#### **4.4 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 4.2.3 for guidance regarding treatment beyond progression),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) as already described in session.

#### **4.5 Duration of Follow Up**

All patients will be followed for adverse events for 12 weeks after last dose of nivolumab, 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 8 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 followed for survival status every 3 months for 2 years after treatment discontinuation or until death, whichever occurs first.

#### **4.6 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
- Patient demonstrates disease progression (per parameters above)
- 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)

**4.7 Patient Replacement**

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

## 5.0 STUDY PROCEDURES

	Screening <sup>1</sup>	On Treatment <sup>9</sup> (1 cycle = 28 days)						Off Treatment	
Time Period	Baseline	Cycle 1		Cycle 2		Cycle 3+		End of Treatment <sup>10</sup>	Follow-up <sup>11</sup>
		D1 (±3 days)	D15 (±3 days)	D1 (±3 days)	D15 (±3 days)	D1 (±3 days)	D15 (±3 days)		
<b>Assessment or Activity</b>									
Informed Consent	X								
Medical history	X							X	
Physical exam <sup>2</sup>	X	X	X	X		X		X	
ECOG status	X	X	X	X		X		X	
Adverse Events & ConMeds	X	X	X	X	X	X	X	X	
Toxicity assessment	X	X	X	X	X	X	X	X	
Tumor Assessments <sup>3</sup>	X					X <sup>3</sup>		X	
CBC with diff <sup>1</sup>	X	X	X	X	X	X	X	X	
Chemistry panel <sup>1</sup>	X	X	X	X	X	X	X	X	
TSH <sup>4</sup>	X								
Pregnancy test <sup>5</sup>	X	X <sup>5</sup>							
Nivolumab administration <sup>6</sup>		X	X	X	X	X	X		
Correlative blood samples		X <sup>7</sup>			X <sup>7</sup>				
Archival tissue collection <sup>8</sup>	X								
Survival status									X

<sup>1</sup> CBC with diff and Chemistry panel should be within 14 days of registration; all other screening procedures should take place within 28 days of registration. CBC should include WBC, Hemoglobin, Platelets, ANC, ALC. Chemistry panel should include glucose, calcium, albumin, ALT, AST, sodium, potassium, total bilirubin, alk phose, and creatinine.

<sup>2</sup> Includes vital signs (pulse, respirations, blood pressure) and height (baseline only) and weight.

<sup>3</sup> CT or MRI (per treating investigator's discretion) will take place within 28 days of registration; the same modality used at baseline should be used throughout. Tumor assessment will be performed at Cycle 3 Day 1 (- 7 days) and every 2 cycles (- 7 days) thereafter, regardless of dosing schedule for the first 13 months then every 3 cycles (-7 days) until progression or treatment discontinuation whichever occurs later. Tumor assessments will incorporate both RECIST and clinical criteria. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is required during screening in all eligible subjects with history of CNS involvement. If PD is confirmed at any time, see section 4.2.3 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.

- <sup>4</sup> If TSH is abnormal, free T4 should be tested
- <sup>5</sup> Serum or urine test for females of child-bearing potential must be completed at screening and within 24 hours of treatment.
- <sup>6</sup> Nivolumab will be administered IV at 240mg over 30 minutes every two weeks.
- <sup>7</sup> A correlative blood sample will be drawn pre-dose at C1D1 and C2D15. Please see separate lab manual for details.
- <sup>8</sup> Archival tissue will be collected at baseline if available. Please see separate lab manual for details.
- <sup>9</sup> Treatment will continue until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Study assessments may take place within 24 hours of scheduled treatment if needed.
- <sup>10</sup> End of Treatment visit will occur approximately 12 weeks after stopping nivolumab treatment, or until the patient starts new treatment, whichever occurs first.
- <sup>11</sup> Patients will be followed (either by routine clinic visit or by phone) every 2 weeks while on treatment and every 3 months for up to 2 years while off treatment to document survival and disease progression. Adverse events will be followed for the first 12 weeks after stopping treatment.

## 6.0 ENDPOINT ASSESSMENT

### 6.1 Definitions

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. 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).

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) [50]. 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 required during screening in all eligible subjects. 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.

Radiographic tumor assessments will be conducted at week 8 ( $\pm 1$  week) and every 8 weeks ( $\pm 1$  week) for the first 13 months and then every 12 weeks ( $\pm 1$  week) until disease progression or treatment discontinuation whichever occurs later. 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. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST.

