PHASE I/II TRIAL OF BMS-986205 AND NIVOLUMAB AS FIRST OR SECOND LINE THERAPY IN HEPATOCELLULAR CARCINOMA

Protocol Number:	UCDCC#276 (BMS #: CA017-084)
Indication:	Hepatocellular carcinoma
Phase:	I/II
Funding Source:	Bristol-Myers Squibb
Agent(s):	BMS-986205 in combination with Nivolumab
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IND # :	[redacted]
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PROTOCOL SIGNATURE PAGE

Protocol Number: UCDCC#276

Protocol Title: Phase I/II Trial of BMS-986205 and Nivolumab as First or Second Line Therapy in Hepatocellular Carcinoma

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

_____
Investigator Name (print)

_____
Investigator Signature

_____
Date

PROTOCOL SYNOPSIS

Title:	Phase I/II Trial of BMS-986205 and Nivolumab as First or Second Line Therapy in Hepatocellular Carcinoma
Protocol No.:	UCDC#276 (BMS ISR: CA017-084)
Phase of Development:	I/II
Investigational Product, Dose Regimen	BMS-986205 100mg daily (provided by BMS at no cost to subject) Nivolumab 240mg every 2 weeks (provided by BMS at no cost to subject)
Primary Objective:	1. To determine the safety and tolerability of BMS-986205 in combination with nivolumab in unresectable / metastatic HCC in the first or second line setting using CTCAE V5.0 criteria. 2. To determine efficacy as defined by objective response rate (ORR) of BMS-986205 in combination with nivolumab in unresectable / metastatic HCC in the first or second line setting using RECIST (version 1.1).
Secondary Objective(s):	1. To determine disease control rate (DCR), duration of response (DOR), progression free survival (PFS), and overall survival (OS) by RECIST 1.1 and ORR using immune RECIST (iRECIST) of BMS-986205 in combination with Nivolumab in unresectable HCC. 2. To further evaluate safety of BMS-986205 in combination with Nivolumab in unresectable HCC.
Correlative Objective(s):	1. To analyze serial blood samples for serum cytokine and tryptophan / kynurenine levels, and to quantify the number, function, and gene expression of peripheral blood mononuclear cells (PBMCs). 2. To evaluate serial tumor tissue biopsies for tumor infiltrating immune cell subsets, expression of immune regulatory proteins including IDO1 and PD-L1, gene expression signatures, and mutational load. 3. To evaluate pre-treatment stool samples for microbiome signatures 4. To explore potential biomarkers.
Study Schema:	Phase I/II study with phase 1 being dose escalation of BMS-986205 with nivolumab and phase 2 being an open-label expansion in patients with HCC.
Study Population and Sample Size:	• Unresectable / metastatic HCC in the first or second line setting. • 3-12 patients in the phase I (50mg or 100 mg daily of BMS-986205 and 240mg every two week of nivolumab) • 17 patients in the phase II expansion cohort at MTD (either 50mg or 100mg daily of BMS-986205 and 240mg every two week of nivolumab) with the 6 patients accrued in the phase I at MTD counting towards the total.
Eligibility Criteria	**Inclusion Criteria:** 1. Men and women ≥18 years of age at the time of study entry. 2. Willing and able to provide written informed consent for the trial. 3. Life expectancy >12 weeks. 4. Histologically or imaging confirmed hepatocellular carcinoma (mixed hepatocellular/cholangiocarcinoma or fibrolamellar subtypes are excluded). 5. Have disease that is not amenable for curative treatment approach.

