THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

Window-of-opportunity trial of Nivolumab and BMS986205 in patients with squamous cell carcinoma of the head and neck (CA017-087)

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Table of Contents

Statement of Compliance 11

List of Abbreviations 12

Study Summary 14

1 Introduction 19

1.1 Background Information 19

1.2 Rationale for the Proposed Study 21

1.3 Correlative Studies 22

1.4 Potential Risks and Benefits 23

1.4.1 Potential Risks 23

1.4.2 Benefits 26

2 Study Objectives 27

2.1 Objectives 27

2.1.1 Primary 27

2.1.2 Secondary 27

2.1.3 Exploratory 27

2.2 Endpoints/Outcome Measures 27

2.2.1 Primary 27

2.2.2 Secondary 28

2.2.3 Exploratory 29

3 Study Design 29

3.1 Characteristics 29

3.2 Number of Participants 29

3.3 Duration of Therapy 29

3.4 Duration of Follow Up from last dose 30

3.5 Treatment Assignment Procedures 30

3.5.1 Randomization Procedures 30

3.6 Study Timeline 30
3.6.1 Primary Completion 30
3.6.2 Study Completion 30
4 Study Enrollment and Withdrawal 30
4.1 Eligibility Criteria 30
4.1.1 Inclusion Criteria 30
4.1.2 Exclusion Criteria 31
4.2 Gender/Minority/Pediatric Inclusion for Research 32
4.3 Strategies for Recruitment and Retention 32
4.4 Sub-Site Enrollment Procedures 33
4.5 Participant Withdrawal 33
4.5.1 Reasons for Withdrawal 33
4.5.2 Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention 33
4.6 Premature Termination or Suspension of Study 34
5 Study Intervention 34
5.1 Study Products 34
5.2 Study Product Descriptions 34
5.2.1 Acquisition 34
5.2.2 Formulation, Packaging, and Labeling 34
5.2.3 Product Storage and Stability 36
5.3 Dosage, Preparation, and Administration 36
5.4 Dose Modifications and Dosing Delays 38
5.4.1 BMS-986205 and Nivolumab Dose Modifications 38
5.4.2 Dose Delays for BMS986205 and Nivolumab 38
5.4.3 BMS-986205 and Nivolumab Dose Discontinuation 39
5.4.4 Discontinuation of BMS-986205 Alone 40

5.4.5 Criteria to Resume Treatment (BMS-986205 and Nivolumab) 40
5.5 Required Contraceptive Elements 41
5.6 Study Product Accountability 42
5.7 Assessing Participant Compliance with Study Product Administration 42
5.8 Concomitant Medications/Treatments 42
5.8.1 Prohibited and/or Restricted Treatments 43
5.9 Dietary Restrictions 45
5.10 Determination of Response 45
6 Study Schedule 46
6.1 Enrollment/Baseline Visit 1, Day 0 46
6.2 Treatment Period 47
6.3 Post-treatment/Follow-Up 49
6.4 Withdrawal Visit/Discontinuation of Therapy 51
7 Study Procedures and Evaluations 51
7.1 Laboratory Procedures/Evaluations 52
7.1.1 Clinical Laboratory Evaluations 52
7.1.2 Special Assays or Procedures 52
8 Evaluation of Safety 52
8.1 Specification of Safety Parameters 52
8.1.1 Unanticipated Problems 52
8.1.2 Adverse Events 52
8.1.3 Serious Adverse Events 53
8.2 Safety Assessment and Follow-Up 53
8.3 Recording Adverse Events 53
8.3.1 Relationship to Study Intervention 53
8.3.2 Expectedness 54

8.3.3 Severity of Event 54
8.3.4 Intervention 54
8.4 Safety Reporting 54
8.4.1 Reporting to IRB 54
8.4.2 Laboratory Test Result Abnormalities 56
8.4.3 Reporting to SKCC DSMC 56
8.4.4 Reporting to Funding Sponsor 57
8.4.5 Reporting to FDA 58
8.4.6 Reporting of Pregnancy 59
8.4.7 Overdose 59
8.4.8 Potential Drug Induced Liver Injury (DILI) 59
8.5 Halting Rules 60
9 Study Oversight 60
10 Clinical Site Monitoring and Auditing 60
11 Statistical Considerations 60
11.1 Analysis Plans 60
11.2 Interim Analyses and Stopping Rules –..... 62
11.3 Sample Size Considerations 62
12 Source Documents and Access to Source Data/Documents 63
13 Quality Control and Quality Assurance 64
14 Ethics/Protection of Human Participants 64
14.1 Ethical Standard 64
14.2 Institutional Review Board 64
14.3 Informed Consent Process 64
14.4 Exclusion of Women, Minorities, and Children (Special Populations) 64
14.5 Participant Confidentiality 64

14.6 Future Use of Stored Specimens and Other Identifiable Data 65
15 Data Handling and Record Keeping 65
15.1 Data Management Responsibilities 65
15.2 Data Capture Methods 65
15.3 Types of Data 65
15.4 Study Records Retention 65
15.5 Protocol Deviations 65
16 Study Finances 66
16.1 Funding Source 66
16.2 Conflict of Interest 66
16.3 Participant Stipends or Payments 66
17 Publication and Data Sharing Policy 66
18 Literature References 67
Appendices 68
APPENDIX A: SCHEDULE OF EVENTS 69
APPENDIX B: ECOG Performance Status: 73
APPENDIX C: Management Algorithms: 74
APPENDIX D: WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION 82
APPENDIX E: Management Algorithms IDO Inhibitor 85
APPENDIX F: Medications associated with qt prologation 87
APPENDIX G: CYP3A4, CYP1A2 AND CYP2B6 GUIDANCE 88
APPENDIX H: P-gp and BCRP Guidance 91
APPENDIX I: AGENTS KNOWN TO CAUSE METHEMOGLOBINEMIA 92
APPENDIX J: BMS-986205 and Nivolumab Dose Delay Criteria 93
APPENDIX K: Sub-Site Unanticipated Problem Form 94
APPENDIX L: Sub-Site Serious Adverse Form 97

APPENDIX M..... 99

APPENDIX N: 100

BMS-986205 DIAGNOSTIC CRITERIA FOR HLH AND DRESS SYNDROME 100

Signature Page

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

Principal Investigator:

Signed: _____ Date: _____

Name:

Title:

Statement of Compliance

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

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
cGMP	Cyclic guanosine monophosphate
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
CTOC	Clinical Trials Oversight Committee
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
HNSCC	Head and Neck Squamous Cell Carcinoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDOI	Indoleamine 2,3-dioxygenase Inhibitor
IND	Investigational New Drug Application
IRB	Institutional Review Board
MDSC	Myeloid Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCI	National Cancer Institute
NIH	National Institutes of Health
NO	Nitric oxide (NO)
NR	Non-Responder
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cells

PDE5	Phosphodiesterase – 5
PDL-1	Programed Death Ligand 1
PHI	Protected Health Information
PI	Principal Investigator
PRC	Protocol Review Committee
QA	Quality Assurance
QC	Quality Control
R	Responder
SAE	Serious Adverse Event/Serious Adverse Experience
SDS	Safety Data Sheet (formerly MSDS; Material Safety Data Sheet)
SKCC	Sidney Kimmel Cancer Center
SOP	Standard Operating Procedure
TAM	Tumor Associated Macrophage
TME	Tumor Microenvironment
TJU	Thomas Jefferson University
TV	Tumor Volume
UAP	Unanticipated Problem
WOCBP	Women of Childbearing Potential

Study Summary

Title: Window-of-opportunity trial of Nivolumab and BMS-986205 in patients with squamous cell carcinoma of the head and neck (HNSCC)

Précis: A randomized (3:1) prospective study in patients with resectable squamous cell carcinoma using Nivolumab+BMS-986205 (with one week lead in) or Nivolumab alone for 4 weeks with progressors going for surgery and partial responders continuing therapy for additional 4 weeks followed by surgical resection. Tumor and blood will be collected pre-, during and post-treatment with analysis of immune cell composition, exosomes and cytokines as secondary endpoints. Post-treatment imaging, pathologic features and safety will be primary endpoints.

Objectives: Our hypothesis states that the combination of the PD-1 directed agent Nivolumab with the IDO1 inhibitor BMS-986205 administered in patients with HNSCC will have a combinatorial effect on the immune and metabolic microenvironment of the tumor enabling improved, durable responses to this combination immunotherapy.

Primary:
To assess the impact of BMS986205 and Nivolumab versus Nivolumab alone on tumor radiographic response both at the primary tumor site and in regional lymph nodes by investigator assessment at 5 weeks. Responders will go on for additional Nivolumab ± BMS 986205. Specifically, we will:

Primary Outcome:

- Analyze objective response at 5 weeks leading to a continuation of treatment. This will be assessed by radiographic criteria as defined in the protocol. Nivolumab± BMS 986205

Secondary Outcomes:

- Objective pathologic response at time of surgery
- We will compare immune cell polarization (Th1/Th2; M1/M2) in peripheral blood and tumor specimens using multiplex cytokine analysis collected before and after exposure to Nivolumab ± BMS986205.
- We will use IHC to determine the prevalence of intratumoral immune cell populations (Teff, Treg, and TAM in patients treated with Nivolumab and BMS986205 as compared to patients treated with Nivolumab alone.

- Intratumoral TCR repertoire and diversity by Next Gen sequencing. Baseline T cell repertoire may be predictive of PD-1 and IDO1 inhibition
- Kynurenine levels (blood and tumor)
- Exosome composition in the peripheral blood of patients both before and after exposure to both Nivolumab and BMS986205 and Nivolumab alone
- Exosome function as it relates to MDSC polarization in the peripheral blood both before and after treatment
- Determine effects of HPV status on intratumoral immune cell populations exosome composition and function before and after treatment
- Determine correlation of intratumoral PD-L1 expression (IHC) with intratumoral immune cell populations and exosome composition/function
- Examine potential intratumoral immune cell populations and exosome composition/function as they relate to severity of drug-related side effects in both patients treated with both Nivolumab and BMS986205 and Nivolumab alone using CTCAE v5.0
- We will review the safety of Nivolumab alone with and without BMS986205 in head and neck cancer patients
- We will review wound healing in the post-operative setting as a function of complication rate.
- Patient reported outcomes will be collected and correlated to both immune cell composition and polarization and tumor radiographic response using scores from PHQ2, PHQ9, FACT-G, and FACT-HN.

Population: Male or female, aged ≥18 years, ECOG performance status of 0-2. Any stage 2 or greater HNSCC (AJCC 8th edition) of the 1) oral cavity, 2) larynx, 3) hypopharynx, 4) nasal cavity/paranasal sinuses or 5) stage 1 oropharyngeal with lymphadenopathy. Only patients with technically resectable disease who can undergo surgery are eligible.

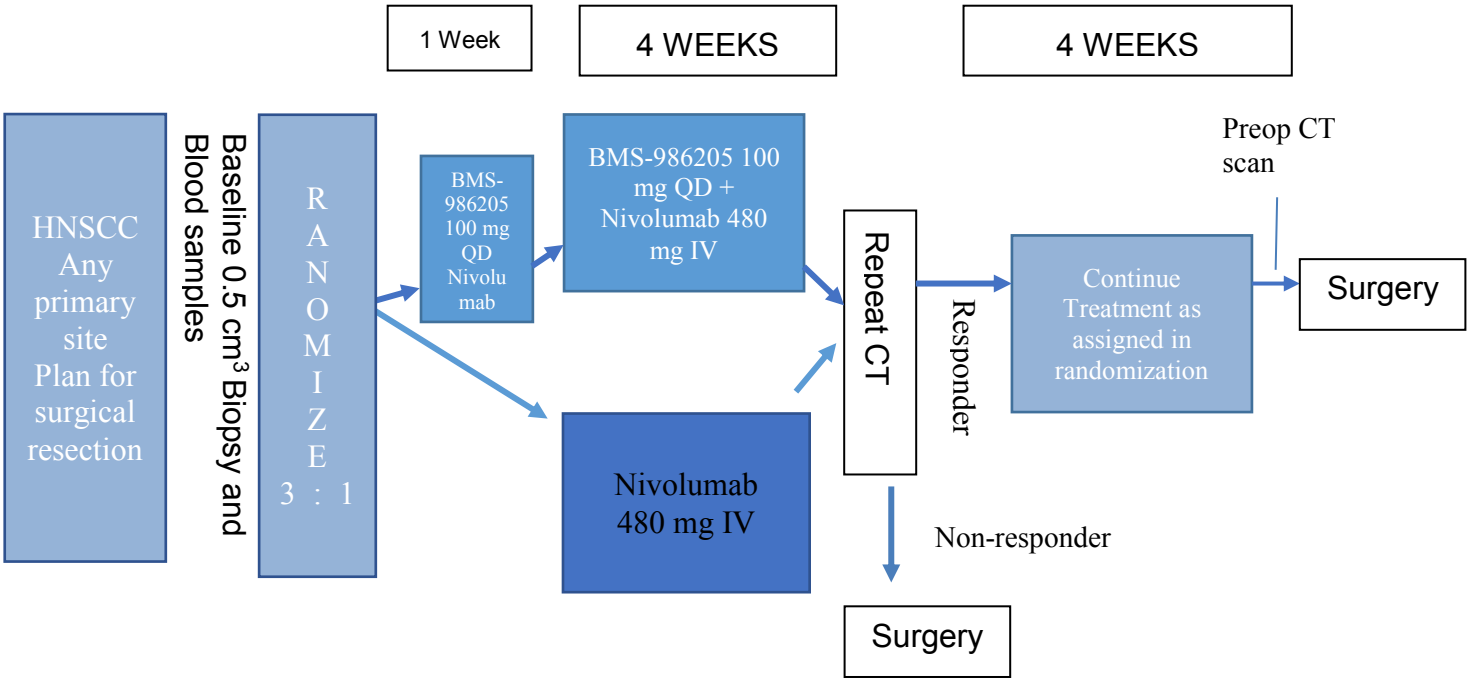
Phase: Pilot

Number of Sites: 2: Thomas Jefferson University as lead site.

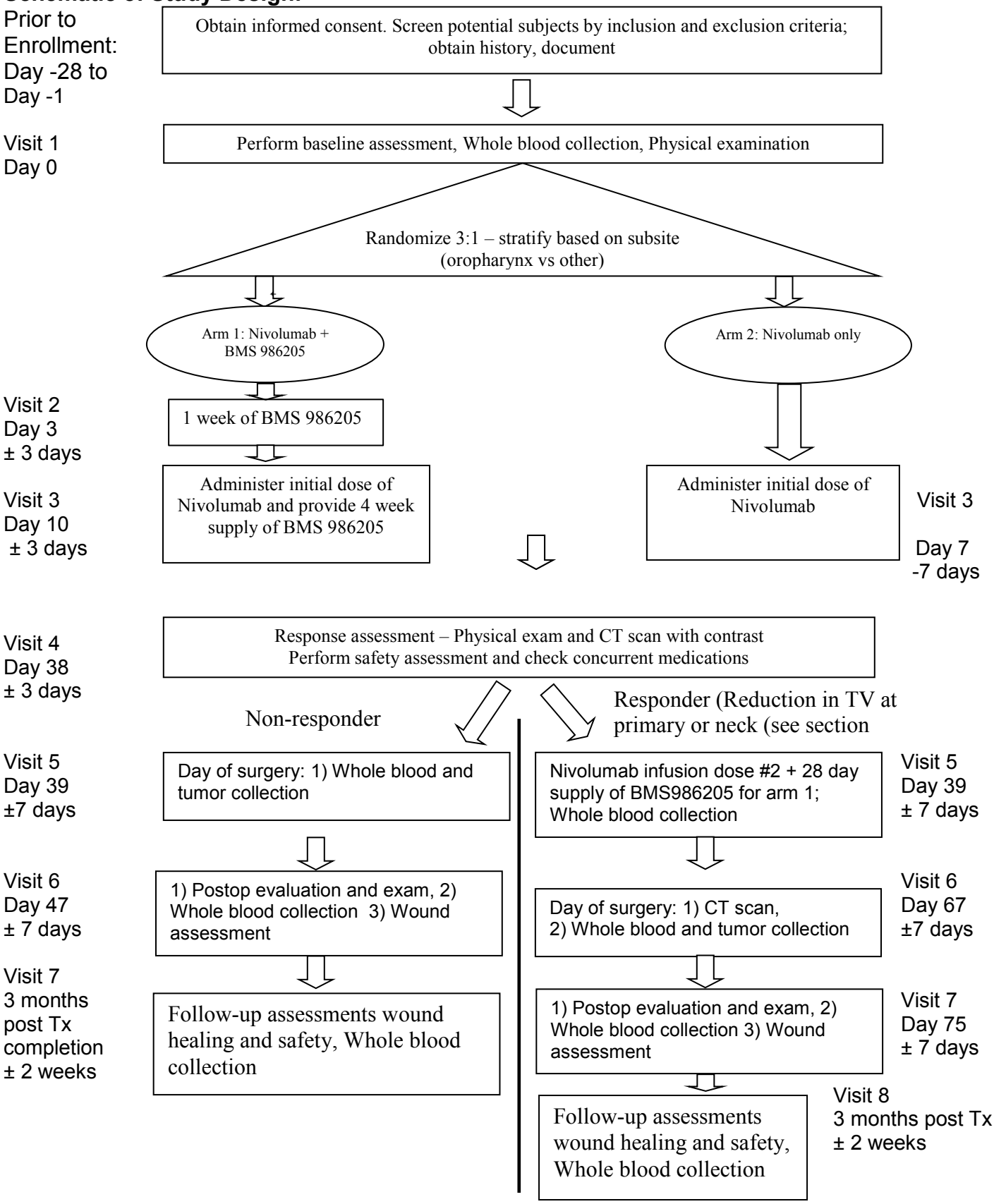
Description of Intervention: Patients will be randomized 3:1 to receive either BMS-986205 100 mg PO per day x 28 days with a single dose of Nivolumab 480 mg IV or a single dose of Nivolumab 480 mg IV alone.