### 6.2 Primary Endpoint

The primary endpoint of this study is overall response rate to treatment and all patients who received at least one dose of nivolumab will be considered for evaluation of response to therapy. For the purposes of this study, patients should be re-evaluated for response every 8 weeks. Overall response will be calculated by sum of the complete and partial response rates according to measurement of target and non-target lesions as described below.

#### 6.2.1 Definitions:

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

Evaluable for objective response. Only those patients who have measurable disease present at baseline, 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.

Evaluable non-target disease response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one dose of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

### **6.2.2 Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm ( $\geq 2$  cm) by chest x-ray or as  $\geq 10$  mm ( $\geq 1$  cm) with CT scan, MRI, or calipers by clinical exam. 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  $\geq 15$  mm ( $\geq 1.5$  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  $\geq 10$  to  $< 15$  mm [ $\geq 1$  to  $< 1.5$  cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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.

### **6.2.3 Response criteria**

#### **6.2.3.1 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.

#### **6.2.3.2 Evaluation of Non-Target Lesions**

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

#### **6.2.3.3 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 4.2.5)

#### **6.2.3.4 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 category when no lesions can be measured is not advised 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.

### **6.3 Secondary Endpoints**

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Progression assessment will be performed by investigator each time the patients has a radiologic evaluation after 8 weeks of treatment. OS is defined as the duration of time from start of treatment to time of death.

Safety and tolerability will be measured by the incidence of all adverse events, serious adverse events, deaths and laboratory abnormalities. Adverse event assessments and laboratory tests will be performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.

## **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 Appendices 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 Definition of Adverse Event**

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the BMS's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

BMS product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by BMS for human use.

Adverse events may occur during the course of the use of BMS product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 6.3.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

### **7.2 Severity of Adverse Events**

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3. The CTCAE v4.0.3 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.

### 7.3 Serious Adverse Events

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 12 weeks after the last administration of study drug, must be reported upon discovery or occurrence and within 2 working days to BMS Global Safety.

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 by 20% over the prescribed dose. No specific information is available on the treatment of overdose of nivolumab. 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“.

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.

#### **7.4 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.

#### **7.5 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 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 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. 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.

#### **7.6 Reporting Requirements for Adverse Events**

##### **7.7.1 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 Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP.

##### **7.7.2 Expedited Reporting to the NU QA/DMC**

All SAEs must be reported to the assigned QAM (as well as BMS – see section 7.7.4) within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form 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 DMC at their next meeting.

### 7.7.3 Expedited Reporting to the Northwestern IRB

- 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.

### 7.7.4 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 209-612). 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](mailto:Worldwide.Safety@BMS.com)

Facsimile Number: 609-818-3804

## 8.0 DRUG INFORMATION

### 8.1 Drug name: Nivolumab

#### 8.1.1 Other names for the drug(s):

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 (100mg/vial) is a sterile, non-pyrogenic single-use, isotonic aqueous solution formulated at 10mg/mL. 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 DP 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. If refrigerated, the vials and/or IV bags should

be allowed to equilibrate to room temperature prior to subsequent use. Nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours under refrigeration conditions (2°-8°) and used within 4 hours for up to 24 hours. Nivolumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of solution in vials, room temperature storage of prepared solution in the syringe and the duration of drug administration.

**8.1.5 Protocol dose:**  
240mg

**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

Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent. Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL [IBV13 Addendum Section 3.2.2] "Channel" or tube systems should not be used to transport prepared infusions of nivolumab.

**8.1.7 Route of administration for this study:**

Intravenous infusion. Do not administer as an IV push or bolus injection. Administer 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 Potential Drug Interactions:**

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.

**8.1.9 Availability:**

The supply for this study will be investigational – not commercially available. Supply will be provided by BMS free of charge. Nivolumab will be supplied as 100 mg/vial (10mg/mL) packaged in cartons of 5 or 10

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. The initial order should be limited to 20 vials. Contact and submission details can be found directly on the Drug Request Form. Deliveries will be made Tuesday through Friday.

#### **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 returned 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.

#### **8.1.13 Side effects**

Local bladder toxicities including but not limited to dysuria, urinary urgency, frequency and hematuria. Immune-related adverse events have been associated with Nivolumab is administered intravenously.

Below are safety data from 268 subjects with unresectable or metastatic melanoma and 117 patients with metastatic squamous NSCLC who received nivolumab alone. 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.