6. Have measurable disease based on RECIST v1.1.
7. ≥1 liver lesions accessible for core biopsy that was either not previously treated by liver-directed therapy or progressed following liver-directed therapy.
8. Child-Pugh score of A
9. ECOG performance status of 0 or 1.
10. Adequate hematology parameters:
    a) Absolute neutrophil count (ANC) ≥ 1000 cell/mm^3
    b) Platelet count ≥ 50,000/mm^3
    c) Hemoglobin (Hgb) ≥ 8 g/dL
11. Acceptable blood chemistry levels:
    a) AST/SGOT, ALT/SGPT ≤ 5 x upper limit of normal (ULN)
    b) Total bilirubin ≤ 2 ULN
    c) Creatinine ≤ 2 x ULN
12. Subjects with active hepatitis B virus (Hep B) are allowed if antiviral therapy for hepatitis B has been given for >8 weeks and viral load is <100 IU/ml prior to first dose of trial treatment. Subjects with untreated hepatitis C virus (HCV) are allowed.
13. Willingness to undergo mandatory pre-treatment biopsy (unless there is adequate archival tumor specimen available) and mandatory on-treatment biopsy.
14. Criterion modified per Amendment v4.0.
    a. 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 24 hr prior to planned treatment initiation.
    b. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception (Appendix 9) for the duration of treatment with study treatment(s) plus 5 months post-treatment completion (i.e., 30 days [duration of ovulatory cycle] plus the time required for nivolumab to undergo approximately 5 half-lives).
    c. 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 (i.e., 90 days [duration of sperm turnover] plus the time required for nivolumab to undergo approximately 5 half-lives). In addition, male participants must be willing to refrain from sperm donation during this time.
    d. Males who are sexually active with WOCBP must agree to use a latex or synthetic condom during sexual activity (see Appendix 4) 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.
    e. 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 not considered highly effective methods of contraception for participants receiving BMS-986205 in this study who are WOCBP.
15. Ability to adhere to the study visit schedule and other protocol requirements
16. Participants must be able to swallow pills intact.

Exclusion Criteria:

1. Received more than 1 prior systemic HCC-related therapy or currently receiving HCC-related systemic treatment or participating in a clinical trial and receiving study therapy.

	2. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). 3. Known diagnosis of immunodeficiency or active autoimmune disease or requiring systemic steroid equivalent of prednisone ≥ 10 mg/day or any immunosuppressive therapies ≤7 days of before the first dose of the study. 4. Active bacterial, viral (except Hepatitis B and C - see Inclusion Criterion 12), or fungal infection(s) requiring systemic therapy, defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, anti-viral therapy, anti-fungal therapy, and/or other treatment. 5. Active pneumonitis or history of interstitial lung disease (ILD) / pneumonitis requiring steroids. 6. Clinically significant ascites. 7. Hepatic encephalopathy. 8. Any significant medical condition including additional malignancies, laboratory abnormalities, or psychiatric illness that would prevent the subject from participating and adhering to study related procedures. 9. Live attenuated vaccine ≤30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. 10. Use of strong inhibitor / inducer of CYP3A4 or CYP1A2. 11. Known history of surgery or medical condition that may affect drug absorption, per investigator discretion. 12. Participants with a history of G6PD deficiency or other congenital or autoimmune hemolytic disorders. All participants will be screened for G6PD deficiency prior to enrollment using quantitative or qualitative G6PD assay results to suggest underlying G6PD deficiency. 13. 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 enrollment using blood methemoglobin > ULN, assessed in an arterial or venous blood sample or by co oximetry. 14. Subjects with screening QTc interval > 480 ms. 15. Liver directed therapy ≤4 weeks before the first dose of study. 16. History of esophageal or gastric variceal bleeding within 3 months of study enrollment. 17. Treatment with botanical preparations (e.g., herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to enrollment. 18. Prior history of serotonin syndrome. 19. Prior treatment with BMS-986205 or any other IDO1 inhibitors. 20. Women who are breastfeeding. 21. History or presence of hypersensitivity or idiosyncratic reaction to methylene blue. 22. History of allergy or hypersensitivity to any study treatment components, specifically to that of BMS-986205.