	All patients will be evaluated by the investigator at 5 weeks and categorized as: a) non-responders, who will then undergo definitive surgical resection by week 6 or b) responders who will continue for an additional 4 weeks of their randomized therapy followed by definitive surgery.
Study Duration:	40 months
Participant Participation Duration:	Patients will receive up to a total of 5 or 9 weeks of therapy followed by surgical resection at week 6 or 10, followed by 12 months of follow up (14 months).
Estimated Time to Complete Enrollment:	26 months

Schematic of Study Design:



Schematic of Study Design:



1 Introduction

1.1 Background Information

Head and Neck Squamous Cell Carcinoma

Over 58,000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed yearly leading to more than 1300 deaths each year in the United States (American Cancer Society (ACS) cancer statistics 2016). Oropharyngeal cancer remains one of the few cancers that is on the rise in our population with an exceptional rate of increase per year[1]. The prognosis of head and neck cancer is highly variable based on sub-site location and stage with an overall survival of 63% whereas advanced stage disease has survival rates of 38-62% (ACS cancer statistics 2016). Earlier stage cancers are often treated with either surgery or radiation, while advanced stages typically require multimodality therapy including concurrent chemoradiotherapy as definitive treatment and surgery followed by adjuvant radiation or chemoradiotherapy.

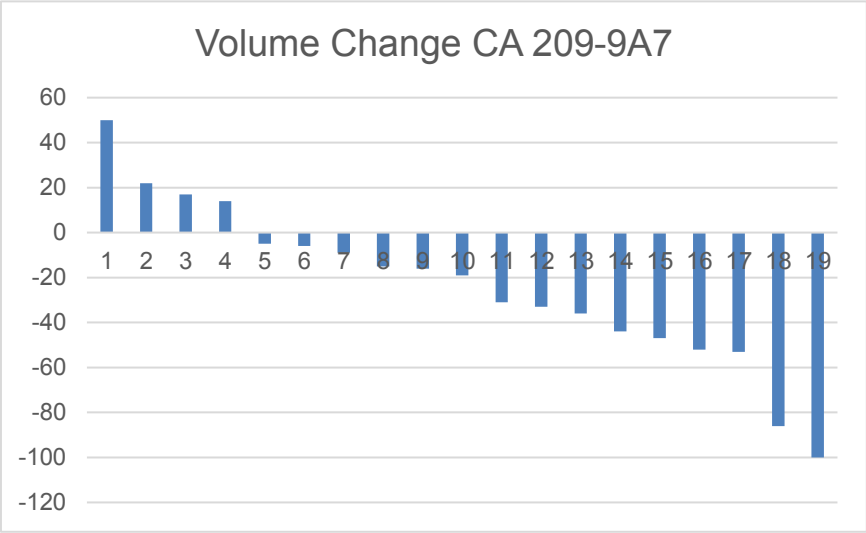
Over the past decades improvements in surgical and radiation techniques have markedly contributed to the improved overall survival of patients with HNSCC. Chemotherapeutic options, however, has seen little progress. Currently, the cornerstone of chemotherapy remains platinum-based treatment which is associated with significant risk of adverse events (ototoxicity, nephrotoxicity, and myelosuppression). Treatment algorithms and multimodality therapy frequently focus on the potential for personalized medicine and de-escalation of treatment, hoping to preserve efficacy while sparing patients from both acute and long-term toxicities by understanding the biology of the patient's tumor.
Novel approaches and agents are needed to improve the cure rates in advanced disease and reduce treatment toxicity of HNSCC. A major recent advancement in the field has come from the new class of novel immunotherapeutic agents including the PD-1 inhibitor Nivolumab.

Nivolumab

Immunotherapy with checkpoint inhibitors has demonstrated clinical efficacy in several solid tumors types, including melanoma, renal cell carcinoma and non-small cell lung cancer. Early success was achieved with the CTLA4 antagonist ipilimumab in the treatment of advanced melanoma[2]. Now, there are 6 different checkpoint inhibitors approved by the FDA targeting either CTLA4 (ipilimumab) or PD1/PD-L1 interactions (Nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab) with 11 different indications. Immunotherapy has become a promising treatment option for recurrent head and neck squamous cell carcinomas. The CheckMate-141 phase III clinical trial was the first randomized trial to show improved overall survival for platinum-refractory recurrent or metastatic HNSCC patients using Nivolumab compared to single-agent chemotherapy of the investigator's choice[3]. Usually these patients with recurrent HNSCCs, who are unresponsive to platinum-based chemotherapy, have a poor prognosis and average survival of less than 6 months. After failing platinum-based therapy for recurrent HNSCC within 6 months, patients were randomized 2:1 to receive Nivolumab (a PD-1 inhibitor) or a single-agent chemotherapeutic or biological agent of the investigator's choice, which included methotrexate, docetaxel, or cetuximab. At interim analysis, there was already a 30% reduction in risk of death with Nivolumab versus standard therapy. Regardless of PD-L1 status or HPV (p16) status, median overall survival was 7.5 months for the Nivolumab cohort versus 5.1 months for the investigator's choice of therapy. Further, HPV+ patients and patients with PD-L1 ≥1% had an even greater benefit and significantly longer overall survival with Nivolumab. These patients also experienced an improvement in their quality of life using multiple measures.
The impressive results of T cell-directed immunotherapies are contrasted by the fact that only a subset of patients (response rates of approximately 20%) enjoys long-lasting remissions after single modality immune checkpoint therapy. This circumstance has reinvigorated interest in understanding how systemic and local factors may interfere with the function of T cells and other effector immune cells critical to tumor control. It is now widely accepted that immunosuppressive cells and factors in the tumor microenvironment (TME) contribute to suboptimal responses to immune checkpoint therapeutics. Thus, there is interest in testing combinatorial approaches to "boost" the responses seen with Nivolumab monotherapy. A better

understanding of how to predict responders verses non-responders and identification of novel drug combinations to increase this response rate will provide the key to personalizing cancer immunotherapy and extending its benefits to a maximum number of patients.

Efforts are ongoing to capitalize on the remarkable findings in the first line recurrent / metastatic, and locally advanced settings. This work is focused on the treatment naïve patient. One example of a method to both elucidate the biology of an immune response and test the efficacy of novel therapeutic combinations is our current window of opportunity trial utilizing Nivolumab ± tadalafil. NCT03238365 (CA 209-9A7) has accrued 25/50 patients that are naive to treatment including all stages of disease. In this trial subjects receive 2 doses of Nivolumab during a 4-week window between enrollment and surgery and are randomized to also receive the PDE5 inhibitor tadalafil. Interim analysis demonstrates 8 non-responders, 10 partial responders, and 1 patient with complete response. Ferris et al. recently presented at the European Society of Medical Oncology results of a similar 4-week window trial utilizing Nivolumab alone in HNSCC and reported good safety with nearly 40% of subjects demonstrating reduction in tumor volume at time of surgery (LBA46, Madrid Spain, 2017). Both our unpublished findings and Ferris's presentation support roughly 50% ± 10% meeting criteria as outlined below to go on to receive additional therapy as outlined in this trial. Thus, immunotherapy prior to planned surgical resection has a reasonable rate of response and provides a mechanism by which large amounts of correlative information can be obtained on both, monotherapy and novel drug combinations.



Indoleamine 2,3-dioxygenase (IDO1) Function

Please refer to the Investigator's Brochure for detailed background information on BMS986205. The following is summary of that background.

IDO1 catalyzes the degradation of tryptophan to N-formyl-kynurenine, which is the first and rate limiting step leading to the production of kynurenine and downstream metabolites. The activity of IDO1 causes immune tolerance by inhibiting T-cell function through local depletion of the essential amino acid tryptophan and through generation of inhibitory kynurenine pathway metabolites. In healthy humans, IDO1 is expressed in the placenta, the mucosa of the female genital tract, the lungs, and the lymphoid organs. IDO1 expression in the placenta is believed to play a role in maternal tolerance to allogeneic fetuses. However, functional roles of IDO1 in the lungs and female genital tract are not as clear, but may be related to combating infections or induction of in immune tolerance. In the immune system, IDO1 is expressed in dendritic cells and macrophages. IDO1 is strongly induced by pro-inflammatory mediators such as IFN-γ and endotoxins during the late phase of inflammatory reactions, in which its immunosuppressive role contributes to the physiologic feedback control of the immune response.

IDO1 is also highly expressed in several types of human malignancies. High levels or frequencies of IDO1 expression are detected in multiple tumor types. IDO1 expression in tumors is believed to induce immune tolerance as evident by a decrease in tumor infiltration of immune cells and an increase in the proportion of regulatory T-cells (Treg) in tumor infiltrating lymphocytic populations. Increased IDO1 is also correlated with diverse tumor progression parameters and shorter patient-survival times in diverse cancer indications. IDO1

has been shown to be significantly up-regulated together with the programmed death receptor ligand 1 (PD-L1). The enzyme is also reported to provide a critical resistance mechanism in anti-tumor T-cell immunotherapy targeting CTLA 4. Furthermore, tumor IDO1 mRNA expression is increased in patients with advanced melanoma and metastatic renal cell carcinoma after treatment with the anti-PD-1 antibody Nivolumab. These findings suggest that IDO1 is an important regulator of the immunosuppressive mechanisms responsible for tumor escape from host immune surveillance. Inhibition of IDO1 using pharmaceutical agents such as BMS-986205 may alleviate the immunosuppressive properties of the tumor microenvironment and achieve more durable responses and greater patient survival benefits, particularly when used in combination with other cancer immunotherapy agents, such as Nivolumab.

IDO-1 Inhibition and Trials in HNSCC

The IDO1 inhibitor BMS-986205 is a potent selective small molecule inhibitor of IDO1 and, in combination with Nivolumab, has shown clinical activity in patients (CA017-003). Preliminary safety data from the CA017-003 study indicated that BMS-986205 is safe and tolerable at a dose of 100mg when given in combination with Nivolumab. Moreover, the overall safety profile of the combination is consistent with that observed with Nivolumab monotherapy. The safety profiles differ only with respect to AEs associated with metabolite production from the BMS-986205 resulting in anemia and methemoglobinemia. This sets the stage for the trial proposed here focusing on the combination of Nivolumab with BMS-986205 in HNSCC patients.

The presence and abundance of intratumoral IDO was associated with poor outcomes in laryngeal squamous cell carcinoma making HNSCC a reasonable tumor type in which to investigate a combination of PD1 and IDO1 inhibition[4]. Phase 1 and 2 trials have been completed utilizing epacadostat with pembrolizumab and with Nivolumab. In the Pembrolizumab + epacadostat trials there was a 34% response rate and a 23% response rate when epacadostat was combined with Nivolumab. Both trials demonstrated acceptable toxicity profiles. These trials where presented at the 2017 American Society of Clinical Oncology meeting (ECHO-202/KEYNOTE -037 and ECHO-204).

A recent phase III trial utilizing epacadostat and pembrolizumab was reported where the combination therapy failed to demonstrate improvement in progression –free survival in melanoma. A neoadjuvant trial with this combination could help to illuminate a path forward, both mechanistically and clinically.

1.2 Rationale for the Proposed Study

Checkpoint inhibitors have been recognized as a promising approach to elicit effective immune responses to HNSCC. The impressive results of T cell-directed immunotherapies, however, are contrasted by the fact that only a subset of patients enjoys long-lasting remissions after single modality immune checkpoint therapy. This circumstance has reinvigorated interest in understanding how systemic and local factors may interfere with the function of T cells and other effector immune cells critical to tumor control. It is now widely accepted that immunosuppressive cells and factors in the tumor microenvironment (TME) contribute to suboptimal responses to immune checkpoint therapeutics.

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous myeloid cell population found in the periphery (spleen, blood) and in tumor tissues where they are referred to as tumor-associated macrophages (TAMs). MDSCs and TAMs share many characteristics with ‘alternatively activated’ M2 macrophages, specifically the expression of scavenger receptors (CD163, CD204, and CD206) and IL-10 secretion[5]. They display high levels of arginase activity and relatively low levels of nitric oxide and potently inhibit T-cell receptor expression and antigen-specific anti-tumor T-cell responses[5-7]. Additionally, MDSCs suppress immune response through expression of IDO-1 combined with the promotion of Tregs[8]. *Based on these observations pharmacological reprogramming of TAMs or MDSCs towards a less immunosuppressive*

phenotype or blocking the pathway that produces the IDO enzyme promises to be an interesting approach to amplify T cell-directed immunotherapies.
In order to further understand the complex effects of immunomodulators on the tumor immune microenvironment we are employing a "window of opportunity" trial approach in which we can gather information about the immune modulatory effects of both the checkpoint inhibitor Nivolumab either with or without the IDO-Inhibitor, BMS96205. **We hypothesize that the combination of the PD-1 directed agent Nivolumab with the ID01 inhibitor BMS-986205 administered in patients with HNSCC will have a combinatorial effect on the immune and metabolic microenvironment of the tumor enabling improved, durable responses.**

1.3 Correlative Studies

Analysis of peripheral blood mononuclear cells and cytokines

We have extensive experience in monitoring immune parameters in the peripheral blood of tumor patients including those with HNSCC. Preliminary studies on tissue collected from patients with HNSCC indicate there is a range of immune polarization potential in the sera and tumor culture supernatant (TCS). In a cohort of HNSCC patients, we found that immune bias begins in tumor draining lymph nodes and extends to the peripheral blood. We have developed a novel in vitro assay of normal human monocytes co-cultured with tumor-derived products to investigate polarization capacity. Using this assay, we can monitor the effects of HNSCC-derived exosomes and soluble factors in sera or TCS for their ability to bias normal monocytes towards M2[9,10].

Evidence collected in other tumor models suggests that IDO expression facilitates M2 polarization and PDL1 is preferentially expressed on M2 monocytes, bolstering the rationale for combination therapy using Nivolumab and BMS986205. To date, there have been no studies looking at the capacity of either drug to alter immune bias or macrophage polarization in HNSCC patients. Therefore, we plan to analyze peripheral blood mononuclear cells (PBMC) subsets before treatment to establish a baseline and at every blood draw thereafter to monitor changes in these compartments due to Nivolumab therapy. We will stain PBMC with monoclonal antibodies specific for human CD3, CD4, CD8, CD11b, CD11c, CD14, CD33, CD163, CD204, and HLA-DR to look at lymphocyte and monocyte subsets and activation status. Samples will be analyzed by flow cytometry. These phenotypic markers will enable us to monitor the effect of Nivolumab therapy sizes of cell populations and activation status.

Multiplex cytokine analysis

Soluble cytokines in sera and TCS samples are routinely analyzed in clinical trial samples collected by the Clinical Cancer Immunology Core at TJU. We plan to utilize magnetic Milliplex assays (HCYTOMAG-60K) to track changes in serum cytokines over the course of treatment.

Exosomes and Nivolumab and BMS986205 therapy

Exosomes are small membranous vesicles released by tumor cells, which modulate the local microenvironment and distant cells and tissues. In order to accomplish these tasks, exosomes contain a variety of RNA species (including miRNA), proteins and specialized lipids. These attributes make exosomes excellent biomarkers, potentially indicating therapeutic responses and therapeutic targets. We have developed novel flow cytometric techniques using fluorescent dyes to track and quantify exosomes directly from patient sera. We plan to monitor exosomes levels in patient sera and look for changes in frequency and content following therapy. Exosome contents will be investigated by use of nanostring technology to analyze microRNAs.

Effects of Nivolumab and BMS986205 on the intratumoral transcriptome

To gain an unbiased insights into the effects of Nivolumab either alone or in combination with BMS986205 we will perform next generation transcriptome (RNAseq) analyses of tumor samples before and after immunotherapeutic intervention. We will analyze expression of immune cell markers including but not restricted to M1/M2 and Th1/Th2 polarization as a function of treatment.

Patient Reported Outcomes (PRO)

There has been increasing recognition that Patient-Reported Outcome (PRO) measures including, in particular, measures of health-related quality of life (HRQOL) can convey essential supplementary information for assessing the overall burden of cancer and the effectiveness of interventions[20]. Hence, we will collect Functional Assessment of Cancer Therapy - General (FACT-G) and cancer specific FACT scales. The FACT questionnaires have been used by researchers previously and have shown to be very effective for use in oncology trials[21].It has also been shown that depression is the most frequently found psychological symptom among individuals with cancer, with up to 38% of cancer patients meeting criteria for a diagnosis of major depression[22]. Prevalence rates of depression in cancer patients differ extensively across studies[23, 24]. Previous studies have also shown that depression might affect behavior and adherence to medical treatment[25]. Hence, we will collect Patient Health Questionnaire (PHQ2&9). The PHQ-2 comprises the first two items of the PHQ-9. It is a screen for depression; patients who screen positive are further evaluated with the PHQ-9 which is used for making a criteria-based diagnosis of depression (based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for depression). The PHQ-2 has been validated in several studies[26]. The diagnostic validity of the PHQ was established in two large studies in primary care and obstetrics[27].

Additional Lab tests and waist to hip ratio

C - reactive protein (CRP) is an acute phase reactant[28], indicative of tissue injury. It is also a well-established marker for inflammation[29]. However, recent reports suggest that CRP may also serve as a predictive biomarker for immunotherapy[30] with elevated CRP being predictive of prognosis and treatment response[31]. The frequency of significant Immune Related adverse Events (irAE) in Immune Checkpoint Inhibitors (ICI) treated patients are about 10–20% and early recognition is critical to prevent serious morbidity and even mortality[32]. New onset autoimmune Diabetes Mellitus (DM) associated with immune checkpoint inhibitor treatment is extremely rare[32, 33]. Even though it is very rare possibility having Glycated Hemoglobin (HbA1c) levels will be beneficial to capture these rare events. Lipid metabolism is altered in proliferating cells and impact tumor progression[34, 35]. Therefore, tumor dependence towards lipids might hold potential for the treatment of the most intractable cancers.

Waist to hip ratio (WHR) has been associated with metabolic syndrome and higher mortality[36, 37]. Hence, WHR should be assessed in combination with BMI as part of risk assessment for obesity related premature mortality and risk of metabolic related conditions.

1.4 Potential Risks and Benefits

1.4.1 Potential Risks

Nivolumab

Consistent with the mechanism of action of Nivolumab, the most frequently reported drug-related adverse events observed in clinical trials are those associated with activation of the immune system. The most common types of immune-mediated adverse events include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis and rash. Immune-mediated adverse events were mostly low grade and manageable with prompt use of corticosteroids.