## **8.2 Safety 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 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 12 weeks 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 anal cancer, to enrollment will stop after 12 participants are treated with nivolumab if none of them have their tumors shrink. Study team conferences will be held monthly or more frequently if needed.

## **9.0 CORRELATIVES/SPECIAL STUDIES**

### **9.1 Tumor biopsy immunohistochemical (IHC) staining and analysis for PD-L1, PD-1, CD8+ and CD4+ tumor infiltrating lymphocytes**

Detection of the selected markers for this study will be performed using immunohistochemistry. After the staining, the slides will be digitally scanned in an Aperio AT system (Aperio™, Leica Biosystems™) to convert the IHC slides into digital pathology files for posterior analysis. IHC expression analyses of markers consider a thorough staining pattern evaluation including distribution (percentage of positive cells) and intensity in the form of H-score, and evaluating the IHC expression in the proper subcellular location (i.e. membrane, cytoplasm or nucleus). IHC analysis and scoring will be performed by a certified pathologist using an image analysis software (Image Toolbox, Aperio™).

Outcome from the analysis will be calculated according to the H-score. The H-score ranges from 0 to 300, and it considers both intensity of the IHC (from 0 to 3) and distribution (percentage of the target cells positive, from 0 to 100). The scoring is the addition of the percentages of cells with intensity 0 + intensity 2 + intensity 3, thus the addition of the final percentage is 100% and the scoring will range from 0 to 300. Hence, the H score will incorporate both percentage of positive cells and intensity of marker expression. Hematoxylin/eosin and PD-1, PD-L1 and PD-L2-stained sections will be reviewed by a pathologist. Criteria to be evaluated include histologic subtype and grade, TNM 2002 pathologic tumor stage, the presence and type of intratumoral lymphocytic infiltration, and the quantity and location of PD-L1 staining. The tumor will be considered positive for PD-1, PD- L1, PD-L2 if >5% of tumor cells had histologic evidence of plasma membrane staining.

### **9.2 Peripheral blood lymphocyte phenotypes**

Lymphocyte subsets (CD3, CD4, CD8, CD19, and CD56) will be analyzed at baseline and after 2 doses according to absolute cell numbers per microliter of whole blood, percent representation among all lymphocytes, and coexpression of the activation markers CD25, HLA-DR, and CD45RO using automated flow cytometric techniques at the Flow Cytometry Core Laboratory, Robert H Lurie Cancer Center of Northwestern University under the supervision of Suchitra Swaminathan, PhD.

### **9.3 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.

Dr. Devalingam Mahalingam 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**

A Simon two-stage optimum Phase II design will be used. Up to 33 patients will be entered into the trial. In the first stage, up to 12 patients will be entered to achieve 10 evaluable. If no patients show a response, then the trial will be terminated due to inactivity of the treatment. If 1 or more of 10 show a response, then up to an additional 22 patients will be added to achieve 19 evaluable. If 3 or fewer of 29 show a response, then the trial will conclude that the response rate could be as low as 5%. If 4 or more respond, then the trial will conclude that the response rate is greater than 5%. This design has a 20% chance of falsely concluding the rate is 5% (false negative Type II error rate = 20%, or power = 80%), and a 5% chance of falsely concluding that the rate is 20% (false positive Type I error rate = 5%). There is a 60% probability of early termination of the trial when the true response rate is 5%. Due to inevaluable patients and dropout, target accrual will be up to 33 patients. It is anticipated that 8 patients will be accrued per year so that accrual to this study will take 4 years.

### **10.2 Statistical Analysis**

Response rates and 95% confidence intervals will be calculated using exact binomial probability distributions. Progression-free survival and overall survival will be analyzed 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) they received. This definition parallels the definition of intention to treat in randomized clinical trials. For response rates, patients will be considered evaluable for response if they meet the criteria in the second paragraph of Section 6.2.1. Otherwise, they are unevaluable for response. The

ITT analysis of response will specify the number of patients unevaluable for response and will determine the response rate in those evaluable for response. For progression-free and overall survival, all registered patients will be included in the analysis, making this ITT. For patients who receive no nivolumab, survival times will be taken from the time of study registration. For toxicity, patients will be considered evaluable for toxicity if they meet the criteria in the first paragraph of Section 6.2.1. Otherwise, they are unevaluable for toxicity. The ITT analysis of toxicity will specify the number of patients unevaluable for toxicity and will perform the toxicity statistical analysis in those evaluable for toxicity.