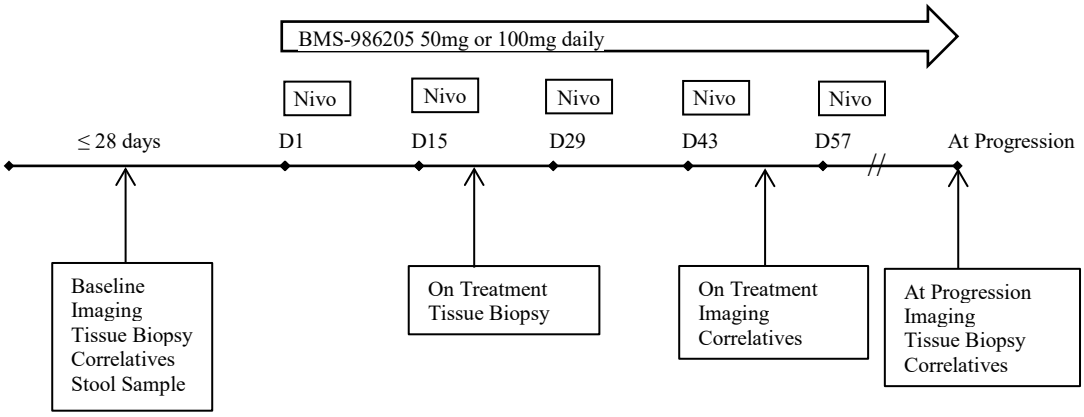
	23. Participants who have had major surgery requiring general anesthesia or significant trauma who have not recovered per physician determination for at least 14 days prior to enrollment. 24. Participants who have had major surgery requiring general anesthesia or significant trauma who have not recovered per physician determination for at least 14 days prior to enrollment. 25. Participants with uncontrolled adrenal insufficiency.
Endpoints:	**Phase I:** • Safety profile of BMS-986205 in combination with nivolumab in unresectable HCC using CTCAE V5.0 criteria **Phase II:** • Safety profile of BMS-986205 in combination with nivolumab in unresectable HCC using CTCAE V5.0 criteria • ORR of BMS-986205 in combination with nivolumab in unresectable HCC using RECIST 1.1 criteria. **Secondary Endpoints** • DCR which include CR, PR and SD from the first report of SD or better until progression by RECIST 1.1 • DOR defined by the first report of SD or better until progression by RECIST 1.1 • ORR using immune RECIST (iRECIST) • PFS defined by date of enrollment until the first date of documented disease progression or death by RECIST 1.1 • OS defined by date of enrollment until death from any cause by RECIST 1.1. • Correlation of PD-1/L1 expression (+/-) and IDO1 expression (+/-) at: 1) baseline, 2) on treatment, and 3) progression, with ORR, PFS and OS.
Statistical Considerations	This is a phase I/II study using a Simon optimal two-stage design for efficacy of BMS-986205 in combination with nivolumab. In the phase I portion, we will treat patients following 3+3 standard design with dose escalation in BMS-986205 along with fixed dose of nivolumab. BMS-986205 dose level 1 will be 50mg and dose level 2 will be 100mg. 3 patients will be treated with BMS-986205 at dose level 1 of 50mg along with fixed dose of nivolumab. If no patient experiences a DLT at dose level 1, we will add 3 patients will be treated at a dose of 100 mg of BMS-986205 with fixed dose of nivolumab. If 1 of 3 patients has a DLT at DL1, we will add 3 patients at a dose of 50 mg. If ≤1 of 6 patients has a DLT at 50mg of BMS-986205, 3 patients will be treated at 100mg. Maximum tolerated dose will be defined as ≤1 of 6 patients at DL1 or DL2 experiencing a DLT. After identifying the MTD, the phase II expansion phase will be initiated with 3 additional patients at the MTD. A maximum total of 17 patients at MTD will be treated on trial including 6 patients treated during phase I portion at MTD. An interim efficacy analysis will be done after 9 patients (including the 6 patients in phase I portion) have been treated. If at least 1 patient out of the 9 initial patients treated at MTD achieves a response, we will accrue 8 more patients at the MTD. If at least 3 of the 17 patients treated at MTD achieve a response, we will deem the treatment worthy of further study, provided the safety profile is acceptable. The Simon optimal two stage design described above provides 80% power to detect the difference between an acceptable response rate of 25% vs. an unacceptable rate of 5% at the 0.05 level (1-sided). The estimated time to accrue 20-23 patients is 18 months, at approximately 1.1 patients per month. The ORR will be estimated as the proportion of participants who experience an objective response, along with its exact 95% confidence