Table 5.5.6.1-1: Summary of Safety with Nivolumab Monotherapy or in Combination with Ipilimumab in Subjects with SCLC by Worst CTC Grade - CA209032

	Nivo 3 N = 98 n (%)		Nivo 1 + Ipi 3 N = 61 n (%)		Nivo 3 + Ipi 1 N = 55 n (%)	
Deaths	56 (57.1)		36 (59.0)		35 (63.6)	
Due to Study Drug Toxicity	0		2 (3.3)		1 (1.8)	
Category	**Any**		**Any**		**Any**	
Preferred Term	**Grade**	**Grade 3-4**	**Grade**	**Grade 3-4**	**Grade**	**Grade 3-4**
AEs	96 (98.0)	23 (23.5)	61 (100.0)	31 (50.8)	54 (98.2)	15 (27.3)
Drug-related AEs	57 (58.2)	13 (13.3)	49 (80.3)	18 (29.5)	41 (74.5)	10 (18.2)
Drug-related AEs in ≥ 10% of Subjects in Any Group						
Fatigue	13 (13.3)	1 (1.0)	18 (29.5)	0	13 (23.6)	0
Pruritus	12 (12.2)	0	13 (21.3)	1 (1.6)	5 (9.1)	0
Diarrhea	9 (9.2)	0	14 (23.0)	3 (4.9)	9 (16.4)	1 (1.8)
Decreased Appetite	8 (8.2)	0	4 (6.6)	0	6 (10.9)	0
Nausea	8 (8.2)	0	8 (13.1)	1 (1.6)	5 (9.1)	0
Rash	4 (4.1)	0	13 (21.3)	3 (4.9)	6 (10.9)	0
Asthenia	4 (4.1)	0	2 (3.3)	0	6 (10.9)	0
Hypothyroidism	3 (3.1)	0	10 (16.4)	1 (1.6)	4 (7.3)	0
Hyperthyroidism	2 (2.0)	0	8 (13.1)	0	3 (5.5)	0
Rash Maculo-papular	1 (1.0)	0	8 (13.1)	2 (3.3)	4 (7.3)	0
Lipase Increased	0	0	7 (11.5)	5 (8.2)	0	0
SAEs	64 (65.3)	19 (19.4)	43 (70.5)	23 (37.7)	37 (67.3)	12 (21.8)
Drug-related SAEs	12 (12.2)	9 (9.2)	11 (18.0)	8 (13.1)	10 (18.2)	8 (14.5)
Drug-related SAEs in > 1 Subject						
Pneumonitis	1 (1.0)	1 (1.0)	2 (3.3)	1 (1.6)	2 (3.6)	1 (1.8)
Diarrhea	0	0	2 (3.3)	2 (3.3)	2 (3.6)	1 (1.8)

Source: Preliminary data for CA209032, database lock date 24-Mar-2016
MedDRA version 18.1; CTC version 4.0.

Note: Safety events were reported between the first dose and 100 days after the last dose of study drug.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; Ipi = ipilimumab; Ipi 1 = ipilimumab 1 mg/kg; Ipi 3 = ipilimumab 3 mg/kg; Nivo = nivolumab; Nivo 1 = nivolumab 1 mg/kg; Nivo 3 = nivolumab 3 mg/kg

BMS-986205

The overall safety experience with BMS-986205 is based on treatment of 477 subjects to date, the majority of whom have been treated with BMS-986205 and nivolumab in Study CA017-003.

As monotherapy and in combination with nivolumab, BMS-986205 overall has been well tolerated in both subjects with malignancies and healthy volunteers. Treatment-related adverse events (TRAEs) have generally been of low grade and are manageable. The safety profile of combination therapy with nivolumab and BMS-986205 has been largely comparable to that of nivolumab given as monotherapy. The most commonly reported TRAEs (in > 10% of subjects) during combination therapy with nivolumab were fatigue (14.1%) and nausea (11.1%). Grade 3 TRAEs have been reported in approximately 11% of subjects receiving the combination and treatment-related SAEs in approximately 7%. There has been 1 treatment-related death due to myocarditis prior to the clinical data cut-off date (15-Nov-2017), which occurred during combination with nivolumab, and 2 additional treatment related deaths due to Stevens-Johnson syndrome and hepatic failure, both of which occurred after the clinical data cutoff date. Safety data on the combination of BMS-986205 with both nivolumab and ipilimumab are limited at this time as only 7 subjects have been treated as of the clinical cutoff date.

With regard to p-chloroaniline, there have been no clinically significant methemoglobin (metHb) events at the 100mg dose level, and the highest reported metHb value was 16% in a subject receiving 200mg of

BMS-986205; no other subjects had reported metHb levels over 10%, none have required specific treatment for methemoglobinemia, and there have been no treatment discontinuations due to methemoglobinemia. Anemia and hemolytic anemia have also occurred infrequently (2.5% and 0.3% of subjects receiving combination therapy with nivolumab, respectively) and responded to dose holding, reductions, and other standard clinical measures.

Investigator Brochure
BMS-986205
IDO1 inhibitor

Table 5.5.1-1: Adverse Events Regardless of Causality Occurring During Monotherapy and Reported in At Least 10% of Subjects

Preferred Term[a] (%)	Grade 1	Grade 2	Grades 3 and 4	Grade 5	Total N = 35
Total Subjects with an Event	10 (28.6)	10 (28.6)	3 (8.6)[b]	1 (2.9)[c]	24 (68.6)
Nausea	8 (22.9)	1 (2.9)	0	0	9 (25.7)
Vomiting	7 (20.0)	1 (2.9)	0	0	8 (22.9)
Fatigue	3 (8.6)	4 (11.4)	0	0	7 (20.0)
Decreased appetite	4 (11.4)	1 (2.9)	0	0	5 (14.3)

Source: preliminary data

[a] MedDRA version 19.1

[b] Three (8.6%) subjects experienced unrelated Grade 3 events of acute kidney injury (2 [5.7%]) and anemia, edema peripheral, urinary tract infection, hematuria, hypercalcemia, lung infection, and lymphocyte count decreased (1 [2.9%] each). No Grade 4 AEs have been reported.

[c] One (2.9%) subject experienced unrelated Grade 5 events of malignant neoplasm progression and respiratory failure.

Detection of Methemoglobinemia

BMS-986205 may produce a p-chloroaniline metabolite. P-chloroaniline has been associated with the production of methemoglobin. Symptoms of methemoglobinemia are related to the lack of oxygen delivery to tissues and are proportional to the fraction of methemoglobin, as described below for participants with normal hemoglobin levels.

Symptoms associated with elevations of methemoglobin are as follows:

0% to 10%	**Usually asymptomatic**
10% to 20%	Cyanosis without other symptoms
20% to 50%	Headache, dyspnea, lightheadedness (possibly syncope), weakness, confusion, palpitations, chest pain
50% to 70%	Coma, seizures, arrhythmias; acidosis
> 70%	Usually death

Note that participants with anemia may experience symptoms at lower methemoglobin percentages than listed above, depending on the degree of anemia. Increasing levels of methemoglobin may confound the results of standard pulse oximeters, with values of around 85% reported consistently as methemoglobin levels increase, regardless of the true oxygen saturation. When methemoglobinemia is suspected, part of the diagnostic work-up includes evaluation for other disorders that can present with a similar clinical picture, including cardiac and pulmonary disease. A fresh peripheral blood sample (either venous or arterial) should be sent for evaluation of methemoglobin levels; methemoglobin levels may vary with storage of blood. Testing is done at Screening and as clinically indicated

Treatment of Methemoglobinemia Associated with BMS-986205

The following management recommendations are intended as guidelines for the investigator and may be modified based on institutional practices or local standard of care, as appropriate. Initial care includes supportive measures and the administration of supplemental oxygen. In mild cases, recovery often occurs simply by interrupting the administration of the offending medication. Concomitant medication lists should be reviewed for medications besides study treatment which can cause methemoglobinemia (see Appendix I)

Further treatment is generally indicated when the methemoglobin level is above 20% or is associated with symptoms.

Intravenous methylene blue is the first-line antidotal agent and works by restoring the oxygen carrying capacity of hemoglobin by reduction of methemoglobin from its oxidized state. It is given as a 1% solution at a dose of 1 to 2 mg/kg. Most participants require only 1 dose, and symptoms should resolve within 1 hour. Methylene blue may confound the interpretation of methemoglobin levels detected by co-oximetry; alternative methods of monitoring should be used after treatment with methylene blue if methemoglobin level monitoring is required. Methylene blue should be used with caution in participants with concurrent use of serotonergic psychiatric medications, as this could increase the risk of serotonin syndrome. Exchange transfusion and hyperbaric oxygen treatment are second-line options for participants with severe methemoglobinemia whose condition does not respond to methylene blue or who cannot be treated with methylene blue. Participant transfer should occur when life-threatening methemoglobinemia that is refractory to treatment occurs in a facility that cannot provide the appropriate critical care.

Potential risks of this study:

Data analyzed from the National Cancer Data Base examined 50,000 cases of head and neck cancer and found a difference in outcome survival, controlled for stage and location of tumor based on time to treatment. Patients receiving definitive treatment within 60 days from diagnosis had a better survival compared to patients who had a delay in starting treatment with a lapse time of greater than 60 days. This same study found that the average time to treatment from diagnosis for an academic institution was 28 days. It is our institutional policy to have patients started on definitive therapy within 1 month of their first encounter. For non-responding patients their definitive treatment (surgery) will be completed within 42 days of their enrollment keeping them well within the window of acceptable standard of care. It will only be for those demonstrating a response to Nivolumab and / or BMS986205 that there is a plan for continued therapy for an additional 4 weeks followed by definitive therapy (surgery).

1.4.2 **Benefits**

The clinical activity of Nivolumab monotherapy in patients with recurrent or metastatic HNSCC who progressed from a platinum-containing therapy was evaluated in the CA209141 randomized phase 3 study, and demonstrated prolonged survival benefit with Nivolumab as compared to investigator's choice (IC) of chemotherapy. In this population, the safety profile of Nivolumab was shown to be favorable as compared to standard of care chemotherapy. Thus, Nivolumab is a proven active agent in this malignancy with potential benefits to be ascertained in other stages of the disease.

There is a low risk profile for BMS 986205 in the general population. If an immune response is generated and changes are found between the biopsy and surgical resection this may lead to further treatment options for patients with head and neck cancer. The potential for a reduction in tumor burden prior to surgical resection may be observed.

2 Study Objectives

2.1 Objectives

Our hypothesis is that the combination of the PD-1 directed agent Nivolumab with the IDO1 inhibitor BMS-986205 administered in patients with HNSCC will have a combinatorial effect on the immune and metabolic microenvironment of the tumor.

2.1.1 Primary

1. To assess the impact of BMS986205 and Nivolumab versus Nivolumab alone on tumor radiographic response both at the primary tumor site and in regional lymph nodes by investigator assessment at 5 weeks. Responders will go on for additional 4 weeks of Nivolumab ± BMS 986205.

2.1.2 Secondary

1. To investigate whether adding the IDO1 - inhibitor, BMS986205, to Nivolumab therapy affects intratumoral and systemic anti-tumor immunity. Specifically, we will determine the effects of Nivolumab alone and in combination with BMS986205 on immune cell composition and polarization (Th1/Th2 ratio and M1/M2 ratio).
2. To assess the impact of BMS 986205 and Nivolumab verses Nivolumab alone on pathologic treatment effect bother at the primary and regional lymph nodes.
3. To determine the effect of BMS986205 and Nivolumab versus Nivolumab alone on immune cell composition within the tumor microenvironment including the presence of Teff, Treg, and TAM.
4. To further characterize the effect of BMS986205 when combined with Nivolumab on kynurenine production and correlate these levels with effects on immune cell composition and polarization.
5. To review the relationship of p16 status by immunohistochemistry with immune cell polarization, tumor radiographic response, and immune cell composition.
6. To review the relationship of PD-L1 status by immunohistochemistry with immune cell polarization, tumor radiographic response, and immune cell composition.
7. To assess the safety and tolerability of BMS986205 and Nivolumab.
8. Evaluate surgical wound healing post treatment.

2.1.3 Exploratory

1. To further characterize the effect of BMS986205 and Nivolumab versus Nivolumab alone through analysis of T cell repertoire

2. To assess the interactions between the immune and metabolic microenvironment through analysis of alterations in exosome composition in peripheral blood as it related to immune, cytokine and metabolic alterations before, during and after treatment.

3. To identify risks for poor physical and mental health outcomes; examine bio-behavioral factors associated with cancer treatment outcomes; and evaluate the physical and psychosocial needs of cancer survivors through patient reported outcomes.

2.2 Endpoints/Outcome Measures

2.2.1 Primary

1. Objective response at 5 weeks will be assessed by CT or MRI scans. The same modality of scan must be used at each time point for comparison. The tumor volume will be computed by obtaining 3

dimensional measurements for primary lesions and all pathologically enlarged lymph nodes. The product of these numbers will be compared between time points to determine percent change from baseline. For subjects with tumor that is not definable by radiographic imaging (e.g. streak artifact), tumor measurements using a ruler will be obtained at the specified evaluation time points in 2 dimensions. The product of these measurements will be compared to baseline measurements. Additionally photographs will be obtained at each evaluation time point. Patients that meet the threshold criteria as outlined below will undergo a second Nivolumab infusion and will continue BMS 986205 if randomized to this group. The number of patients that meet criteria to go on will be compared. We will use historical controls of patients who received Nivolumab alone under our current window of treatment (WOT), to bolster our control group.

2.2.2 **Secondary**

1. Objective pathologic response at time of surgery

2. We will analyze and compare immune cell polarization (Th1/Th2; M1/M2) in peripheral blood and tumor specimens using multiplex cytokine analysis collected before and after exposure to Nivolumab ± BMS986205.
    a. Immune polarization Th1 vs Th2 : To Analyze the immune cell polarization Th1/Th2; M1/M2) in peripheral blood and tumor specimen supernatants we look at an entire panel of inflammatory markers, utilizing Luminex technology with the Milliplex MAP Human Cytokine/chemokine Magnetic kit I (focusing on 5 of the 41 analytes) (IFN-γ, IL-2, IL-10, IL-12 (p70), and TNF-β.
    b. Additional secondary analysis will be performed on the other 36/41 analytes: sCD40L, EGF, Eotaxin, FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO, IFN-α2, IL-1α, IL-1β, IL-1ra, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-12 (p40), IL-13, IL-15, IL-17A, IP-10, MCP-1, MCP-3, MDC (CCL22), MIP-1α, MIP-1β, PDGF-AA, PDGF-AB/BB, RANTES, TGF-α, TNF-α, VEGF

3. We will use IHC to determine the prevalence of intratumoral immune cell populations (Teff, Treg, and TAM in patients treated with Nivolumab and BMS986205 as compared to patients treated with Nivolumab alone.
    a. Immune cell complement within the tumor: The immune cell complement in tumor tissues will be analyzed by a combination of immunohistochemical and FACS-based analyses. Immunohistochemical analysis of tumor samples will be done using antibodies to lymphocyte and myeloid lineage differentiation markers. These include CD45 (pan–immune cell marker); CD4 (Th cells); CD8 (CTL); CD19 (B cells); CD11b, CD14, CD33, CD163 (myeloid cells).
    b. Localization of immune cells within the tumor will be analyzed using confocal microscopy.
    c. Multiplex colocalization of resident immune cells utilizing 5-6 markers per section.

4. We will measure kynurenine levels (blood and tumor) to ensure on target effects of BMS986205 via commercial quantitative ELISA kits.

5. We will review the intratumoral immune cell populations, immune polarization data, exosome composition, and exosome function in HPV + and HPV – tumors.
    a. HPV Status: Baseline IHC staining for P16 will be performed as a surrogate for HPV status
6. We will review the intratumoral immune cell populations, immune polarization data, exosome composition, and exosome function relative to PD-L1 expression levels by IHC.

a. PD-1 and PDL-1 Status: Baseline staining for programmed death-ligand and programmed cell death protein -1 will be performed in tumor tissues pre- and post-treatment.

7. We will review the safety of Nivolumab alone ± BMS986205 in head and neck cancer patients using CTCAE v5.0
    a. A record of wound healing in the post-operative setting will be assessed beyond the CTCAE criteria as mentioned above. Descriptive definitions of wound breakdown include the presence of absence of wound dehiscence, postop wound infection (requiring antibiotics), and fistula formation.

2.2.3 Exploratory

1. We will analyze intratumoral TCR repertoire and diversity by Next Gen sequencing. Baseline T cell repertoire may be predictive of PD-1 and IDO1 inhibition

2. We will analyze exosome abundance and composition in the peripheral blood of patients both before and after exposure to both Nivolumab and BMS986205 and Nivolumab alone

   We will analyze exosome function as it related to MDSC polarization of patients both before and after exposure to both Nivolumab and BMS986205 and Nivolumab alone
    a. Exosome enrichment: Tumor explant culture supernatant and patient serum samples will be subjected to ultracentrifugation in order to obtain samples enriched for exosomes (pellet) or soluble factors/cytokines (supernatant).
    b. Serum exosome quantitation Human serum samples are diluted 1:5 with PBS and stained with mAb specific for human CD63 and fluorescent lipophillic dyes to label exosome membranes. Samples are washed and analyzed immediately by flow cytometry Guava EasyCyte 8HT which provides particle (exosome) abundance as previously described.
    c. Exosome microRNA analysis: Exosomes isolated from blood and supernatant will be lysed and microRNA will be sequenced using nanostring.

3. Patient reported outcomes will be collected and correlated to both immune cell composition and polarization and tumor radiographic response using scores from PHQ2/9, FACT-G, and FACT-HN.

3 Study Design

3.1 Characteristics

This is a pilot trial for patients with head and neck squamous cell carcinoma intended for surgical resection as the initial part of their oncologic care. Patients will be treated with 4 weeks of either Nivolumab alone or the combination of Nivolumab and BMS986205. If there is treatment response determined by tumor volume (TV) (see Section 5.10), subject will continue on treatment arm for 4 additional weeks followed by planned surgery.

3.2 Number of Participants

48 patients, randomized 3:1 Nivolumab+BMS986205: Nivolumab alone. Enrollment will be competitive for all participating sites.