## **11.0 STUDY MANAGEMENT**

### **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.

### **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](mailto: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 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 Appendices 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 Appendices 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).

#### **11.5 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.

##### **11.5.1 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.

##### **11.5.2 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 Promptly Reportable Non-Compliance (PRNC) 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.

#### **11.6 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.

#### **11.7 Publication Policy**

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. The assigned QAM will prepare a preliminary data summary (to be approved by the DMC) 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 DMC-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 DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-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 – Contraception Requirements

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. 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 WOCBP subject or male subject's WOCBP 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 WOCBP subject or male subject's WOCBP partner
- f) Female Condom\*

\*A male and female condom must not be used together

Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this sections.

**Appendix C**

**ECOG Performance Status**

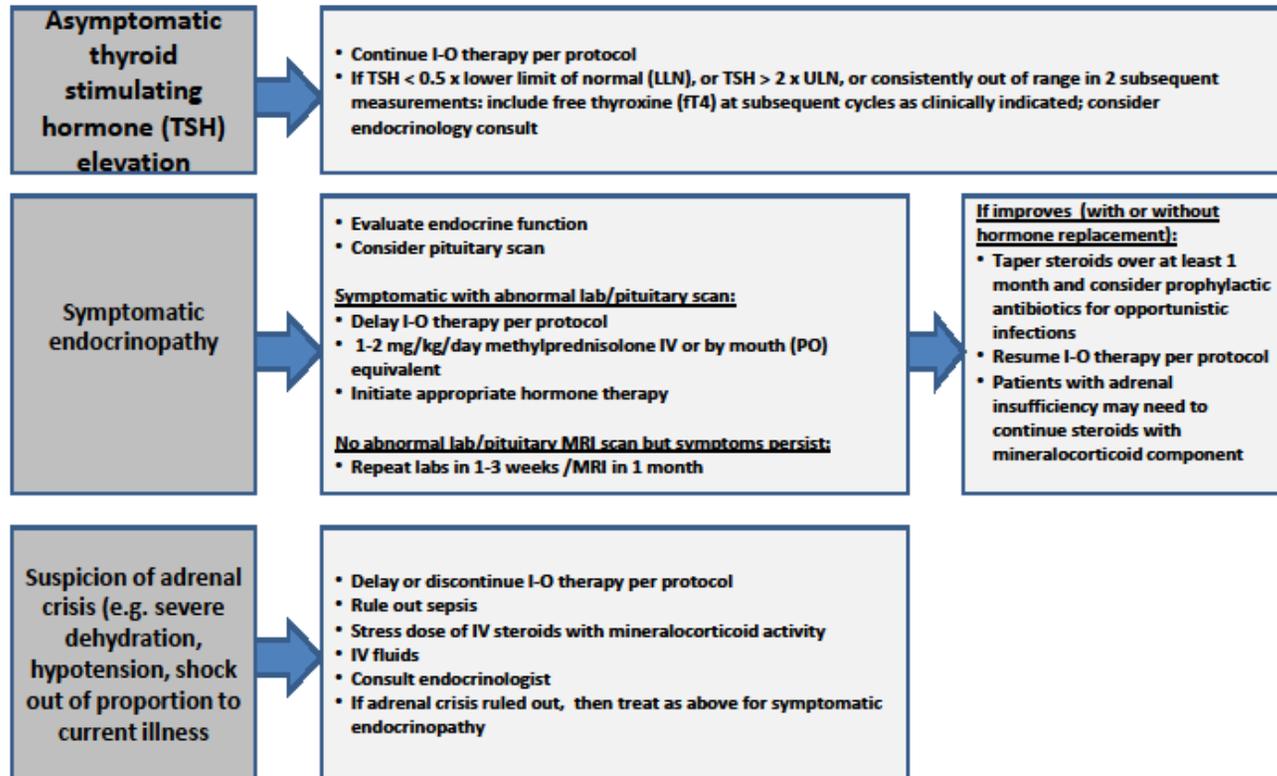
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
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.
<p>* As published in Am. J. Clin. Oncol.: <i>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.</i> The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.</p>	

## Appendix D – Adverse Events Algorithm

Recommended management algorithms for suspected nivolumab related endocrinopathy, gastrointestinal toxicity, hepatotoxicity, neurologic toxicity, pulmonary toxicity, renal toxicity and skin toxicity