	interval; the disease control rate will be analyzed similarly. DOR, PFS, and OS will be analyzed using Kaplan-Meier methods; medians and 95% confidence intervals will be computed. DLTs, adverse events, serious adverse events, and clinical laboratory values outside normal limits will be listed for each patient and summarized by body system and dose level in frequency tables.
Estimated Accrual Period: **Estimated Duration of Participation:** **Estimated Study Duration:**	24 months 30 months to complete study assessments 36 months
Correlatives:	**Tissue** - Multi-plex IHC/IF for PD-L1, IDO, CD3, FOXP3 and other markers of interest. Immune related gene expression analysis. Flow cytometry of fresh tumor core to analyze TME with focus on T-cell and dendritic cell activation/functional markers. TCR deep sequencing to evaluate T cell clonal diversity and proliferation. **PBMCs** - Flow cytometry to determine peripheral immune phenotype. Ex-vivo analysis of PD-1+ T-cells for proliferative and cytokine production activity and metabolic analysis using the Seahorse platform. TCR deep sequencing to evaluate T cell clonal diversity and proliferation. **Plasma** - Cytokine analysis by Luminex. Tryptophan and Kynurenine levels. **Stool** – Microbiome Analysis

STUDY SCHEMA

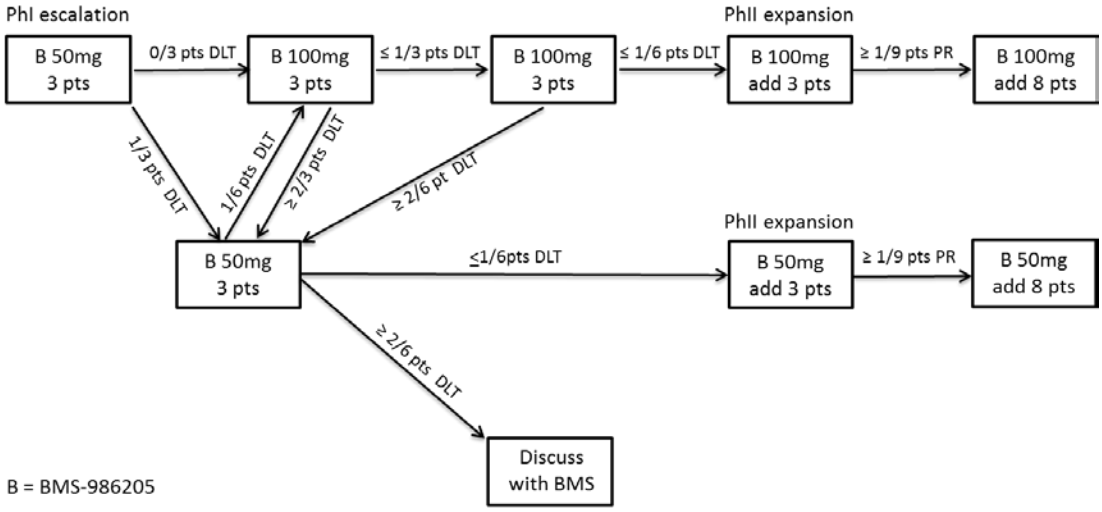
General Enrollment Criteria

- Advanced HCC with Child Pugh A
- Age ≥18
- At least one candidate lesion to biopsy
- At least one candidate target lesion for response per RECIST 1.1
- Adequate hematologic and end organ function
- No active autoimmune disease
- No more than 1 prior systemic therapy



Phase I Dose Finding
3+3 Design: (3-6 patients per dose level)
Dose level 1: 50 mg PO daily of BMS-986205 + 240mg IV of nivolumab
Dose level 2: 100 mg PO daily of BMS-986205 + 240mg IV of nivolumab

Phase II Dose Expansion (Simon Two-stage) Design
17 patients including those from Phase 1 at MTD
P0=0.05, p1=0.20, r1=1, n1=16, rTot=3, nTot=30, α=0.05, power=0.8



LIST OF ABBREVIATIONS AND TERMS

Abbreviation/Term	Definition
°C	degrees Celsius
μM	micromolar
AE	adverse event
ALP	alkaline phosphatase
ANC	absolute neutrophil count
ALT	alanine transaminase (SGPT)
AST	aspartate transaminase (SGOT)
BCG	Bacillus Calmette–Guérin
BN	BMS-986205 and nivolumab
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
DCR	disease control rate
Dbil	direct bilirubin
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EBV	Epstein-Barr Virus
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
HCV	Hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IDO	indoleamine-2,3-dioxygenase
IEC	independent ethics committee
IND	Investigational New Drug
INR	international normalized ratio
irAE	immune related AEs
IRB	institutional review board
IV	intravenous
LDH	lactate dehydrogenase
MAOI	Monoamine oxidase inhibitor
m^3	cubic meters