3.3 Duration of Therapy

5 weeks- 9 weeks based on response

3.4 Duration of Follow Up from last dose

12 months

3.5 Treatment Assignment Procedures

3.5.1 Randomization Procedures

A randomization schedule will be created by the study statistician using the method of random permuted blocks within strata defined by location of tumor (oropharyngeal vs non-oropharyngeal). Randomization assignments will be loaded into a REDCap database and randomization assignments will be accessed through the REDCap randomization facility after the patient has completed all eligibility screening, consented to study participation, and completed all baseline data collection.

All patients enrolled on this study at both the lead site and the sub-site will be randomized at Thomas Jefferson University, once eligibility is confirmed. Randomization assignments will be completed by the TJU Research Coordinator or the Study Statistician.

3.6 Study Timeline

3.6.1 Primary Completion

We anticipate accrual of 48 patients to the study over a 26-month time period. Patients will remain on study for 14 months' time total.

3.6.2 Study Completion

We anticipate completion of the study in 40 months.

4 Study Enrollment and Withdrawal

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

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

1. Pathologically confirmed HNSC
2. Any stage 2 or greater HNSCC (AJCC 8th edition) of the 1) oral cavity, 2) larynx, 3) hypopharynx, 4) nasal cavity/paranasal sinuses or 5) stage 1 oropharyngeal with lymphadenopathy. Patients with resectable disease that is amenable to surgery are eligible. Patients must have been determined to be candidates for surgical resection by a multi-disciplinary team including a surgeon, a medical oncologist
3. Male or female, aged ≥18 years of age
4. ECOG Performance status 0-2.
5. Adequate organ function:
    a. While blood cells 2000/µl or more
    b. Absolute neutrophil count 1500/µl or more;
    c. Platelets 100,000/µl or more,
    d. Hemoglobin 9 g/dl or more;
    e. Bilirubin less than or equal to 1.5 x the upper limit of normal (except subjects with Gilbert syndrome, who can have total bilirubin <3 mg/dl);
    f. AST and ALT less than or equal to 3 x the upper limit of normal,

g. GFR greater than or equal to 40 ml/min using the Cockcroft-Gault formula or Serum creatinine less than or equal to 1.5 x ULN

6. Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 14 days of study enrollment.
7. WOCBP must agree to follow instructions for method(s) of contraception (See Appendix D) for the duration of treatment with study treatment(s) plus 5 months post-treatment completion.
8. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) plus 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.
9. Males who are sexually active with WOCBP must agree to use a condom during any sexual activity (See Appendix D) for the duration of treatment with study treatment plus 7 months after the last dose of the study treatment (i.e., 90 days [duration of sperm turnover] plus the time required for Nivolumab to undergo approximately 5 half-lives). This criterion applies to azoospermic males as well. In addition, male participants must be willing to refrain from sperm donation during this time.
   a) Male mandatory condom use is regardless of whether the participant has undergone a successful vasectomy or if the female partner is pregnant.
   b) Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly. Hormonal contraceptives are prohibited methods of contraception for participants receiving BMS-986205 this study who are WOCBP.
10. Informed Consent: All subjects must be able to comprehend and sign a written informed consent document.

4.1.2 **Exclusion Criteria**

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

1. Patients with nasopharyngeal carcinoma, salivary gland or skin primaries.
2. Patients with recurrent head and neck cancer treated previously with chemotherapy, radiation or immunotherapy.
3. Any history of a sever hypersensitivity reaction to any monoclonal antibody.
4. Any history of allergy to the study drug components.
5. Participants with a personal or family (i.e., in a first-degree relative) history or presence of cytochrome b5 reductase deficiency (previously called methemoglobin reductase deficiency) or other diseases that puts them at risk of methemoglobinemia. All participants will be screened for methemoglobin levels prior to randomization.
6. Participants with a history of G6PD deficiency or other congenital or autoimmune hemolytic disorders. All participants will be screened for G6PD deficiency prior to randomization.
7. Participants with history of serotonin syndrome.
8. Participants with active ILD/pneumonitis or history of ILD/ pneumonitis requiring steroids.
9. Prior treatment with BMS-986205 or any other IDO1 inhibitors
10. Quantitative or qualitative G6PD assay results suggesting underlying G6PD deficiency

11. Blood methemoglobin > ULN, assessed in an arterial or venous blood sample or by co-oximetry
12. History or presence of hypersensitivity or idiosyncratic reaction to methylene blue
13. History of allergy or hypersensitivity to any study treatment components, specifically to that of BMS-986205.
14. Any concurrent malignancies; exceptions include- basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer or in situ cervical cancer that has undergone potentially curative therapy. Patients with a history of other prior malignancy must have been treated with curative intent and must have remained disease-free for 2 years post-diagnosis.
15. Any diagnosis of immunodeficiency or receiving systemic steroid therapy (> 10 mg daily prednisone equivalents) or any other form of immunosuppressive therapy within 14 days of initiation of therapy
16. Patients that have an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids (> 10 mg daily prednisone equivalents) or immunosuppressive agents. Subjects with vitiligo, type I diabetes mellitus, or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study
17. Patients must not be receiving any other investigational agents.
18. Patients with uncontrolled intercurrent illnesses including, but not limited to an active infection requiring systemic therapy or a known psychiatric or substance abuse disorder(s) that would interfere with cooperation with the requirements of the trial.
19. Patients must not be pregnant or breastfeeding
20. Patients with a known Human Immunodeficiency Virus infection (HIV 1/2 antibodies) or Acquired Immunodeficiency Syndrome (HIV/AIDS), active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
21. Patients with any evidence of current interstitial lung disease (ILD) or pneumonitis
22. Patients with prior history of ILD or non-infectious pneumonitis that required steroids
23. Patients who have received a live vaccine within 30 days of the planned start of study therapy.

4.2 Gender/Minority/Pediatric Inclusion for Research

We will not exclude potential subjects from participating in this study based on ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients in this protocol and therefore address the study objectives in a patient population representative of the entire head and neck squamous cell cancer population treated at Thomas Jefferson University Hospital and sub-sites. In Philadelphia 33% of presenting patients with head and neck cancer are of ethnic minority. Based on our previous enrollment in clinical trials of similar nature we are maintaining this ratio of Caucasian to ethnic minority. We will monitor this in our MDG on a semiannual basis. There is nearly a 3:1 predominance of males to females in this diagnosis. We will review accruals to this trial quarterly in the Head and Neck MDG and review the number of males and females accrued. If this deviates from the expected ratio we will review our actual patient ratio for that time and determine a remediation plan within the MDG to ensure accrual of women.

Patients under the age of 18 will not be include in this trial.

4.3 Strategies for Recruitment and Retention

48 subjects will be recruited. No advertisement will be conducted. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Surgical offices at Thomas Jefferson

University and sub-sites. Investigators will screen the patient's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study. Patients will be screened based on pathology, image studies etc. 48 patients will be enrolled (see Section 11) with replacement of patients who do not begin therapy.

4.4 Sub-Site Enrollment Procedures

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

1. Notify them of the pending patient registration
2. Confirm the method of sending registration documents (i.e. fax, email, etc.)
3. Communicate the desired timeline of the registration.

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

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

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

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

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

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

4.5 Participant Withdrawal

4.5.1 Reasons for Withdrawal

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

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

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

4.5.2 Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention

Patients who withdraw or are discontinued prior to delivery of first dose of Nivolumab will not be considered as evaluable and will be excluded from the final analysis.

4.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination include, but are not limited to:

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

5 Study Intervention

5.1 Study Products

Nivolumab
BMS986205 – IDO Inhibitor

5.2 Study Product Descriptions

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

- BMS-986205-04 (a mesylate of BMS-986205) was selected for dosage form development and is also referred to as BMS-986205. The physical and chemical properties of BMS-986205-04 drug substance are provided in Table 3.1-1.

5.2.1 Acquisition

Nivolumab will be supplied by Bristol-Myers Squibb directly to each site involved in the research (Thomas Jefferson University and sub-site).

BMS986205 will be supplied by Bristol-Myers Squibb directly to each site involved in the research (Thomas Jefferson University and sub-site).

5.2.2 Formulation, Packaging, and Labeling

Nivolumab:

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

BMS Number	*BMS-936558-01*
Other Names	Nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
Appearance	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present
Solution pH	5.5 to 6.5

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

BMS986205

BMS-986205-04 Film-coated Tablet, 100 mg, is a light pink to pink, oval-shaped, plain-faced, film-coated tablet. In addition to BMS 986205-04 drug substance, the following formulation excipients are used: anhydrous lactose, microcrystalline cellulose, crospovidone, silicon dioxide, magnesium stearate, and Opadry® pink color dispersion. The tablets are supplied in tightly-closed high-density polyethylene bottles with child-resistant closures containing a desiccant.

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Table 3.1-1: Physical and Chemical Properties of BMS-986205-04

BMS Number	BMS-986205-04
Molecular Formula	$C_{25}H_{28}ClFN_2O_4S$
Molecular Weight	507.02
Appearance	White to off-white powder which may contain lumps
Solution pH	2.5 (0.132 mg/mL)
pH-Solubility Profile	The solubility of BMS-986205-04 is pH-dependent pH 6.8 0.001 mg/mL pH 4.5 0.001 mg/mL pH 2.7 0.085 mg/mL pH 2.0 0.561 mg/mL pH 1.0 0.073 mg/mL
pKa	4.6

5.2.3 Product Storage and Stability

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

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

BMS986205:
BMS-986205-04 tablets should be stored at 2°C to 30°C (36°F to 86°F) in a tightly-closed container protected from light.

5.3 Dosage, Preparation, and Administration

Justification for Nivolumab Dose 480 mg Q4W
The Nivolumab dose of 480 mg Q4W was selected for adults in this study based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses examining relationships between Nivolumab exposures and efficacy (eg, OS, OR) and safety responses, using data from studies in multiple tumor types (melanoma, NSCLC, and RCC) with body weight-normalized dosing (mg/kg). A flat dose is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provides numerous benefits to patients as they would have increased flexibility between clinical visits. The PPK analyses have shown that exposure to Nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as body weight increases but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing represents an over-adjustment for the effect of body weight on Nivolumab PK.

Using the PPK and exposure-response models, Nivolumab exposures and probabilities of efficacy responses and risks of AEs were predicted following Nivolumab 480 mg Q4W and were comparable to those following Nivolumab 3 mg/kg Q2W. The overall distributions of average Nivolumab steady state exposures (C_{avgss}) were comparable following administration with either Nivolumab 3 mg/kg Q2W or Nivolumab 480 mg Q4W over a wide range of body weight ranges. Nivolumab 480 mg Q4W is predicted to result in approximately 43% greater steady state peak concentrations (Cmaxss) compared to Nivolumab 3 mg/kg Q2W; however, these exposures are predicted to be lower than the exposure ranges observed at doses up to Nivolumab 10 mg/kg Q2W used in the Nivolumab clinical program. Although the Cmaxss of Nivolumab is expected to be greater following Nivolumab 480 mg Q4W compared to Nivolumab 3 mg/kg Q2W, the predicted Cmaxss following Nivolumab 480 mg Q4W is well below the median Cmaxss achieved following administration of Nivolumab 10 mg/kg Q2W, a safe and tolerable dose level.

Exposure-safety analysis demonstrated that the exposure margins for safety are maintained following Nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE ≥ Grade, and IMAEs Grade 2+, are predicted to be similar following Nivolumab 480 mg Q4W relative to Nivolumab 3 mg/kg Q2W across tumor types. Safety analyses using available data following Nivolumab 3 mg/kg Q2W

and 10 mg/kg Q2W administration indicated there were no differences in AE profiles across body weight groups. Finally, initial evidence demonstrates that, following administration of Nivolumab 480 mg Q4W, Nivolumab has been well tolerated.

Nivolumab 480 mg Q4W is predicted to have approximately 16% lower steady-state trough concentrations (C_{minss}) compared to Nivolumab 3 mg/kg Q2W. While these exposures are predicted to be lower, they are on the flat part of the exposure-response curves and are not predicted to affect efficacy. Exposure-efficacy analyses of multiple PK measures and efficacy endpoints (e.g., OS, ORR) indicated that, following administration of Nivolumab 480 mg Q4W, efficacy is predicted to be similar to that following administration of Nivolumab 3 mg/kg Q2W across multiple tumor types. Based on these data, Nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to Nivolumab to Nivolumab 240 mg Q2W or Nivolumab 3 mg/kg Q2W.

Justification for Nivolumab 30-Minute Infusion

Long infusion times place a burden on participants and treatment centers. Using shorter infusion times of 30 minutes duration in participants will diminish the burden provided there is no change in safety profile. Previous clinical studies show that Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over a long treatment duration. For example, in CA209010 (a Phase 2, randomized, double-blinded, dose-ranging study of Nivolumab in participants with advanced/metastatic, clear cell RCC, N = 167), a dose association was observed for infusion site reactions and hypersensitivity reactions (5.1% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. Establishing that Nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. The safety of Nivolumab 3 mg/kg administered as a 30-minute infusion was assessed in CA209153 in participants with previously treated advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in participants administered Nivolumab over a 30-minute infusion time compared with that reported for participants with the 60-min infusion time. An infusion duration of 30 minutes for Nivolumab 480 mg (~ 60% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg Nivolumab dose infused over a 60-minute duration. Key safety results from the interim safety population of CA209511 (Part 2) demonstrate that the safety profile of Nivolumab 480 mg IV over 30 minutes Q4W (N=142) is consistent with the established safety profile of Nivolumab (3 mg/kg Q2W administered IV over 60 minutes) across multiple indications with respect to Grade 3-4 AEs, SAEs, AEs leading to discontinuation, and IMAEs including hypersensitivity/infusion reactions IMAEs. There were no new safety concerns identified. In addition, in Study CA017003, the Phase 1/2a trial of BMS-986205 combined with Nivolumab, Nivolumab was administered at doses of 240 mg Q2W and 480mg Q4W, both over 30 minutes, in combination with BMS-986205 given daily. There have been no signals of adverse tolerability with Nivolumab given over 30 minutes at a dose of 480 mg Q4W in that study.

BMS-986205 Dose Justification

All participants randomized will receive BMS-986205 100 mg (2 50mg Tablets) PO QD in combination with Nivolumab 480mg Q4W. The selection of the dose and schedule for BMS-986205 is primarily based on available data from the ongoing Phase 1/2, first-in-human Study CA017003.

While 200 mg QD was the MTD established in dose escalation of BMS-986205 in combination with Nivolumab, preliminary PK, PD, and safety data support the selection of 100 mg QD. At 100 mg, preliminary PK data indicated that average trough plasma levels of BMS-986205 exceeded the in vitro human whole blood IC90. Significant and sustained inhibition of serum kynurenine levels was observed at all dose levels. PK-pharmacodynamic analysis of BMS-986205 exposure and kynurenine inhibition further suggests the effects to plateau at doses starting at 100 mg QD. Maximum inhibition of serum kynurenine levels was predicted to be similar at 100 mg QD and 200 mg QD. Marked but variable inhibition of intratumoral kynurenine levels was also observed at both dose levels.

The preliminary safety data presented herein from Study CA017-003 indicate that BMS-986205 is safe and tolerable at both 100 mg QD and 200 mg QD. The data suggest a more favorable tolerability profile at 100 mg, with fewer participants experiencing treatment-related ≥ Grade 3 AEs (10.9% at 100 mg QD [n=303] versus 23.5% at 200 mg QD [n=68]) and TRAEs requiring dose discontinuation (3.6% versus 5.9%, respectively) in participants receiving the 100 mg QD dose.

Furthermore, treatment-related Grade 3 anemia was reported in 0.3% of participants receiving the 100 mg dose versus 4.4% of participants receiving the 200 mg dose, and hepatic events may also occur more frequently at 200 mg compared to 100 mg (see Section 7.1.2 of the Investigator Brochure). Lastly, the only methemoglobin elevation over 10% occurred in a participant receiving 200 mg, while the peak methemoglobin reported in the 100 mg group was 6%.

No formal evaluation of efficacy between the 100 and 200 mg dose was included in the study or planned for future studies, but responses have been seen in participants treated with both doses when combined with Nivolumab.

Frequency of Treatment:
For the duration of the study, Nivolumab is to be administered on a Q4 weeks and BMS986205 daily until day prior to surgery.

5.4 Dose Modifications and Dosing Delays

5.4.1 BMS-986205 and Nivolumab Dose Modifications

No dose modifications are permitted for Nivolumab

A dose reduction of BMS-986205 is defined as a change from 2-50 mg QD tablet to a single 50 mg QD tablet. Only one dose reduction is permitted. The participant must discontinue study treatment if a subsequent dose reduction of BMS-986205 is required.

Re-escalation of BMS-986205 will not be permitted once the dose of BMS-986205 has been reduced for a participant.

Doses of BMS-986205 should be reduced for the following AEs attributable to study therapy that do not otherwise meet criteria for discontinuation:

- Grade 3 fatigue, nausea, vomiting, or anemia related to study treatment
- Methemoglobin ≥ 15%
- Clinically significant elevations in methemoglobin (generally 10%, with a normal hemoglobin level) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline

Dose modification and delay of BMS-986205 may occur in the setting of lower grade AEs and/or be more conservative than indicated above based on the clinical judgment of the investigator. For an AE requiring dose modification, BMS-986205 should be delayed to allow improvement of the AE, even if the AE does not otherwise meet criteria for dose delay)

5.4.2 Dose Delays for BMS986205 and Nivolumab

BMS-986205 and Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue, nausea, vomiting and anemia
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities

- Grade 3 skin, drug-related AE
- Grade 3 drug-related fatigue, nausea, vomiting, and anemia
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase elevations do not require dose delay
    - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation in most cases

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. For example any laboratory test result that is clinically significant or meets the definition of an SAE, any laboratory abnormality that required the participant to have study drug discontinued or interrupted, or any laboratory abnormality that required the subject to receive specific corrective therapy. It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

In addition, **only BMS-986205** should be delayed for the following:

- Methemoglobin ≥ 15%
- Clinically significant elevations in methemoglobin (generally 10% with a normal hemoglobin level) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline
- If Nivolumab dosing is delayed for reasons other than study drug toxicity (eg, administrative issues, holidays, etc), BMS-986205 dosing should continue uninterrupted.

Participants may continue to receive Nivolumab during dose delays of BMS-986205 for elevations of methemoglobin and associated events, as well as QTcF prolongations.
For participants with methemoglobin elevations with associated Grade 3 AEs, if contribution of Nivolumab to the associated AE cannot be ruled out (e.g., a participant with dyspnea in whom pneumonitis has not yet been ruled out), Nivolumab dosing should be delayed as well.