### Endocrinopathy Management Algorithm

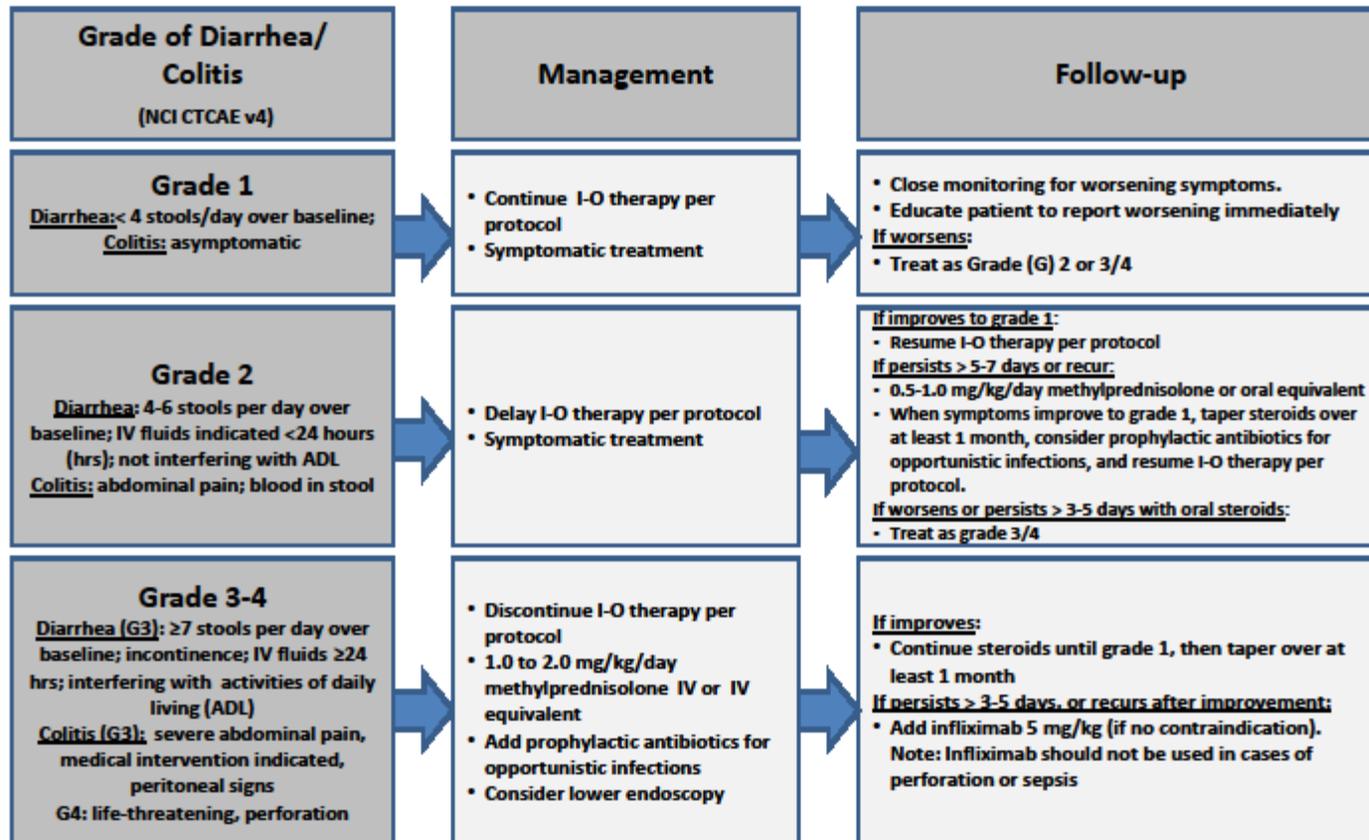
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