Abbreviation/Term	Definition
mg	milligram
Min	minute
mL	milliliter
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OCR	Office of Clinical Research
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand
PFS	progression-free survival
PI	principal investigator
PR	partial response
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended phase II dose
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase
SRC	Scientific Review Committee
SSRI	serotonin reuptake inhibitors
Tbil	total bilirubin
TSH	Thyroid-Stimulating Hormone
UCD	University of California, Davis (UC Davis)
UCDCCC	UC Davis Comprehensive Cancer Center
ULN	upper limit of normal
US	United States

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1.0 INTRODUCTION

1.1 Cancer Immunotherapy

The allure of cancer immunotherapy as a magic bullet against cancer has intrigued researchers for over a century. The rationale underlying anti-cancer immunotherapy stems from the concept of immune surveillance first attributed to Ehrlich and colleagues over a century ago[1]. It was founded in the idea that tissue rejection is actually a manifestation of an immune surveillance mechanism that guards against spontaneous arising tumors. If such a mechanism does exist then it stands to reason that it can be re-invigorated and harnessed to battle malignancy in cancer patients. This idea, in its simplest form, is particularly attractive given that the immune system should be able to identify and specifically eradicate malignant cells based on the expression of abnormal antigens not expressed or present in normal tissues [2]. On a cellular level antigen presenting cells (APCs), such as dendritic cells, phagocytize fragments of dying cancer cells and present them on their cell surface. CD8+ T cells can recognize these abnormal antigens and become activated to kill cells expressing that antigen. CD4+ T cells can either help this process by expressing ligands and cytokines which help activate and sustain the APCs or they can become immunosuppressive regulatory T cells (Tregs) which express FOXP3 (forkhead box P3) and inhibit CD8+ T cells. In reality this is a gross oversimplification and the true complexity of the interactions between the host immune system and cancer are not fully understood but many cell types and factors are involved.

1.2 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide and US and incidence of HCC is rising and estimated 782,000 new cases per year worldwide[3]. Surgery is the mainstay of therapy for early stage disease but due to medical comorbidities or advanced disease many patients are not candidates for surgical resection or liver-directed therapies and effective and tolerable systemic treatment options are desperately needed[4]. The only first line systemic therapy is sorafenib, a multi-targeted tyrosine kinase inhibitor (TKI) with moderate overall survival (OS) of 3 months over supportive care with commonly intolerable side effects[5]. Regorafenib, another multi-targeted TKI was recently approved in the second-line setting with median OS 10.6 months compared to 7.8 months with placebo[6]. Nivolumab has recently been approved in patients with unresectable HCC, refractory to sorafenib, as second line therapy with the objective response rate of 20%[7].

1.3 BMS-986205

BMS-986205 (FLX287 or F-1287) potently and selectively inhibits human IDO1 with no activity against another tryptophan degradation enzyme, tryptophan 2,3-dioxygenase (TDO). 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 involved in combating infections or play a role 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 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 many 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 transcript is increased in patients with advanced melanoma and metastatic renal cell carcinoma (RCC) 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.

A series of studies have demonstrated the role of IDO in the immune escape of multiple types of tumors, specifically correlating with reduced intratumoral T cell infiltration, disease progression, and shorter survival[19]. With regards to HCC specifically, increased expression and activation of IDO has been associated with both the early and late phases of liver carcinogenesis. Moreover, HCC tumors with IDO overexpression have been associated with poor prognosis[20, 21] . Notably, persistent IDO expression within the liver microenvironment may play a critical role in declining HBV and HCV specific T-cell response [22, 23].