If BMS-986205 dosing is delayed, dose reduction may be necessary.

If dosing is resumed after a delay, BMS-986205 may be resumed as soon as the criteria to resume treatment are met. Nivolumab should be resumed as soon as possible after criteria to resume treatment are met but may be resumed later than BMS-986205 given the differences in each drug's administration.

Participants who require delay of any study treatment should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met.

5.4.3 BMS-986205 and Nivolumab Dose Discontinuation

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the time frame permitted for dose delays OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
    - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
    - 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
  - Grade ≥ 3 drug-related AST, ALT or total bilirubin requires discontinuation*
  - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 calendar days of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Investigator.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued BMS-986205 and Nivolumab dosing
- Any event that leads to delay in dosing lasting > 4weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Investigator*.

    ***** In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and BMS must occur.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 4 weeks or more frequently if clinically indicated during such dosing delays.

Participants who are discontinued from Nivolumab, must also discontinue BMS-986205.

5.4.4 Discontinuation of BMS-986205 Alone

BMS-986205 treatment should be permanently discontinued for the following:

- Any event requiring discontinuation of Nivolumab
- Any event requiring more than 1 dose reduction of BMS-986205
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued BMS-986205 dosing
- For participants who delay BMS-986205 but continue Nivolumab, any dose delay of BMS-986205 lasting > 10 weeks will result in the discontinuation of BMS-986205 only and participants may continue treatment with Nivolumab
- Any occurrence of serotonin syndrome

5.4.5 Criteria to Resume Treatment (BMS-986205 and Nivolumab)

Participants may resume treatment with study treatments when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

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

- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT and/or Total Bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Investigator.
    - Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

For participants who have BMS-986205 held for elevations of methemoglobin, dosing may resume when the methemoglobin levels have decreased to below the institutional ULN and any associated AEs have resolved to Grade $\leq$ 1 or baseline value. Dose modification of BMS-986205 should be considered when resuming after a delay.

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and BMS-986205 are considered as immuno-oncology agents 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 (For participants with dyspnea, CBC and methemoglobin should be measured)
- Hepatic
- Endocrinopathy
- Skin
- Neurological (For participants with confusion, methemoglobin should be measured)

The above algorithms are found in the Nivolumab IB.

5.5 Required Contraceptive Elements

For detailed information on methods of contraception for women of childbearing potential (WOCBP), see Appendix D.

Note: Hormone-based contraceptives are <u>not</u> considered highly effective methods of contraception for WOCBP participants in Arms, which include BMS986205 IDO.

In addition, male participants are required to use a latex or synthetic condom with female partners who are using one highly effective method of contraception for the duration of treatment with study treatment(s) plus 7 months post-treatment completion (i.e., 90 days [duration of sperm turnover] plus the time required for nivolumab to undergo approximately 5 half-lives). This is mandatory regardless of whether the participant has undergone a successful vasectomy or if the partner is pregnant.

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female patients who choose abstinence as a contraceptive

method 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.

Unacceptable Methods for Contraception

1) Vaginal sponge with spermicide
2) Progestin only pills
3) Cervical cap with spermicide
4) Diaphragm with spermicide
5) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
6) Withdrawal (coitus interruptus)
7) Spermicide only
8) Lactation amenorrhea method (LAM)
9) Male condoms with or without spermicide for partners of female patients, as the only method of contraception
10) Female Condoms
11) A male and a female condom must not be used together

5.6 Study Product Accountability

Table 1 Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial	5-vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
BMS986205	100mg/ tablet	30 tablets /bottle		light pink Oval shaped	Store at room temperature /shielded from light

5.7 Assessing Participant Compliance with Study Product Administration

Patient records will be reviewed for compliance with therapy. At the completion of the 4 week study period the patient will return unused BMS986205 pills to be counted. Delays or deviations of the protocol will be noted.

5.8 Concomitant Medications/Treatments

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial and prohibited for 7 months after last dose of drug. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the subject.

All treatments that are not prohibited in exclusion criteria the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of

medical care. All concomitant medication and therapies will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the CRF.

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

5.8.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to and during study treatment administration in the study are described below. Medications taken within 14 weeks prior to study treatment administration must be recorded on the case report form (CRF). Document vaccine use for 30 days prior to first dose of study drug as well as prohibition of vaccine for 100 days after last dose of treatment.

The development of serotonin syndrome has been associated with exposure to another investigational agent that inhibits the IDO1 enzyme. No case of serotonin syndrome has been observed with administration of BMS-986205. Given the possibility of a class effect, there is a theoretical risk that BMS-986205 could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome when administered in combination with serotonergic agents or tryptophan supplements. Use caution and monitor for symptoms of serotonin syndrome in participants receiving concurrent serotonergic psychiatric medications and/or tryptophan supplements.

Prohibited Treatments

The following medications are prohibited during the study:

- Prior exposure to BMS-986205 or other IDO inhibitor
- Concomitant use of strong inhibitors of CYP3A4 and/or CYP1A2 or strong inducers of CYP3A4 and/or CYP1A2 (see Appendix G) Immunosuppressive agents (except used to treat a drug-related AE)
- Immunosuppressive doses of systemic corticosteroids (Except: Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed type hypersensitivity reaction caused by a contact allergen) is permitted.)
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of malignancy)
- Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Please see restrictions on use of marijuana in Restricted Treatments section
- Any live / attenuated vaccine, such asvaricella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

Restricted Treatments

Restricted therapies are not prohibited but are not recommended; Investigators should consider possible benefit/risk implications of enrolling and treating participants in whom the following are clearly medically indicated:

- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 (See Appendix G and should not be consumed while on treatment.
- Concurrent use of moderate inhibitors or inducers of CYP3A4 and/or CYP1A2 may affect the systemic exposure of BMS-986205. The Investigator should be consulted prior to use. See Appendix G for a list of CYP3A4 and CYP1A2 modulators.
- Concurrent smoking (tobacco, marijuana, etc.) may induce CYP1A2 and decrease the systemic exposure of BMS-986205.
- Caution is warranted when consuming marijuana by means other than smoking as it may lead to increased exposure of BMS-986205 through interaction with metabolic enzymes.
- Caution is warranted when administering BMS-986205 to participants taking drugs that are highly dependent on CYP3A4 or CYP2B6 for metabolism. See Appendix G for a list of sensitive CYP3A4 and CYP2B6 substrates.
- Caution is warranted when administering BMS-986205 to participants taking drugs that may be associated with QT prolongation. See Appendix F for a list of common medications associated with QT prolongation.
- Caution is warranted when administering BMS-986205 to participants taking drugs that are subject to extensive intestinal efflux by P-gp/BCRP. See Appendix H for a list of common P-gp/BCRP substrates.
- In vitro solubility data indicate that BMS-986205 has decreased solubility with increasing pH. Participants should avoid taking proton pump inhibitors during the treatment period if possible. H2 antagonists and short-acting antacid agents may be taken, but it is recommended that these not be taken 4 hours before or 4 hours after dosing of BMS-986205.
- Caution is warranted when using other agents known to cause methemoglobinemia (see Appendix I). Dapsone, topical anesthetics, and antimalarial drugs are the most likely agents, and thus these medications should only be used after discussion with the Investigator.

All other medications are permitted except those that are contraindicated in the exclusion criteria (Section 4.1.2).

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

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

All supportive measures consistent with optimal patient care will be given throughout the study.

5.9 Dietary Restrictions

Justification for Administration of BMS-986205 with Food

In preclinical studies in dogs, approximately 2- to 3-fold higher exposures were observed when BMS-986205 was administered with food compared to under fasting condition. In the ongoing Study CA017003, BMS-986205 has been administered after a light meal in order to optimize its systemic exposure. Effects of food on the PK of BMS-986205 are further evaluated in a clinical pharmacology sub-study in oncology participants in Study CA017003. Available preliminary PK results suggest a moderate effect of food on exposure to BMS-986205 in humans compared to that observed in dogs. In 7 participants, the geometric mean (90% CI) Cmax and AUC (0-168h) for BMS-986205 were 23% (-17%, 80%) and 43% (11%, 84%) higher when administered with a high fat meal compared to under fasting conditions. Preliminary data are also available in 4 participants who received BMS-986205 with both a high fat meal and a light meal. The geometric mean (90% CI) Cmax and AUC(0-24h) for BMS-986205 were 17% (-18%, 66%) and 13% (-15%, 49%) higher, respectively, when administered with a high fat meal compared to dosing with a light meal. Observed variability in BMS-986205 PK was generally similar among the different dosing conditions. Given the modest exposure differences observed between dosing with a high fat meal vs a light meal, BMS-986205 will be administered after a meal in the current study without further restriction on the types of meal. Grapefruit and Seville oranges and their juices can inhibit CYP3A4 (See Appendix G and should not be consumed while on treatment.

5.10 Determination of Response

At the completion of the 5 week window of treatment subjects will undergo staging neck CT scan with contrast + physical exam. Radiographic response in the primary tumor and/or lymph nodes as defined below. Comparing pre-treatment and Week 5 scans in both the primary tumor and any lymph nodes if there is lymph node involvement (see rules below). Where tumor is not definable by scan the clinician will define amount of treatment response based on 2 dimensional measurements utilizing a ruler as well as pre and post photographs. If there is **NO response in both the tumor and the lymph nodes or if there is increase in disease at either site,** subjects will be scheduled for definitive surgical resection within 7 DAYS.

If there is a **Treatment Response** of greater than 10% reduction, by investigator=assessed radiographic response or physical exam measurement in overall tumor volume or in the lymph nodes without any increase in the other site of disease or new sites of disease the subject will go on to obtain 2nd dose of Nivolumab ± BMS 986205 based on previous randomization. At the completion of 9 weeks, surgery will be scheduled ± 5 DAYS.

Investigator-assessed radiographic response is defined as cumulative volume of measurable tumor primary plus lymph nodes in 3 dimensions. Each dimension will be measured at the same level in pre and post scan. The sum of these values will be compared.

INCREASE= 10% INCREASE BY VOLUME
STABLE= -9 to 9% CHANGE IN VOLUME (+ OR -)
DECREASE= 10% DECREASE IN VOLUME

		TUMOR		
		DECREASED	STABLE	INCREASED
LYMPH NODES	DECREASED	RESPONDER	RESPONDER	NONRESPONDER
	STABLE	RESPONDER	NONRESPONDER	NONRESPONDER

	INCREASED	NONRESPONDER	NONRESPONDER	NONRESPONDER

Example Formula: Imaging measurements for primary site and 1 positive lymph node:
Target lesion: Short axis mm (axial plane) * Long axis mm (axial plane) * Craniocaudal mm (sag or coronal plane) = $volume_{primary}$

Lymph node: Short axis mm (axial plane) * Long axis mm (axial plane) * Craniocaudal mm (sag or coronal plane) = $volume_{lymph\ node}$

The following will be calculated for both the primary site and the lymph node:

Measurement for time point at 5 weeks post treatment – Measurement for baseline time point = Difference in volume.

% Change = Difference in Volume / Measurement for baseline time point

Scan measurements will be completed by two individuals (head and neck radiologist and head and neck surgeon). Difference between these two evaluators in measurements resulting in a difference in moving forward with a 2nd dose or moving to surgery will involve a third independent head and neck radiologist review.

Patient with new sites of disease including new pathologically enlarged lymph nodes will not be eligible to go on for second dose of Nivolumab and be considered a non-responder regardless of measurements at other sites.

If the opinion of the surgeon remains concerned that the patient may be losing the window of opportunity for resectable disease as defined by him/her for that case patient will not be eligible for 2nd dose of Nivolumab and go on for surgery.

If patient has a CTCAE v 5.0 grade 3 or higher adverse event attributable to drug, the patient will not be eligible for continued dosing regardless of tumor response (defined in Appendix b) and will be scheduled for surgery as soon as possible based on their recovery from that AE.

The surgical intervention will be determined prior to treatment based on presenting stage and will be scheduled as above based on the duration of treatment. In the event there is a change in staging due to the window treatment, surgical intervention will remain the same and not be deescalated.

On the day of surgery blood samples will be collected prior to incision. Intraoperative tissue samples will be collected put on ice and brought to the lab for processing.

6 Study Schedule

6.1 Enrollment/Baseline Visit 1, Day 0

See Section 4.4 for sub-site enrollment procedures.

- Obtain and document consent from participant on study consent form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Verify inclusion/exclusion criteria.
- Obtain demographic information, medical history, medication history, alcohol, and tobacco use history.

- Record results of physical, and the completion of ECOG Performance Status, Vital Signs, Complete Physical Exam.
- Collect blood for baseline correlative studies (Luminex panel and exosomes),
- Collect fresh tumor tissue for primary and secondary endpoints
- Randomize patient to Nivolumab monotherapy or Nivolumab plus BMS986205*
- Schedule study visits.
- Surgical evaluation

Patients who have been randomized to receive the IDO inhibitor must have received at least 75% of the planned doses. If this threshold is not met, they will be taken off study

The following procedures must be completed within 38± 3 days of initiation of therapy unless otherwise noted:

- CT w/contrast or MRI w/contrast of the Head and/or Neck
- CT of the chest as clinically indicated
- Serum chemistries (CBC w/diff, CMP (liver and kidney function), Mg, Phos, amylase and lipase, Free T3, Free T4, and TSH), viral studies (HepB surface antigen and hepatitis C antibody or hepatitis C RNA)
- G6PD test and Methemoglobin draw within 28 days prior to randomization.
- serum or urine pregnancy test for women of childbearing potential (within 14 days of study enrollment)
- Oxygen saturation by pulse oximetry within 14 days prior to randomization

The following procedures must be completed only for patients enrolled at Thomas Jefferson University:

- C-reactive Protein (CRP), glycated hemoglobin (HbA1c), and lipid panel
- BMI, and waist hip ratio (WHR)
- Patient Reported Outcomes (PROs)
    - PHQ2
    - PHQ9
    - FACT-G
    - FACT-HN

6.2 Treatment Period

Visit 2, Day 3 ± 2 days

- Review entry labs, performed within 38 days± 3 days of first administration of Nivolumab or BMS986205. For WOCBP serum or urine pregnancy should be within 24 hours of the first drug administration
- Targeted physical examination
- Methemoglobin draw
- Review of concomitant medications

If patient is in the arm 1 to receive BMS 986205: Dispense dosing of BMS986205 and provide instruction on dosing, side effects and recording.

Visit 3 Day 7 -7 days Nivolumab only group -Arm 2

- Administer Nivolumab (dose #1)

- Review entry labs, performed within 28 days of first administration of Nivolumab. For WOCBP serum or urine pregnancy should be within 24 hours of the first drug administration
- Targeted physical examination
- Review of concomitant medications

Visit 3 Day 10 ± 2 days Nivolumab plus BMS986205 group Arm 1

- Administer Nivolumab (dose #1)
- Review entry labs, performed within 28 days of first administration of Nivolumab. For WOCBP serum or urine pregnancy should be within 24 hours of the first drug administration
- Targeted physical examination
- Review of concomitant medications

Visit 4, Day 38, ± 3 days- CT evaluation +Physical Exam

- Record adverse events as reported by participant or observed by investigator.
- Targeted physical examination.
- Serum chemistries (CBC w/diff, CMP (liver and kidney function), Mg, Phos, amylase and lipase, Free T3, Free T4, and TSH),
- Determine if NON-RESPONDER OR RESPONDER based on investigator assessment of radiology (Section 5.10), or, when radiographic appearance of tumor is limited, by physical examination
- Review of concomitant medications
- CT w/contrast or MRI w/contrast of the Head and/or Neck

Visit 5 NON-RESPONDER, Day 39 ± 7 days (Surgery scheduled)

- Record adverse events as reported by participant or observed by investigator.
- Correlative labs
- Safety Assessment
- Intraoperative specimens sent fresh on ice for correlative studies.
- Review of concomitant medications

Surgery is to be performed any time Days 39 ± 7 with surgery to be no later than 46 days from randomization barring any change in their overall medical status that would make them unfit for surgery.

Visit 5 RESPONDER, Day 39 ± 7 days (2nd infusion of Nivolumab)

- Record adverse events as reported by participant or observed by investigator.
- Targeted physical examination.
- CBC w/diff, CMP (liver and kidney function), Mg, Phos, amylase, lipase, Free T3, Free T4, TSH, to be drawn within 72 hours of administration of the study drug
- urine pregnancy test 24 hours prior to administration of the study drug

- Review concomitant medications
- Draw correlative laboratory studies
- Methemoglobin draw (Arm 1 only)
- Oxygen saturation by pulse oximetry (Arm 1 only)
- Administer the Nivolumab (dose #2).
- Review BMS986205 – side effects (Arm 1 only)
- Confirm day of surgery and CT scan (4 weeks out)
- Correlative labs

Visit 6 RESPONDER, Day 67 ± 7 days (Surgery scheduled)

- Record adverse events as reported by participant or observed by investigator.
- Correlative labs
- Safety Assessment
- Intraoperative specimens sent fresh on ice for correlative studies.
- Review of concomitant medications
- CBC, CMP, TSH as a standard of care pre-operative testing
- CT scan with contrast on the day of surgery

Surgery is to be performed any time Days 67 ± 7 with surgery to be no later than 74 days from randomization barring any change in their overall medical status that would make them unfit for surgery. Fresh tissue for correlative studies must be collected intraoperatively.

6.3 Post-treatment/Follow-Up

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

Non-responder follow-up

Visit 6 (non-responder), Day 47 ± 7 days Postop visit

- Postop evaluation and exam
- Whole blood Collection – Correlative labs
- Wound assessment
- Safety Assessment
- Review of concomitant medications

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

- C-reactive Protein (CRP), glycated hemoglobin (HbA1c), and lipid panel
- Patient Reported Outcomes (PROs)
    - PHQ2
    - PHQ9
    - FACT-G
    - FACT-HN

Visit 7 (non-responder), 3 months ± 2 weeks post all treatment completion

- Focused physical assessment
- History
- Wound assessment
- Whole Blood collection- Correlative labs.
- CMP (liver and kidney function), Mg, Phos, amylase, lipase, Free T3, Free T4, TSH
- Review of concomitant medications

Visit 8 (non-responder), 6 months ± 1 month post all treatment completion

- Focused physical assessment
- History
- Wound assessment
- Whole Blood collection- Correlative labs.