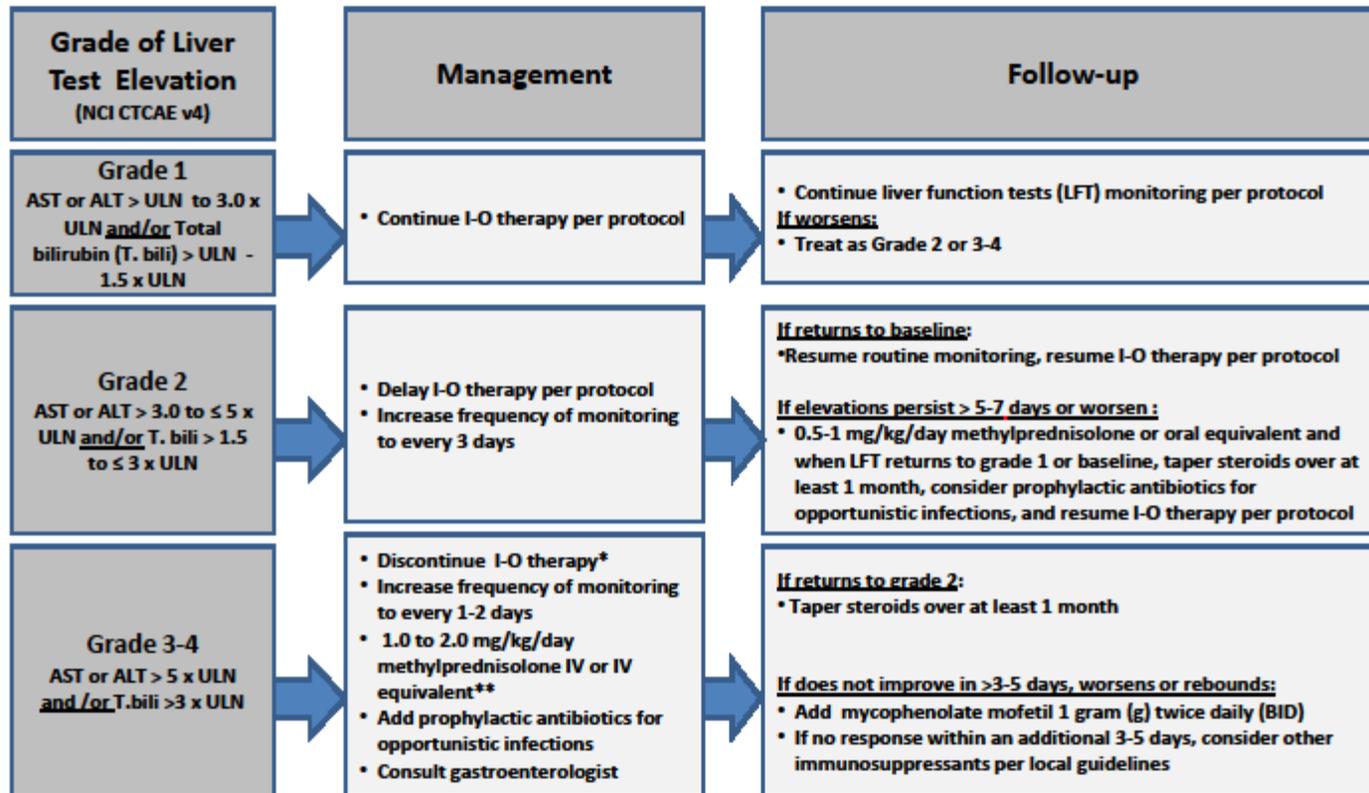
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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 and T.bili ≤ 5 x ULN.