Of the studies in humans in which BMS-986205 has been administered as of 15-Nov-2017, Study CA017-003, Study CA017-048, and Study CA018-001 include efficacy endpoints. No preliminary efficacy data are currently available from Study CA017-048 or Study CA018-001. Preliminary efficacy data are available from a 13-Oct-2017 data cutoff date from select cohorts from Part 2 (Cohort Expansion) of Study CA017-003, in which BMS-986205 was administered with nivolumab in subjects with advanced malignancies. Objective responses have been observed in subjects with bladder, cervical, SCCHN, pancreatic, DLBCL, melanoma, NSCLC,

renal, triplet negative breast, and endometrial cancers. Mature but preliminary aggregate data have been presented for bladder and cervical cancers below (please see IB for more details)

In a cohort of 25 previously treated advanced bladder cancer subjects, 8 partial responses (7 confirmed) led to an objective response rate of 32.0%, with a disease control rate of 44.0%. The overall response rate (ORR) was 40% for participants with 1 prior therapy and 20% for participants with 2 or more prior therapies. The ORR was 46.2% for PD-L1 positive participants (tumor PD-L1 expression 1%), and 22.2% for PD-L1 negative participants (tumor PD-L1 expression < 1%).

In a cohort of 22 previously treated advanced cervical cancer subjects, 3 partial responses (1 confirmed) led to an objective response rate of 13.6%, with a disease control rate of 63.6%. The ORR was 18.2% for participants with 1 prior therapy and 29.1% for participants with 2 or more prior therapies. The ORR was 25.0% for PD-L1 positive participants (tumor PD-L1 expression 1%), and 0% for PD-L1 negative participants (tumor PD-L1 expression < 1%).

1.3.1 Safety Profile of 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.

The selection of the RP2D for BMS-986205 in combination with nivolumab is primarily based on available data from the ongoing Phase 1/2, first-in-human Study CA017-003. 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 subjects receiving the 100 mg QD dose. Furthermore, treatment-related Grade 3 anemia was reported in 0.3% of subjects receiving the 100 mg dose versus 4.4% of subjects 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). Lastly, a single case of methemoglobin elevation over 10% occurred in a subject 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 subjects treated with both doses when combined with nivolumab.

In summary, BMS-986205 at 100 mg QD achieves trough plasma concentrations that exceed the human whole blood IC90, produces substantial serum kynurenine reductions similar to those observed at higher dose levels, demonstrates target engagement in the tumor microenvironment, appears (in combination with nivolumab) to have a more favorable tolerability profile compared to higher doses and overall similar to that of nivolumab monotherapy, and demonstrates clinical activity in combination with nivolumab[24]. Based on this evidence, BMS-986205 100 mg QD is the recommended phase 2 Dose (RP2D) in combination with nivolumab. For this study, we have chosen 50 mg QD as the starting dose level to be given with nivolumab 240mg to observe hepatotoxicity in an HCC population. BMS-986205 will be escalated to 100 mg QD with nivolumab when dose 1 level is shown to be tolerated.

1.3.2 BMS-986205 Dose Justification

All participants enrolled will receive BMS-986205 50 mg or 100 mg PO QD according to each cohort in combination with nivolumab 240mg Q2W. 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.

1.3.3 Justification for Administration of BMS-986205 with Food

Effect of food on the PK of BMS-986205 was evaluated in healthy subjects in Study CA017 053. Preliminary PK data indicate that following a single 100 mg dose, BMS-986205 geometric mean Cmax and AUC(0-168h) are 114% and 52.8% higher, respectively, when dosed after a high fat meal compared to under fasting condition. BMS-986205 Cmax and AUC(0-168h) are 96.5% and 42.6% higher respectively, when dosed after a light meal compared to under fasting condition. Tmax ranged from 2 hours to 4 hours when dosing fasted and from 2 hours to 5 hours when dosed after a meal. PK variabilities are generally smaller when dosed after a meal. The terminal half-life averaged from 52 hours to 62 hours across the treatment groups. 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 substudy 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.

Based on these results, the BMS-986205 is recommended to be taken after a meal in the current study.

1.4 Nivolumab

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) 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.

The pharmacokinetics (PK), clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, clear-cell renal cell carcinoma (RCC), classical Hodgkin Lymphoma (cHL), urothelial carcinoma (UC), squamous cell carcinoma of the head and neck (SCCHN), in addition to other tumor types [25]. Nivolumab monotherapy is approved in multiple regions, including the US and EU, for unresectable or metastatic melanoma, previously treated metastatic NSCLC, previously treated advanced RCC, previously treated relapsed or refractory cHL, and previously treated advanced or metastatic UC, previously treated recurrent or metastatic SCCHN and previously treated HCC in the US. In addition, nivolumab has been approved for use in combination with ipilimumab for unresectable

melanoma in multiple countries, including the US and EU. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies for the treatment of several types of cancer. Single dose nivolumab monotherapy is also being investigated for the treatment of sepsis.