CMP (liver and kidney function), Mg, Phos, amylase, lipase, Free T3, Free T4, TSH

End of Study (12 months from completion of Treatment with Nivolumab)

- Review of current medications
- Focused physical exam
- Vital signs
- Assessment of AEs
- CBC w/diff, CMP (liver and kidney function), Mg, Phos, amylase, lipase, Free T3, Free T4, TSH

All participant charts will be reviewed every 3 to 6 months for disease status.

Responder follow-up

Visit 7 (responder), Day 75 ± 7 days Postop visit

- Postop evaluation and exam
- Whole blood Collection – Correlative labs
- Wound assessment
- Safety Assessment
- Review of concomitant medications

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

- C-reactive Protein (CRP), glycated hemoglobin (HbA1c), and lipid panel
- Patient Reported Outcomes (PROs)
    - PHQ2
    - PHQ9
    - FACT-G
    - FACT-HN

Visit 8 (Responder), 3 months ± 2 weeks post all treatment completion

- Focused physical assessment

- History
- Wound assessment
- Whole Blood collection- Correlative labs.
- CMP (liver and kidney function), Mg, Phos, amylase, lipase, Free T3, Free T4, TSH

Visit 9 (Responder), 6 months ± 1 month post all treatment completion

- Focused physical assessment
- History
- Wound assessment
- Whole Blood collection- Correlative labs.
- CMP (liver and kidney function), Mg, Phos, amylase, lipase, Free T3, Free T4, TSH

End of Study (12 months from completion of Treatment with Nivolumab or Nivolumab +BMS986205)

All participant charts will be reviewed every 3 to 6 months for disease status.

6.4 Withdrawal Visit/Discontinuation of Therapy

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

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

7 Study Procedures and Evaluations

- Medical History including intercurrent illnesses and specific attention to autoimmune disorders, may be obtained from the medical record
- Concomitant meds: prescription medications taken for the 28 days prior to enrollment
- Physical exam: height, weight, obtained from the medical record
- ECOG performance status from the medical record
- Obtain histologic confirmation of disease, including p16 status for oropharyngeal primaries from the medical record
- Vital Signs
- CT scan prior to surgery

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

- PROs are self-administered

Waist Hip Ratio: measurement to be taken per the NHLBI, NIH guideline to measure waist circumference. https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf

- To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration.

- Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor.

Body Mass Index (BMI) to calculated as kg/m^2

7.1 Laboratory Procedures/Evaluations

7.1.1 Clinical Laboratory Evaluations

- Pregnancy Test: WOCBP within 14 days prior to randomization, 24 hours prior to first drug administration
- Laboratory testing prior to each dose of either Nivolumab or BMS986205: Within 28 days of the 1st dose and within 72 hours prior to second dose – CBC w/diff, CMP (liver and kidney function, Mg, Phos, amylase, and lipase, Free T3, Free T4, and TSH
- C-reactive Protein (CRP), glycated hemoglobin (HbA1c), and lipid panel (Thomas Jefferson University only)
- Methemoglobin draw – assessed on arterial or venous blood sample or by co-oximetry
- G6PD

7.1.2 Special Assays or Procedures

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

See Laboratory Manual for additional information and specific shipping information.

8 Evaluation of Safety

8.1 Specification of Safety Parameters

8.1.1 Unanticipated Problems

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

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

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

8.1.2 Adverse Events

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

8.1.3 Serious Adverse Events

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

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

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

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious Adverse Event Collection and Reporting

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

8.2 Safety Assessment and Follow-Up

Adverse event reporting will begin after study treatment, unless the AE/SAE is caused by a study specific screening procedure, and continue until 100 days (for non-serious AEs) or 100 days (for SAEs) after the last day of study participation. At each study visit, the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

8.3 Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 8.2.

8.3.1 Relationship to Study Intervention

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

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

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

8.3.2 Expectedness

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

8.3.3 Severity of Event

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

8.3.4 Intervention

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

8.4 Safety Reporting

8.4.1 Reporting to IRB

8.4.1.1 *Unanticipated Problems*

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

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

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

Unanticipated problems occurring at the sub-site are to be reported to the sub-site IRB per institutional guidelines.

8.4.1.1.1 Sub-Site Unanticipated Problems Reporting

Unanticipated problems (UAPs) occurring at the sub-site are to be reported to the sub-site IRB per institutional guidelines.

UAPs occurring at the sub-site must also be reporting to Thomas Jefferson University using the Unanticipated Problems Form (see Appendix K). The TJU Study Site Contact will submit UAPs occurring at the sub-site to the TJU IRB.

8.4.1.2 *Adverse Events*

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

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

8.4.1.3 *Serious Adverse Events*

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

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

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

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

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

SAEs occurring at the sub-site are to be reported to the sub-site IRB per institutional guidelines.

8.4.1.4 *Sub-Site SAE Reporting Procedures*

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

SAEs should be reported to TJU using the BMS SAE reporting form or FDA Medwatch 3500A as appropriate, and should comprise a full written summary, detailing relevant aspects of the adverse events in questions, including grading and attribution to study drug. Where applicable, information from relevant hospital case records and autopsy reports should be included.

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

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

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

All reportable Adverse Events (AEs) should be reported to the TJU Research Coordinator within 48 hours using the appropriate OHR-10 form (See Appendix L).

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

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

Unanticipated problems (UAPs) that pose risk to subjects or others, and that are not AEs/SAEs should be reported to TJU within 5 working days using Unanticipated Problems Form (see Appendix K) and should be emailed to the Thomas Jefferson University Study Site Contact within 5 business days.

8.4.1.5 *Adverse Events of Special Interest*

Adverse events of special interest (AEOSI) requiring expedited reporting by the investigator have been defined for this protocol. These are:

- Hemophagocytic lymphohistiocytosis (HLH; also known as histiocytosis haematophagic)
- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

These AEOSI, whether related or not related to study drug, must be reported to BMS or designee within 24 hours of awareness of the event. These AEOSI are medically important events and are therefore considered SAEs. The reporting system for SAEs should be used (see Section 17).

HLH and DRESS syndrome may both pose diagnostic challenges due to varying clinical manifestations and signs and symptoms that may overlap with other clinical events. To assist investigators in identifying constellations of clinical symptoms that may be consistent with one of these diagnoses, standardized scoring criteria are provided in Appendix 8. Formal evaluation and documentation of diagnostic scores based on these systems is not required; investigators should use their best clinical judgement as informed by these provided criteria to determine if a participant has experienced one of these AEOSI.

8.4.2 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities must be captured as appropriate

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory test result that required the subject to receive specific corrective therapy
- It is expected that wherever possible the clinical rather than laboratory term would be used by the reporting investigator

8.4.3 Reporting to SKCC DSMC

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

For expedited reporting requirements, see table below:

DSMC AE/SAE Reporting Requirements.

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

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

8.4.4 Reporting to Funding Sponsor

SAEs, whether related or not related to study drug, and **pregnancies** must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS on any of the following form(s):

1. **MedWatch or, CIOMS or**
2. **BMS Pregnancy Surveillance Form or,**
3. **Approved site SAE form**

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

Site specific forms will be requested for review.

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

A summary of the process for the sponsor/investigator:

- Sponsor/Investigator sends a request to BMS GPV&E for a "*GPV&E reconciliation report"*. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The request should provide the BMS protocol ID, study title and PI, and sponsor/investigator protocol ID.
- BMS will send a report back to the sponsor/investigator. The data elements listed on the GPV&E reconciliation report will contain information the investigator can use for individual case identification. Cases on the list from BMS GPV&E should be compared to the SAE cases in the clinical database.
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.
- If the sponsor/investigator determines a SAE case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS

The TJU Study Site Contact is responsible for submitting all SAE reports occurring at TJU and the sub-site to the study funder.

8.4.5 Reporting to FDA

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. Thomas Jefferson University will submit SAE reports for all sites to the FDA.

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

MedWatch SAE forms should be sent to the FDA at:

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

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

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

- An SAE report should be completed for any event even when doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

The TJU Study Site Contact is responsible for submitting all SAE reports occurring at TJU and the sub-site to the FDA.

8.4.6 Reporting of Pregnancy

- Women of childbearing potential" is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level more than 40 mIU/ml.
- Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. *WOCBP should use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for Nivolumab to undergo five half-lives) after the last dose of investigational drug*
- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of Nivolumab or BMS986205
- Women must not be breastfeeding

Men who are sexually active with WOCBP *Men receiving Nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product.* Azospermic men, including men who underwent successful vasectomies, must use a condom during any sexual activity with a WOCBP, even if the partner is pregnant.

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

8.4.7 Overdose

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

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

8.4.8 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

Any patient who develops a concurrent elevation of bilirubin 2 times the upper limit of normal AND elevation AST/ALT 3 times the upper limit of normal not due to liver metastasis should be permanently discontinued from study drug.

8.5 Halting Rules

Please see Section 11.3 for stopping rules.

9 Study Oversight

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

10 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SKCC DSMP.

11 Statistical Considerations

11.1 Analysis Plans

All outcomes will be summarized by randomization arm. Continuous outcomes that are not normally distributed will be transformed prior to analysis. If standard transformations (e.g., log) do not result in outcomes that satisfy model assumptions, non-parametric tests will be used.

Primary Endpoint Analyses: The primary endpoint will be objective response at 5 weeks (4 weeks of Nivolumab) leading to a continuation of treatment. This will be assessed by CT or MRI scans. Investigator radiographic evaluation will be used as defined in the protocol. The proportions of the primary endpoint in the two treatment groups will be compared at 25% significance level using a two-sided test in proportions.

Secondary Endpoint Analyses:

We will re-analyze the primary endpoints using a combined patients collection. Historical controls of patients who received Nivolumab alone for 4 weeks in previous window of opportunity trial (CA209-9A7) will be included in the control group of this study, as they were subject to the identical inclusion and exclusion criteria with enrollment at the same institution with unchanged management pathways. Patients' demographic as well as pre-treatment clinical measurements will be compared between the combined control group vs. the treatment group to ensure the homogeneity of the two groups. A multivariable logistic regression model will be used in the statistical analysis, if any difference in the demographic and clinical predictors between treatment groups is detected. Otherwise, the proportions of the primary endpoint in the two treatment groups will be compared at 5% significance level using a two-sided test in proportions.

Secondary efficacy outcomes are changes in:

- Objective pathologic response at time of surgery.
- IHC measures of the prevalence of intratumoral immune cell populations: Teff, Treg, and TAM
- IHC and FACS-based measures of myeloid lineage differentiation markers: CD45 (pan–immune cell marker); CD4 (Th cells); CD8 (CTL); CD19 (B cells); CD11b, CD14, CD33, CD163 (myeloid cells).
- Luminex panel of inflammatory markers with the Milliplex MAP Human Cytokine/chemokine Magnetic kit I (41 analytes): IFN-γ, IL-2, IL-10, IL-12 (p70), TNF-β sCD40L, EGF, Eotaxin, FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO, IFN-α2, IL-1α, IL-1β, IL-1ra, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-12 (p40), IL-13, IL-15, IL-17A, IP-10, MCP-1, MCP-3, MDC (CCL22), MIP-1α, MIP-1β, PDGF-AA, PDGF-AB/BB, RANTES, TGF-α, TNF-α, VEGF.

If there is at least one significant difference between groups among the primary outcomes, the two randomization arms will be compared with respect to each secondary outcome using two-sample t-tests. P-values for comparisons of changes in secondary outcomes will be adjusted using the method of Benjamini and Hochberg to control the FDR among the secondary outcomes at 5%[12].

Exploratory Analyses

Change in exosomes from before to after treatment will be compared between treatment arms using two-sample t-tests.

Differences in primary and secondary outcomes by P16 status (as a surrogate for HPV), PD-1, and PDL-1 status will be evaluated across treatment arms using two-sample t-tests.

Rates of wound dehiscence, postop wound infection (requiring antibiotics), and fistula formation will be summarized by treatment arm and compared using Fisher's exact test.

Changes in tumor volume and rates of radiographic response will be summarized by treatment arm and compared using two-sample t-tests or Fisher's exact test, as appropriate.

We plan to conduct descriptive statistics. We will also summarize variables of interest using standard statistics such as frequency tables, means, and standard deviations. All measures will be evaluated for reliability and factor analyses will be conducted. Other exploratory analysis may also be conducted to attain information that will be helpful for future improvement.

For the correlative studies on patient reported outcomes (PROs) and metabolic measures (e.g., CRP, HbA1c, and lipid panel), we plan to conduct descriptive statistics and will summarize variable of interest

using standard statistics such as frequency tables, means, and standard deviations. All measures will be evaluated for reliability and factor analyses will be conducted. Other exploratory analysis may also be conducted to attain information that will be helpful for future improvement.

Safety Analyses
Safety outcomes will be summarized overall and by treatment arm.

11.2 Interim Analyses and Stopping Rules –

Interim Analysis: There is no interim analysis planned.

Stopping Rules: The selected doses of Nivolumab were safe in previous studies. There is no dose escalation or de-escalation planned in this study.

Safety Stopping Rule: The selected doses of Nivolumab were safe in previous studies. There is no dose escalation or de-escalation planned in this study.

The grade 3-4 toxicity rate for Nivolumab monotherapy therapy is about 10% and has been well-characterized in multiple clinical trials. For the stopping rules, we will consider grade 3-5 toxicities and any toxicity leading to an excessive delay (defined as surgery occurring >35 days after randomization) in definitive surgery. Incidence of grade 3-5 toxicities will be monitored continuously within each arm with potential stopping after 10 patients have been enrolled based on the Bayesian method of Thall and Simon[13]. The expected rate of toxicity in either arm is 10% and we assume a Beta(0.2,1.8) prior for the grade 3-5 toxicity rate which is equivalent to a 10% rate with information from 2 patients. We consider toxicity greater than 15% to be unacceptable. We will stop the study for safety if the posterior probability that the rate of grade 3-5 toxicities in a given arm is 15% or more is greater than 90%. Stopping rules are outlined in the table below.

Number of patients enrolled	Stop if number of patients with Grade 3 or higher toxicities is ≥
10-12	4
13-17	5
18-22	6
23-27	7
28-32	8
33-35	9

11.3 Sample Size Considerations

For the comparison of the primary endpoint we have an evaluable number of patients at Group 1: Nivolumab alone n = 12 and Group 2: Nivolumab + BMS986205 n= 36 for primary endpoint at 4 weeks. Evaluable is defined as anyone who has samples to evaluate and received at least one dose of Nivolumab (and one dose of IDOI for subjects in Group 2). It is anticipated that up to 10% of patients may withdraw prior to completion of the trial. The 11 patients (=12*.9) in Group 1 and 32(=36*.9) patients in Group 2 provide 82.3% power to detect a difference of 35% (e.g., 40% response rate in Group 1, 75% response rate in Group 2), at a two-sided significance level of 25%.

The power analysis of primary endpoint on combined patients (part of secondary analysis) is also provided as reference. Including the 25 Nivolumab alone patients from our current Nivolumab ± tadalafil trial (CA209-9A7) will allow for an evaluable number of patients at Group 1: Nivolumab alone n = 37 (12+25) and Group 2: Nivolumab + BMS986205 n= 36 for primary endpoint at 4 weeks. Evaluable is defined as anyone who has samples to evaluate and received at least one dose of Nivolumab (and one dose of IDOI for subjects in Group 2). It is anticipated that up to 10% of patients may withdraw prior to completion of the trial. The 36 patients (25 existing and 12*.9 = 11 new patients) in Group 1 and 32(=36*.9) patients in Group 2 provide 84.7% power to detect a difference of 35% (e.g., 40% response rate in Group 1, 75% response rate in Group 2), at a two-sided significance level of 5%.

12 Source Documents and Access to Source Data/Documents

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

13 Quality Control and Quality Assurance

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all of the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

14 Ethics/Protection of Human Participants

14.1 Ethical Standard

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

14.2 Institutional Review Board

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

14.3 Informed Consent Process

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

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

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

14.5 Participant Confidentiality

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

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

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

14.6 Future Use of Stored Specimens and Other Identifiable Data

No identifiable data will be retained.

15 Data Handling and Record Keeping

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

15.1 Data Management Responsibilities

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

15.2 Data Capture Methods

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

15.3 Types of Data

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

15.4 Study Records Retention

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

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

15.5 Protocol Deviations

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

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

16 Study Finances

16.1 Funding Source

Bristol-Myers Squibb, who is providing the investigational product, Nivolumab and BMS986205for this study.

16.2 Conflict of Interest

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

16.3 Participant Stipends or Payments

Patients randomized to receive Nivolumab+BMS986205 will receive a $75 stipend for Study Visits 1, 2, 3 and 4. Patients randomized to receive Nivolumab alone will receive a $75 stipend for Study Visits 1, 3, 4, and 5.

17 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

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

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

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

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

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

18 Literature References

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Appendices

The following documents are officially affiliated with the protocol and will be submitted to the IRB as a part of the protocol. As such, changes to these items require a protocol amendment.