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

e

**Appendix E Protocol History of Changes by Amendment**

<b>Original Version Approved by the Northwestern University IRB – 2/4/2016</b>			
<b>Updated Version Approved by the Northwestern University IRB –</b>			
<b>Amendment 1 – March 16, 2016</b>			
<i>Approved by Scientific Review Committee – 3-17-2016</i>			
<b>Section(s) Affected</b>	<b>Prior Version</b>	<b>Amendment 1 Changes</b>	<b>Rationale</b>
Header	n/a	Adds BMS Study Number (CA 209-612)	Administrative – study number now available
3.1.2 (Inclusion Criteria)	An exception to patients having received one line of therapy read: “Patients declining first line treatment...based on limited efficacy are also eligible for this study”	Now reads: “Patients who are deemed ineligible to receive first line treatment... or who decline first line treatment may be eligible for this study after discussion with the PI.”	PI decision to expand eligibility. PI thinks it is reasonable to include patients who are ineligible as well as those who decline
3.1.8 (Inclusion Criteria), 5.0 (Study Procedures)	FOCBP must have a negative pregnancy test within 72 hours of drug	FOCBP must have a negative pregnancy test within 24 hours of drug	New language provided by sponsor
3.1.9 (Inclusion Criteria), Appendix B	Listed contraception requirements separately for men and women, including specifics on contraception methods and timing	<ul style="list-style-type: none"> <li>Adds Appendix B with specific contraception language from BMS.</li> <li>Combines two inclusion criteria (3.1.9 and 3.1.10) into one, referencing contraception for both men and women with specific instructions listed in Appendix B</li> </ul>	<ul style="list-style-type: none"> <li>Additional language provided by sponsor</li> <li>Simplifies inclusion criteria</li> </ul>
3.2.7 (Exclusion Criteria)	Incomplete sentence	Rewords to make complete phrase	Grammatical clarification
4.2.1 (Treatment Discontinuation Criteria)	Referred to sponsor Medical Monitor for non-drug related dose delays >6 weeks	Removes Medical Monitor references and replaces with PI & DMC	Administrative – PI and DMC will serve as “medical monitor” for NU IIT
5.0 (Study Procedures)	#1: n/a #5: Pregnancy test only required at screening	#1: Adds specific labs required for CBC and Chem panel #5: Pregnancy test required within 24 hours of study drug	#1: Clarification #5: Sponsor requirement
6.1 (Definitions)	Non-descript symbol included inadvertently	Replaces non-descript symbol with ± symbol	Administrative
7.3 (Serious Adverse Events)	SAE’s to be collected through 30 days after last study drug	Changes to SAE’s being collected 12 weeks after last study drug	Clarification to align with procedures table
7.7.4 (Reporting to the FDA)	Includes a section on FDA Reporting	Removes FDA Reporting instructions	FDA reporting is not required since the study is IND-exempt
8.2 (Safety)	Patients were to be followed for	Patients will be followed for side	Clarification to

Monitoring Plan)	side effects for 100 days	effects for 12 weeks	align with Study Procedures Table
9.1 (Correlative Studies)	IHC was to be analyzed using Dako kits provided by BMS	IHC is now being analyzed at NU PCF-CTU using a different assay methodology. Language referring to Dako kits and analysis at MD Anderson has been removed	Dako kits were not available, and a different analysis method will be utilized.
<b>Amendment 2 – July 5, 2016</b> <i>Approved by Scientific Review Committee – 7-27-2016</i>			
Cover Page	Listed Benedito Carneiro under the Northwestern Medicine Developmental Therapeutics Institute	<ul style="list-style-type: none"> <li>• Changes to Northwestern University, Developmental Therapeutics Program of the Division of Hematology Oncology</li> <li>• Removes Timothy Kuzel as sub-investigator</li> </ul>	Administrative
Cover Page; 3.0 (Eligibility Criteria)	Study listed as a single-center trial	<ul style="list-style-type: none"> <li>• Adds the following sub-sites:                             <ul style="list-style-type: none"> <li>-Ohio State University</li> <li>-Moffitt Cancer Center</li> <li>-Johns Hopkins University</li> </ul> </li> <li>• Removes specific locations at Northwestern where research will take place</li> </ul>	Administrative – sub-sites have been confirmed and specific treatment locations at Northwestern are not needed.
3.1.6 (Inclusion Criteria)	<ul style="list-style-type: none"> <li>• Platelets were required to be 100,000/mcL</li> <li>• Hemoglobin was required to be 9 g/dL</li> <li>• Requirement for AST(SGOT) / ALT (SGPT) was <math>\leq 2.5 \times \text{ULN}</math></li> </ul>	<ul style="list-style-type: none"> <li>• Platelets must now be 75,000/mcL</li> <li>• Hemoglobin must now be 8 g/dL</li> <li>• Increases AST(SGOT)/ALT(SGPT) requirement to <math>\leq 3 \times \text{ULN}</math>. Also notes that if liver metastases are present, <math>\text{AST/ALT} \leq 5 \times \text{ULN}</math> is permitted</li> </ul>	PI determined that the new eligibility values will allow for easier accrual and are clinically appropriate.
3.2.8 (Exclusion Criteria)	Patients cannot have “Hypertension that is not controlled on medication(Note: Hypertension is defined as blood pressure $\geq 140/90$ )”	Changes exclusion to “Uncontrolled hypertension – blood pressure $\geq 150/90$ mmHg despite medical therapy”	Clarification; PI does not feel that a cut-off of 140/90 for blood pressure is appropriate
4.2 (Dosing delays, support care, and discontinuation of therapy); Appendix D	n/a	Adds specific algorithms, and a reference to such algorithms, for AE’s related to Immuno-Oncology agents: Gastrointestinal <ul style="list-style-type: none"> <li>• Renal</li> <li>• Pulmonary</li> <li>• Hepatic</li> <li>• Endocrinopathy</li> <li>• Skin</li> <li>• Neurological</li> </ul>	BMS provided algorithms to align with most current guidelines for Immuno-Oncology agents, including nivolumab
4.2.1 (Treatment Discontinuation)	Included statement: “Tumor assessments for all subjects should continue as per	Removes statement	Patients do not need to have scans after the