The HCC tumor microenvironment has been shown to have an abundance of immunosuppressive factors and the correlation between the presence of tumor infiltrating lymphocytes and outcomes present an opportunity for immunotherapeutic approaches in this disease setting[26]. PDL-1 overexpression is shown to have poor prognosis in HCC. The safety and efficacy of nivolumab were evaluated in a phase 1/2 dose escalation and expansion trial in patients with advanced HCC among whom a majority of patients had progressed on prior sorafenib [7]. In that study, 48 patients participated in a dose escalation phase (which allowed Child-Pugh score (CP) of 7 or less) and 214 patients were treated in the dose expansion phase limited to patients with CP 6 or less. The objective response rate was 15% in dose-escalation phase and 20% in dose expansion phase. Interestingly, patients with no prior therapy experienced better objective response of 23% and 9 month overall survival of 82%. Transient reduction in HCV RNA was observed in some patients and no viral reactivation was reported in the study.

Any grade and grade 3/4 treatment-related adverse were reported in sixteen (7%) and nine (4%) patients respectively. Grade 3/4 adverse events were observed as AST increase in nine (4%), ALT increase in five (2%), diarrhea in three (1%) and fatigue in three (1%).

1.4.1 Justification for Nivolumab Dose 480 mg Q4W

The US FDA has recently approved nivolumab 480 mg Q4W for the indications of adjuvant melanoma, unresectable and metastatic melanoma, metastatic NSCLC, advanced RCC, cHL, head & neck cancer, and urothelial carcinoma and hepatic carcinoma (HCC). The EMA has recently approved nivolumab 480 mg Q4W for the indications of advanced melanoma and RCC. Data in support of the 480 mg dosing regimen for these indications included extensive clinical pharmacology analyses, population pharmacokinetic and safety analyses, using data from studies in multiple tumor types 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 (Cavgss) 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 (Cminss) 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 (eg, 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.

1.4.2 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. The US FDA has recently approved nivolumab 30-minute infusion with both 240 mg Q2W and 480 mg Q4W. 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. 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.

1.5 Combination of BMS-986205 and Nivolumab

Despite the overall impressive results of immune checkpoint inhibitors as therapeutic anti-cancer agents, clinical efficacy of PD-(L)1 pathway inhibition as a monotherapy has been limited to subsets of patients, with response rates of 20% or less in most tumor types. Additionally, many responsive patients eventually develop resistance to monotherapy, making combinatorial strategies attractive.

Preclinical and clinical data suggest that IDO may be a pathway contributing to primary and acquired resistance of PD-(L)1 inhibitors. Both pathways are up-regulated by interferon signaling suggesting that many PD-L1 positive tumors may also up-regulate IDO. Our data from clinical sarcoma samples confirms this (Figure 1) and others have demonstrated this in NSCLC[27]. Additionally, preclinical data and preliminary clinical reports have shown synergy of IDO inhibitors and immune checkpoint blockade[19]. Inhibition of IDO inhibition in combination with Ipilimumab in patients with advanced melanoma suggested potential improved overall response rates and PFS in immunotherapy-naïve patients compared to monotherapy (NCT01604889). Importantly, early reports also suggest the relative safety of combining IDO and checkpoint inhibition. A number of clinical trials are currently underway testing combinatorial strategies of IDO inhibitors plus CTLA-4 or PD-(L)1 inhibition in various tumors with promising results in preliminary reports.