APPENDIX A: Schedule of Events

APPENDIX B: ECOG Performance Status:

APPENDIX C: Management Algorithms for Nivolumab

APPENDIX D: WOCBP

APPENDIX E: Management algorithms for BMS986205

APPENDIX F : QT prolongation

APPENDIX G : CYP3A4 Guidelines

APPENDIX H: PGP and BCRP guidelines

APPENDIX I: Methemoglobinemia

APPENDIX J: Delay Criteria

APPENDIX K: Unanticipated Report Form

APPENDIX L: Sub-site Serious Adverse Event Form

APPENDIX M: New York Heart Association

APPENDIX N: BMS-986205 Diagnostic Criteria for HLH and DRESS Syndrome

APPENDIX A: SCHEDULE OF EVENTS

Procedures		Study Visit 1 (Day 0)	Study Visit 2 (Day 3 ± 2)	Study Visit 3 Arm 2 (Day 7 -7)	Study Visit 3 Arm 1 (Day 10± 2)	Study Visit4[6] (Day 38 ± 3)	Study Visit 5a(nr) (Day 39 ± 7)	Study Visit 6a(nr) (Day 47 ± 7)	Study Visit 5b(r) (Day 39 ± 7)	Study visit 6b (r) (Day 67 ± 7)	Study Visit 7b (r) (Day 75 ± 7)	Study Visit 7a/8b (3 months post completion of Tx ± 2 weeks)	Study Completion (Month 6)[11]	Premature Discontinuation
Signed Consent Form		X												
Assessment of Eligibility Criteria		X												
Review of Medical History		X												
Review of Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X
Study Intervention	Nivolumab (number of doses)			1	1				1					
	BMS986205 (number of doses if randomized to this group- Arm 1)		60 pills[5]						30 pills[5]					
Physical Examination	Complete[1]	X												
	Targeted		X	X	X	X	X	X	X	X	X	X	X	
	Vital Signs	X	X	X	X	X	X	X	X	x	X	X	X	
	Surgical evaluation	X							X					
	BMI and Waist Hip Ratio*	X										X		
Assessment of Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcomes (PROs)*		X						X			X	X		

	Procedures	Study Visit 1 (Day 0)	Study Visit 2 (Day 3 ± 2)	Study Visit 3 Arm 2 (Day 7 -7)	Study Visit 3 Arm 1 (Day 10± 2)	Study Visit4[6] (Day 38 ± 3)	Study Visit 5a(nr) (Day 39 ± 7)	Study Visit 6a(nr) (Day 47 ± 7)	Study Visit 5b(r) (Day 39 ± 7)	Study visit 6b (r) (Day 67 ± 7)	Study Visit 7b (r) (Day 75 ± 7)	Study Visit 7a/8b (3 months post completion of Tx ± 2 weeks)	Study Completion (Month 6)[11]	Premature Discontinuation
Clinical Laboratory[5]	Pregnancy test[2]	X	X				X		X	X				
	Chemistry[7, 9]	X				X						X	X	
	Endocrine (Free T3, Free T4, TSH)[7, 9]	X				X						X	X	
	Hematology[7, 9]	X				X							X	
	Viral Studies (Hepatitis B, Hepatitis C, and Hepatitis C RNA)	X												
	C-Reactive protein (CRP), HbA1c, Lipid panel*	X										X		
	Methemoglobin draw[12, 13]	X	X						X					
	G6PD test[12]	X												
Research Laboratory	Luminex	X					X	X	X	X	X	X		X
	Exosomes	X					X	X	X	X	X	X		X
Other Procedures	Fresh Biopsy[3]	X					X			X				
	Imaging (CT/MRI)	X[4]				X				X				

Procedures	Study Visit 1 (Day 0)	Study Visit 2 (Day 3 ± 2)	Study Visit 3 Arm 2 (Day 7 -7)	Study Visit 3 Arm 1 (Day 10± 2)	Study Visit4[6] (Day 38 ± 3)	Study Visit 5a(nr) (Day 39 ± 7)	Study Visit 6a(nr) (Day 47 ± 7)	Study Visit 5b(r) (Day 39 ± 7)	Study visit 6b (r) (Day 67 ± 7)	Study Visit 7b (r) (Day 75 ± 7)	Study Visit 7a/8b (3 months post completion of Tx ± 2 weeks)	Study Completion (Month 6)[11]	Premature Discontinuation
Assessment of Tumor (Size/Response)	X				X[6] Responder →								
Surgery						X[8]			X[10]				

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

1. Baseline and end of treatment physical examination includes ECOG Performance Status.
2. Serum or urine pregnancy test must be within 14 days of study enrollment and within 24 hours of first drug administration (Women of child bearing potential only) then within 24 hours of drug administration for subsequent cycles (urine test only).
3. Mandatory to confirm presence of squamous cell carcinoma, stratification will be based on subsite. A fresh biopsy of 0.5cm^3 is needed prior to starting therapy.
4. CT w/contrast or MRI w/contrast of the Head and/or Neck, CT of chest as clinically indicated must be completed within 38 ± 3 days of initiation of therapy
5. 100mg tabs – 1 tab per day. Plus the ramp up 7 days (7 tabs) of BMS 986205 prior to getting Nivolumab. Patients who have been randomized to receive the IDO inhibitor must have received at least 75% of the planned doses. If this threshold is not met, they will be taken off study
6. Visit #4 is to obtain imaging, make calculation of tumor response and determine responder or non-responder. If non responder (nr) then follow visit 4a, 5a, 6a. If responder (r) follow schedule 4b,5b, 6b, 7b.
7. Entry labs should be performed within 38 ± 3 days of first administration of Nivolumab. The following labs are to be performed: serum chemistries (CBC w/diff, CMP [liver and kidney function], Mg, Phos, amylase and lipase, Free T3, Free T4, TSH,) viral studies
8. Non-responders - Surgery is to be performed any time Days 39 ± 7with surgery to be no later than 46 days from randomization barring any change in their overall medical status that would make them unfit for surgery. Fresh tissue for correlative studies must be collected intraoperatively.
9. The following labs are to be performed within 3 days [72 hours] of 2nd study drug administration: serum chemistries (CBC w/diff, CMP [liver and kidney function], Mg, Phos, amylase and lipase, Free T3, Free T4, TSH)
10. Responders - Surgery is to be performed any time Days 67 ± 7 with surgery to be no later than 74 days from randomization barring any change in their overall medical status that would make them unfit for surgery. Fresh tissue for correlative studies

must be collected intraoperatively. CBC, CMP, TSH as a standard of care pre-operative testing. CT scan with contrast on the day of surgery.

11. Participant charts will be reviewed every 3 months for one year
12. Must be done within 28 days of initiation of therapy.
13. Can be done more frequently if clinically indicated.

APPENDIX B: ECOG Performance Status:

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

APPENDIX C: Management Algorithms:

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 a immuno-oncology agents 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:

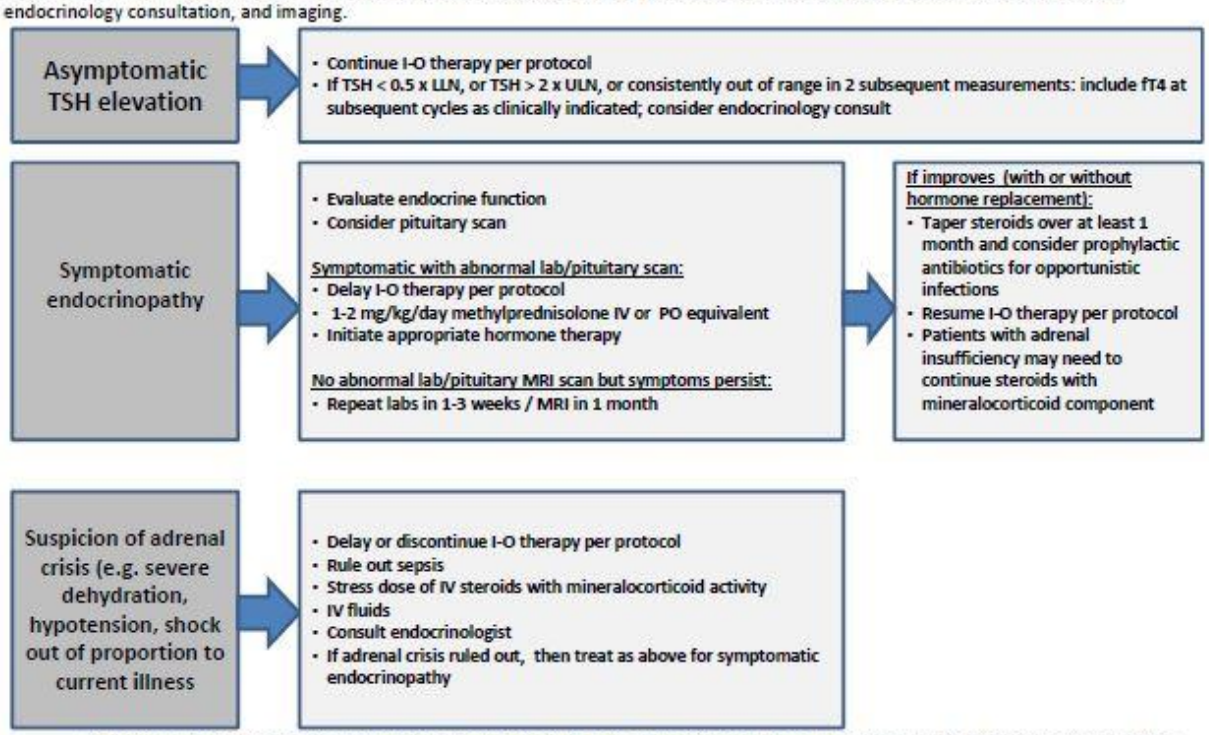
- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in both the Nivolumab and ipilimumab Investigator Brochures.
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non inflammatory etiologies should be considered and appropriately treated.
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.
The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

Endocrinopathy Management Algorithm

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

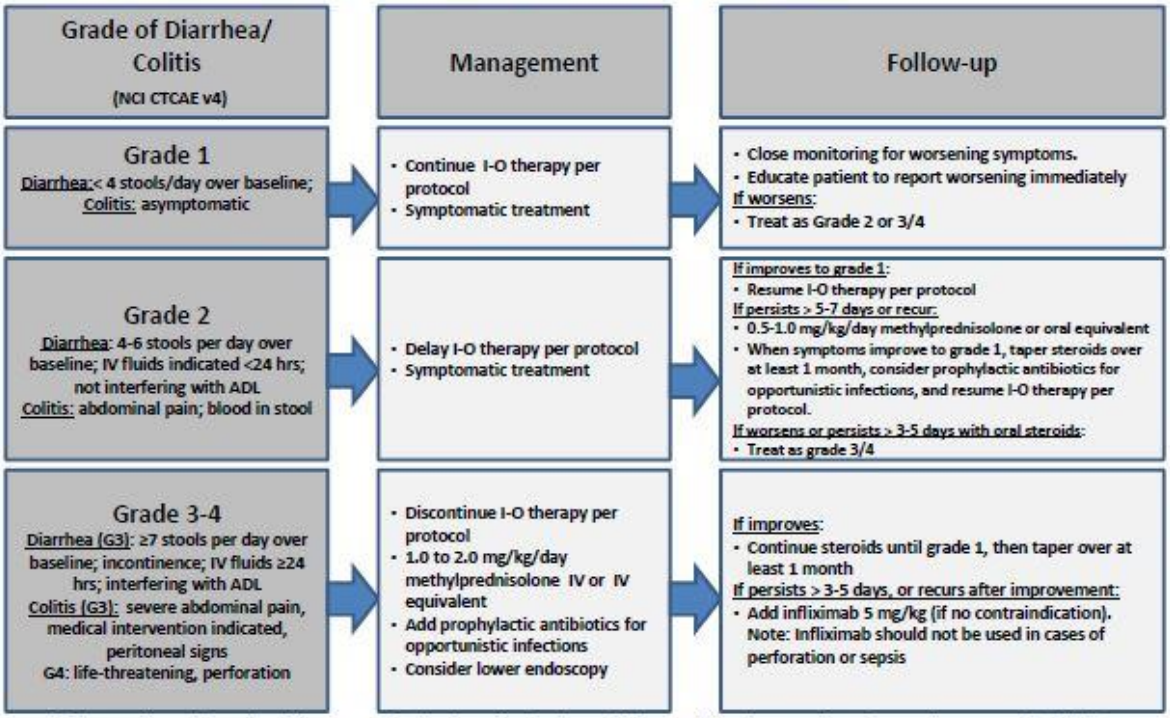


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

GI Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

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.

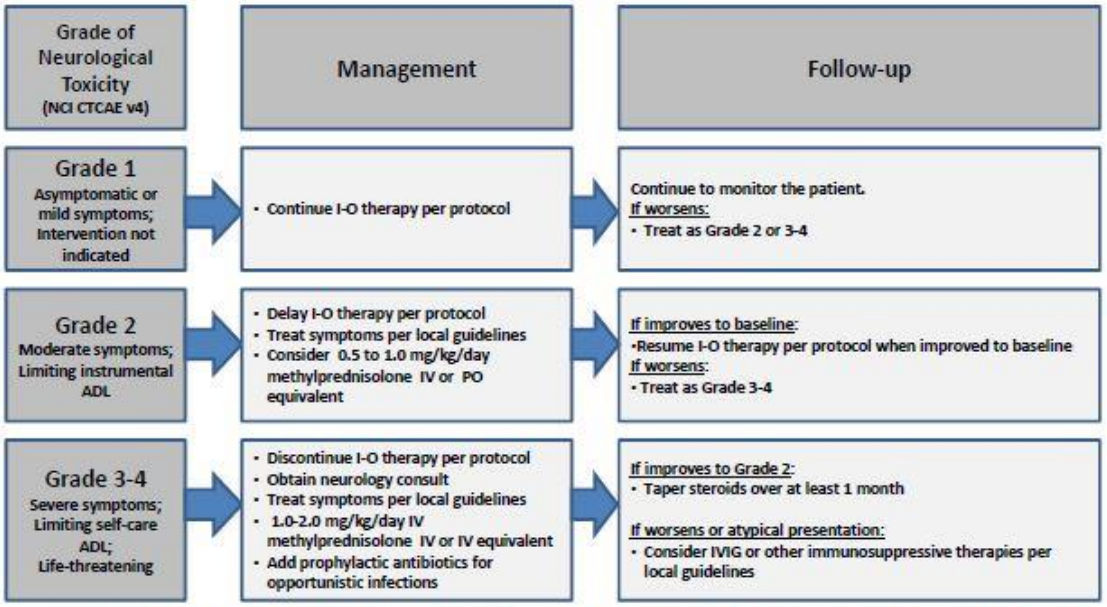
Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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

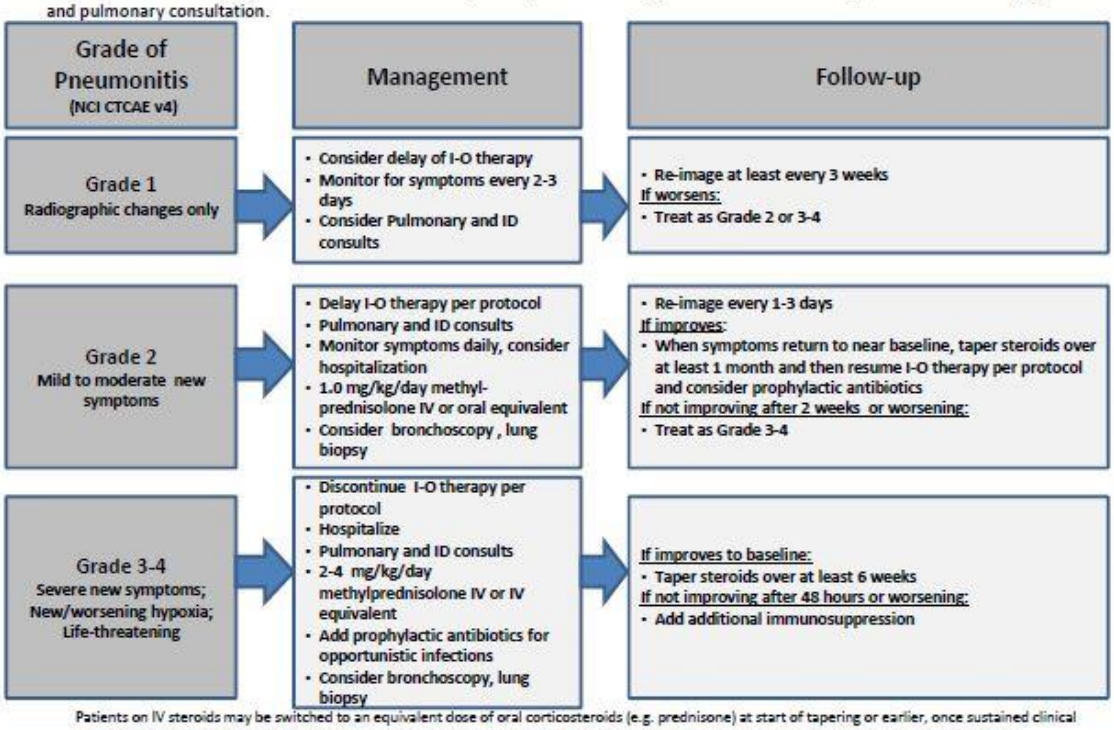


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

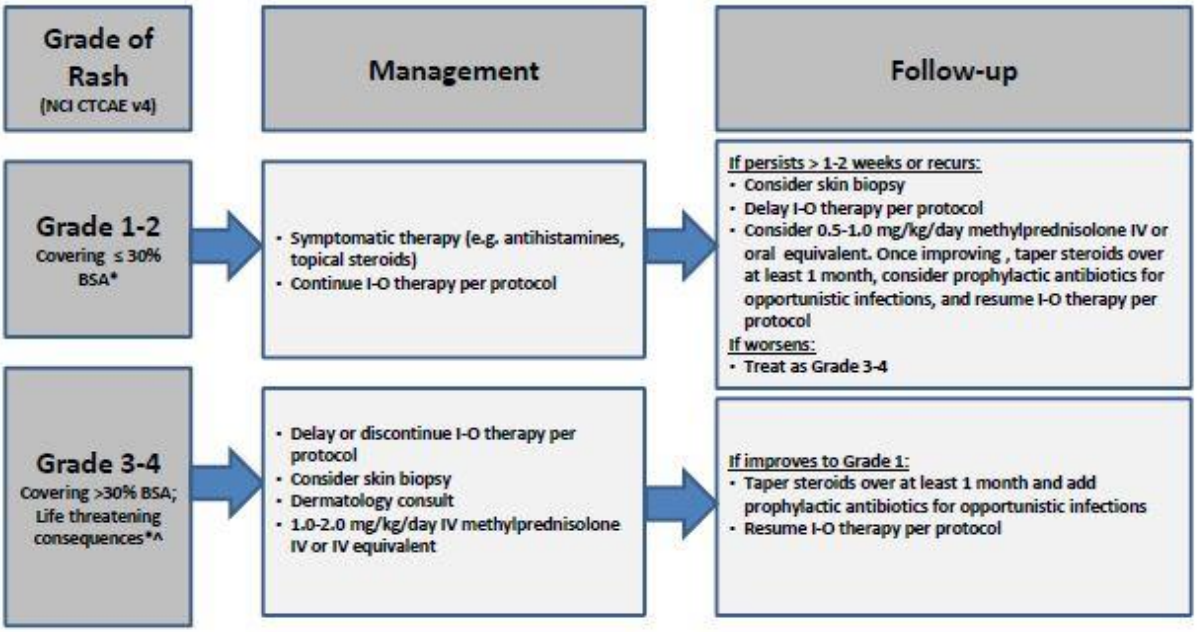
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

APPENDIX D: WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*****

Note: Hormone-based contraceptives are <u>prohibited</u> methods of contraception for WOCBP participants in Arms, which include BMS986205 IDO.