	protocol even if dosing is discontinued.”		“treatment discontinuation”
4.3 (Concomitant Medications/ Treatments)	n/a	<ul style="list-style-type: none"> <li>Splits section into “4.3.1 Permitted Medications” and “4.3.2 Prohibited Medications”</li> <li>Adds more specific language about permitted corticosteroids. In general, corticosteroids &gt;10mg prednisone are not permitted unless they meet specific criteria</li> </ul>	Clarifications
5.0 (Study Procedures Table)	<ul style="list-style-type: none"> <li>Listed visits by weeks (“every 2 weeks” and a column for scans “every 8 weeks”) with a <math>\pm</math> 2 day window for visits and <math>\pm</math> 7 days for scans</li> <li>Unclear if physical exam should take place at every treatment visit</li> <li>#7: “A correlative blood sample will be drawn at baseline and after 2 doses of nivolumab”</li> <li>#9: n/a</li> </ul>	<ul style="list-style-type: none"> <li>Changes visits to cycles where 1 cycle = 28 days, and visits have a <math>\pm</math> 3 day window. Scans take place every 2 cycles (rather than 8 weeks) for consistency, and the window has been changed to -7 days</li> <li>Physical exam is only required at Day 1 of each cycle</li> <li>#7: “A correlative blood sample will be drawn <b>pre-dose at C1D1 and C2D15</b>”</li> <li>#9: Study procedures can take place within 24 hours of planned study treatment</li> </ul>	<ul style="list-style-type: none"> <li>Clarification to simplify table; longer visit window accounts more inclusively for unexpected dose delays. +7-day scan window has been removed so that scans take place before dosing</li> <li>Clarification #7: Clarification</li> <li>#9: To allow flexibility if a patient comes from out of town</li> </ul>
7.7.2 (Expedited Reporting to the NU QAM/DMC; 7.7.4 (Reporting to BMS)	<ul style="list-style-type: none"> <li>7.7.4 stated “SAE reports will be reported within 24 hours to BMS Global Safety (using the NU CRO SAE Form)”</li> <li>Email was listed incorrectly: <a href="mailto:woldrwidesafety@BMS.com">woldrwidesafety@BMS.com</a>;</li> </ul>	<ul style="list-style-type: none"> <li>Added language: “<b>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 209-612).</b>”</li> <li>7.7.2 references BMS reporting instructions in 7.7.4</li> <li>Corrects email typo: <a href="mailto:worldwidesafety@BMS.com">worldwidesafety@BMS.com</a></li> </ul>	<ul style="list-style-type: none"> <li>Clarification for SAE reporting to avoid oversight or deviations</li> <li>Administrative update with correct email</li> </ul>
10.1 (Study Design / Study Endpoints)	Statistical conclusion stated that “If 4 or more respond then the trial will conclude that the response rate is at least 20%.”	Changes conclusion to: “If 4 or more response then the trial will conclude that the response rate is greater than 5%”	Correction for statistical accuracy
10.2 (Statistical Analysis)	n/a	Adds information on evaluable patients and the intention to treat (ITT) plan	Statistical clarifications for accuracy
11.7	n/a	Adds language relating to the	To align with

(Publication Policy)		BMS agreement for publications with NU	contract language
<b>Amendment 3 – July 31, 2017</b>			
Cover Page	<ul style="list-style-type: none"> <li>• Listed Benedito Carneiro as the PI</li> <li>• Listed Manisha Shah as the participating site PI at Ohio State University</li> </ul>	<ul style="list-style-type: none"> <li>• Changed to Devalingam Mahalingam as the PI</li> <li>• Removed Sub-Is - Ricardo Costa, Sachin Pai, Cord Sturgeon, Dina Elaraj, Anthony Yang, Peter Kopp</li> <li>• Added Sub-I - Maha Hussain</li> <li>• Changed Ohio State University participating PI to Bhavana Khondra</li> </ul>	Administrative