Highly Effective Contraceptive Methods That Are User Dependent ***Failure rate of <1% per year when used consistently and correctly.***[a]
• **Not in Arms, which include BMS986205 IDO: Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation**[b] – **oral** – **intravaginal** – **transdermal**
• **Not in Arms, which include BMS986205 IDO. Progestogen-only hormonal contraception associated with inhibition of ovulation**[b] – **oral** – **injectable**
Highly Effective Methods That Are User Independent

- **Not in Arms, which include BMS986205 IDO. Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]**
- **Not in Arms, which include BMS986205 IDO. Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c]**
- **Intrauterine device (IUD)[c]**
- **Bilateral tubal occlusion**

- **Vasectomized partner**

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- **Sexual abstinence**

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- **It is not necessary to use any other method of contraception when complete abstinence is elected.**
- **WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.**
- **Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence**

NOTES:

[a] **Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.**

[b] **Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.**

[c] **Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. The absence of such interactions is not known for BMS-986205 when administered with Nivolumab. Therefore, for participants of child-bearing potential who receive these 2 medications, intrauterine hormone releasing systems are not acceptable methods of contraception.**

Unacceptable Methods of Contraception*

- **Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously**

- **Diaphragm with spermicide**
- **Cervical cap with spermicide**
- **Vaginal Sponge with spermicide**
- **Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action**
- **Periodic abstinence (calendar, symptothermal, post-ovulation methods)**
- **Withdrawal (coitus interruptus).**
- **Spermicide only**
- **Lactation amenorrhea method (LAM)**

*** Local laws and regulations may require use of alternative and/or additional contraception methods.**

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment. This is mandatory regardless of whether the participant has underwent a vasectomy or partner is already pregnant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX E: Management Algorithms IDO Inhibitor

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

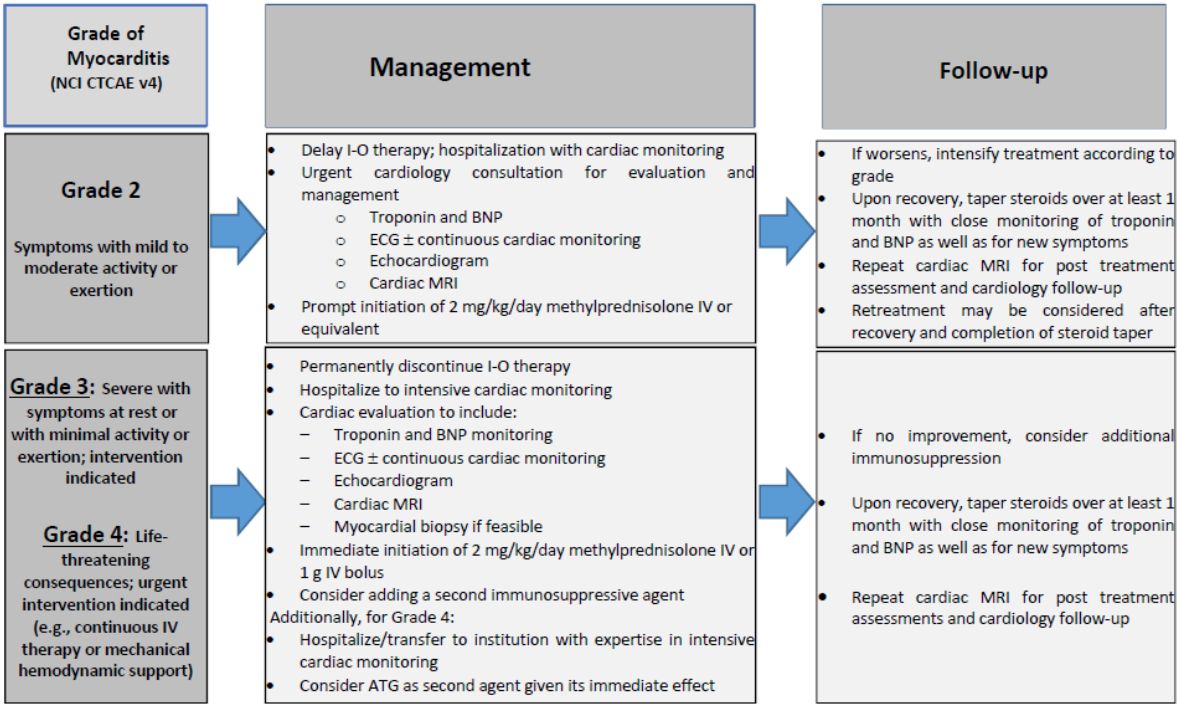
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

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

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

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

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

APPENDIX F: Medications associated with qt prologation

The list below is not meant to be all inclusive. Please consult individual drug labels for further information.

quinidine, procainamide, disopyramide,
amiodarone, sotalol, ibutilide, dofetilide,
erythromycins, clarithromycin,
chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide,
cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone,
halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

APPENDIX G: CYP3A4, CYP1A2 AND CYP2B6 GUIDANCE

The lists below are not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Table 1: Classification of In Vivo Inhibitors of CYP Enzymes

CYP Enzymes	Strong Inhibitors[a] ≥ 5-fold Increase in AUC or > 80% Decrease in CL	Moderate Inhibitors[b] ≥ 2 but < 5-fold Increase in AUC or 50-80% Decrease in CL	Weak Inhibitors[c] ≥ 1.25 but < 2-fold Increase in AUC or 20-50% Decrease in CL
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,[d] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[e] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[d] imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[f] goldenseal,[f] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine[g], zafirlukast	methoxsalen, mexiletine, oral contraceptives	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton

Please note that this is not an exhaustive list.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.

[b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

[c] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 1.25-fold.

[d] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).

[e] Withdrawn from the United States market because of safety reasons.

[f] Herbal product.

[g] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 2: Classification of In Vivo Inducers of CYP Enzymes

CYP Enzymes	Strong Inducers **≥ 80% Decrease in AUC**	**Moderate Inducers 50-80% Decrease in AUC**	Weak Inducers **20-50% Decrease in AUC**
CYP3A	Avasimibe,[a] carbamazepine, phenytoin, rifampin, St. John's wort[b]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide
CYP1A2		Phenytoin[d], rifampin[e], ritonavir[f], smoking, teriflunomide	

Please note that this is not an exhaustive list.

[a] Not a marketed drug.

[b] The effect of St. John's wort varies widely and is preparation dependent.

[c] Herbal product.

[d] Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.

[e] Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.

[f] Strong inducer of CYP2C19 and moderate inducer of CYP1A2, CYP2B6, CYP2C9.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 3: Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Sensitive Substrates[a]	Substrates with Narrow Therapeutic Range[b]
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole,[c] cisapride,[c] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[c]
CYP2B6	Bupropion, efavirenz	

Please note that this is not an exhaustive list.

[a] Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[b] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

[c] Withdrawn from the United States market because of safety reasons.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

APPENDIX H: P-gp and BCRP Guidance

The list below is not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Table 1: Examples of In Vivo Substrates for Selected Transporters

Transporter	Gene	Substrate
P-gp	***ABCB1***	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	***ABCG2***	Methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan

Please note that this is not an exhaustive list.

Abbreviations: BCRP = breast cancer resistance protein; P-gp = P-glycoprotein.

APPENDIX I: AGENTS KNOWN TO CAUSE METHEMOGLOBINEMIA

- Acetanilid
- p-Amino salicylic acid
- Aniline, aniline dyes
- Benzene derivatives
- Clofazimine
- Chlorates
- Chloroquine
- Dapsone
- Local anesthetic agents
  - Benzocaine
  - Lidocaine
  - Prilocaine
- Menadione
- Metoclopramide
- Methylene blue*
- Naphthoquinone
- Naphthalene
- Nitrites
  - Amyl nitrite
  - Farryl nitrite
  - Sodium nitrite
  - Nitroglycerin
  - Nitric oxide
- Nitrobenzene
- Paraquat
- Phenacetin
- Phenazopyridine
- Primaquine
- Rasburicase
- Resorcinol
- Sulfonamides

* While methylene blue is a recognized treatment for methemoglobinemia, it is an agent with oxidant potential (and may worsen the clinical situation) since in individuals with glucose-6-phosphate dehydrogenase deficiency, it induces acute hemolysis that can further decrease oxygen delivery to the tissues. Paradoxically, in high doses, methylene blue can also increase methemoglobinemia.

APPENDIX J: BMS-986205 and Nivolumab Dose Delay Criteria

Table 1: BMS-986205 and Nivolumab Dose Delay and Reduction

Situation	Nivolumab delay	BMS-986205 delay	BMS-986205 Reduction after Delay
Grade 2 non-skin, drug-related AE, except fatigue, nausea, vomiting and anemia	Yes	Yes	No
Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities	Yes	Yes	No
Grade 3 skin, drug-related AE	Yes	Yes	No
Grade 3 drug-related laboratory abnormality (exceptions apply, consult protocol)	Yes	Yes	No
Grade 3 drug-related fatigue, nausea, vomiting, and anemia	Yes	Yes	Yes
Methemoglobin $\geq$ 15% or any clinically significant elevation with associated Gr 3 AE not attributable to another etiology	No	Stop Tx	Stop Tx
QTcF > 500 msec (and > 60 msec above baseline)	No	Yes	Yes
Other lower grade AEs (in consultation with MM)	Possibly	Possibly	Possibly

APPENDIX K: Sub-Site Unanticipated Problem Form

The form to be used for sub-sites to report unanticipated problems (UAPs) to the lead site follows on the next page.

UNANTICIPATED PROBLEM REPORT FORM
For Sub-Site Reporting

Thomas Jefferson University Principal Investigator: _____

Sub-Site Principal Investigator: _____

TJU IRB Control Number/Sub-Site Identifier: _____

Protocol Title: _____

_____

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

Description of Problem: _____

_____

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

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

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

Describe the Corrective Action Plan: _____

_____

Has the problem been resolved? Yes ☐ No ☐

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

_____
Signature of person preparing report Date Email/Phone number

_____
Sub-site PI signature Date Email/Phone number

APPENDIX L: Sub-Site Serious Adverse Form

The form to be used for sub-sites to report serious adverse events to the lead site follows on the next page.

SAE REPORT FORM FOR SUBSITE REPORTING

Thomas Jefferson University Principal Investigator: _____

Sub-Site Principal Investigator: _____

TJU IRB Control Number/Sub-Site Identifier: _____

Protocol Title: _____

_____

Subject Initials and ID: _____

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

Study Drug(s)/Device: _____

Description of adverse event: _____

Severity of adverse reaction: _____

Action Taken: _____

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

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

If other explain:

If List concomitant medications:

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

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

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

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

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

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

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

_____
Signature of person preparing report Date Email/Phone number

_____
Sub-site PI signature Date Email/Phone number

APPENDIX M

NEW YORK HEART ASSOCIATION (NYHA)

FUNCTIONAL CLASSIFICATION
(Class and Description)

I Patients with cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, palpitations or anginal pain.

II Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, dyspnea, palpitations or anginal pain.

III Patients with marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, dyspnea, palpitations or anginal pain.

IV Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX N: BMS-986205 DIAGNOSTIC CRITERIA FOR HLH AND DRESS SYNDROME

Table 1. Diagnostic criteria for HLH used in the HLH-2004 trial*

The diagnosis of HLH† may be established:
A. Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*
or
B. Five of the 8 criteria listed below are fulfilled:
1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)
Platelets < 100×10^3/mL
Neutrophils < 1×10^3/mL
4. Hypertriglyceridemia (fasting, > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL‡
8. Elevated sCD25 (α-chain of sIL-2 receptor)§

*Adapted from Henter et al.

†In addition, in the case of familial HLH, no evidence of malignancy should be apparent.

‡Although the HLH-2004 protocol uses ferritin > 500 ng/mL, we generally view ferritin > 3000 ng/mL as concerning for HLH and ferritin > 10 000 as highly suspicious.

§Elevations above age-adjusted, laboratory-specific normal levels (defined as > 2 SD from the mean) appear more meaningful than the original designation of > 2400 U/mL because of variations between laboratories.

Jordan et al. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041. Epub 2011 Aug 9

Table 2 Scoring system for classifying HSS/DRESS cases as definite, probable, possible or no case

Score	−1	0	1	2	Min.	Max.
Fever ≥ 38·5 °C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			0·7–1·499 × 10^9 L^{-1}	≥ 1·5 × 10^9 L^{-1}		
Eosinophils, if leucocytes < 4·0 × 10^9 L^{-1}			10–19·9%	≥ 20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Skin rash extent (% body surface area)		No/U	> 50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement*					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			−1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥ 3 of above negative			Yes		0	1
Total score					−4	9

U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus. *After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5, definite case.

Kardaun et al., Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS SHBr J Dermatol. 2007 Mar;156(3):609-11.

Table I. RegiSCAR DRESS validation score

Score	−1	0	1	2	Min	Max
Fever ≥ 38.5° C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			700-1499/μL	≥1500/μL		
Eosinophils, if leukocytes <4000			10-19.9%	≥20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Rash extent (>50% BSA)		No/U	Yes			
Rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement*					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ(s)		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			−1	0
Evaluation other potential causes:					0	1
ANA						
Blood culture						
Serology for HVA/HVB/HVC						
Chlamydia-/*Mycoplasma pneumoniae*						
Other serology/PCR						
If none positive and ≥ 3 of above negative			Yes			
TOTAL SCORE					−4	9

U = unknown/unclassifiable.
*After exclusion of other explanations: 1 = 1 organ, 2 = ≥ 2 organs
Final score <2: No case
Final score 2-3: Possible case
Final score 4-5: Probable case
Final score >5: Definite case

Comments on Table I:
Specifics for evaluation of diagnostic features in DRESS
Fever (−1, 0)
If core temperature is < 38.5°C (Fahrenheit 101.3): deduction of 1 point

Lymphadenopathy (0, 1)
Tender enlarged lymph nodes (>1 cm) at least at 2 different anatomic locations: 1 point

Peripheral blood:
Eosinophilia: (0, 1, 2)
- Absolute eosinophilia of 700-1500 10^9E/l: 1 point, if ≥ 1500 10^9E/l: 2 points
- If leukocyte count is < 4000 10^9E/l: % eosinophils ≥ 10%-19.9%: 1 point, eosinophils ≥ 20%: 2 points

Atypical lymphocytes: (0, 1)
If present: 1 point

Skin reaction (extent, morphology) **(−2, −1, 0, 1, 2)**
a. *Extent rash (0, 1)* If morphology is compatible with DRESS and extent eruption > 50% body surface area (BSA): 1 point
b. *Morphology rash (−1, 0, 1)*: If morphology is suggestive for DRESS: 1 point; if suggestive for a different type of reaction: deduction of 1 point; otherwise 0 points
Morphology is considered suggestive for DRESS at presence of ≥ 2 of following criteria:
- scaling/desquamation, eg, exfoliative dermatitis
- edema, especially facial edema (excluding lower leg edema)
- purpura (excluding lower leg)
- infiltration

c. *Histology (−1, 0):*
When histology is compatible with DRESS: 0 points; when suggestive for another diagnosis: deduction 1 point

Involvement internal organs: (0, 1, 2)
For acute involvement of each organ, 1 point is given, with a maximum of 2 points. Organ involvement is based on history, clinical investigation, medical imaging, biopsy, or other tissue/fluid investigation. Organ involvement is also calculated at presence of the following abnormal laboratory values:

Liver (0, 1)
- ALAT > 2 times upper normal limit (*UNL) on at least 2 successive dates **or**
- conjugated bilirubin > 2* UNL on at least 2 successive dates **or**
- ASAT, total bilirubin, alkaline phosphatase (AP) all > 2* UNL at least

Kidney (0, 1)
Serum creatinine more than 1.5 times above the base value for the patient on at least 2 successive dates, and/or proteinuria above 1 g/day, hematuria, decreased creatinine clearance, decreased GFR

Lungs (0, 1)
Cough and/or dyspnea in conjunction with
- evidence of interstitial involvement on imaging and/or
- abnormal broncho-alveolar lavage fluid, or biopsy and/or
- abnormal blood gases

Muscle, heart: (0, 1)
- Muscle pain and/or weakness, myocarditis (often nonspecific symptoms: hypotension, fatigue, chest pain, dyspnea, malaise, palpitations, tachycardia, cardiac dysfunction, cardiomegaly, sudden cardiac death), with
- Raised serum creatine phosphokinase (CPK) > 2*UNL
- Raised isoenzymes: CPK-3/CPK-MM (indicative for skeletal muscle), raised CPK-2/MB fraction (indicative for heart muscle involvement)
- Serum troponin T > 0.01 μg/L
- Abnormal imaging: chest X-ray/ECHO/CT/MRI/EMG including ECG: ST-T electrocardiogram abnormalities or conduction defects (ST-segment depression, T-wave inversions, or nondiagnostic ECG changes (paced or bundle branch block)
- Endomyocardial biopsy

Pancreas (0, 1):
Amylase and/or lipase ≥ 2*UNL

Other organs: spleen, thyroid gland, central nervous system, gastrointestinal tract
- Clinical symptoms and additional investigations: enlargement/imaging, including EEG
- Abnormal lab values: TSH, FT4, FT3.
- Biopsy

Duration: (−1, 0)
If the total duration of the reaction is ≤ 15 days or unknown: deduction 1 point

Exclusion of other causes, eg, infections, virus (re)activation: (0, 1)
- Hepatitis A/B/C
- *Mycoplasma-/Chlamydia pneumoniae*
- Blood cultures ≤ 3 days of index date
- Other (infections): serology, PCR, microbiological cultures
- ANA

In case of a positive result for any of these, organ involvement is reevaluated for a possible alternative cause. If ≥ 3 mentioned groups are investigated and no positive result is found, an extra point is given to express thorough investigation for alternative causes.
Viral (re)activation of EBV, CMV, and HHV6/7 are also recorded; results, however, do not influence the score.