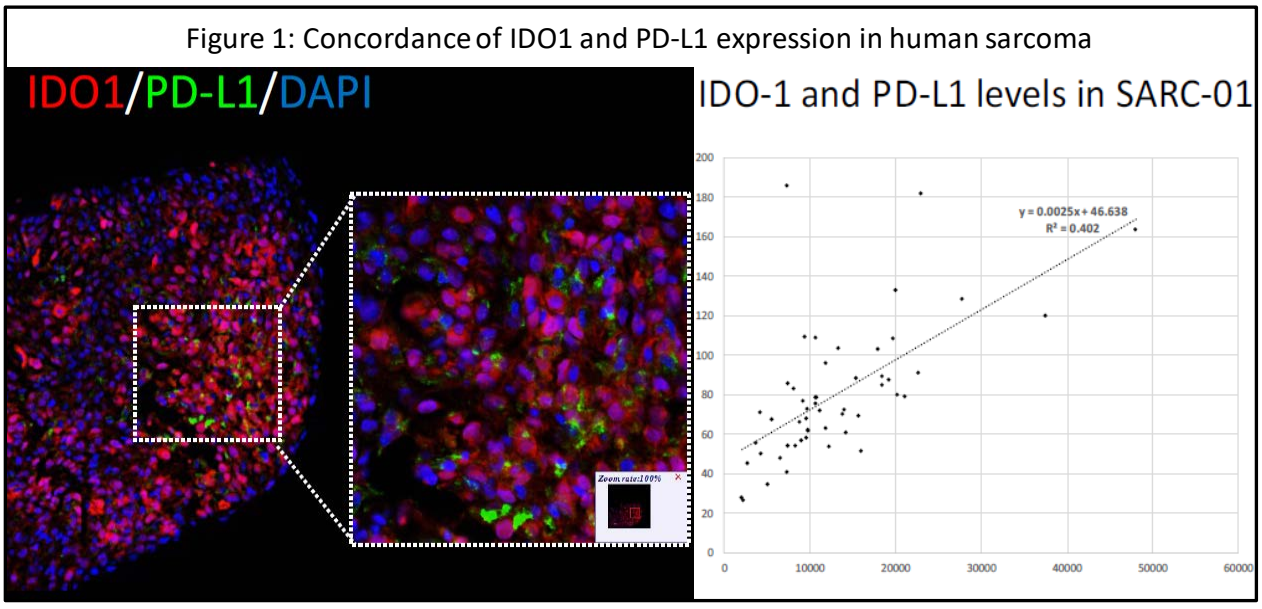
Phase I/II study of the ECHO-202/KEYNOTE-037 trial showed that combination of IDO1 inhibitor (epacadostat) and pembrolizumab produced ORR of 56% and DCR of 71% in untreated melanoma patient. The median PFS was 12.4 months for all protocol patients. Response occurred in all subgroups including BRAF positive or negative tumor, normal vs elevated LDH, the

presence or absence of liver metastases. The most common adverse events were rash (46%), fatigue (43%), pruritus (29%), arthralgia (17%), diarrhea (15%), nausea (12%), increased AST (12%), increased lipase (11%), ALT increased (11%), and liver enzyme elevation (11-12%). However, only 4 patients (6%) discontinued the study due to adverse event[28].

In particular, the CA017-003 Phase 1/2a study reported that the maximum tolerated dose of BMS-986205 was 200 mg when combined with nivolumab, [24]. Anti-tumor activity was found during the dose expansion phase of BMS-986205 100mg among a group of heavily pre-treated bladder (25 patients) and cervical cancer patients (22 patients). In the bladder group, the objective response rate (ORR) was 32 percent (8/ 25 patients) and the disease control rate (DCR) was 44 percent (11/25 patients). In the cervical cancer cohort, ORR was 14 percent (3/ 22 patients) and DCR was 64 percent (14/22 patients). Patients with more than 1% of PD-L1 had ORR of 46% and 25% in bladder and cervical cancer respectively. The combination regimen was well tolerated with only 4 patients (1.4%) discontinuing from the study due to the drug toxicity. The most commonly reported adverse effect of any grade were fatigue (13.6%), nausea (11.5%), and decreased appetite (10.5%).

Given the success of immune checkpoint blockade in HCC, the existing data for synergistic effects with IDO inhibition and the known expression of IDO in HCC, we propose a phase I/IIa evaluating the safety and demonstrating the efficacy of BMS-986205 + nivolumab in unresectable HCC.

Figure 1. Concordance of IDO1 and PD-L1 Expression in Human Sarcoma



1.6 Summary of Available Nonclinical and Clinical Data

Refer to the investigator's brochures for nivolumab and BMS-986205 for preclinical and clinical study data.

1.7 Correlative Studies

One of the major shortcomings of immunotherapy trials has been the lack of in depth correlative studies to help identify the mechanism of action, identify biomarkers of response, and explain the mechanisms governing treatment response or failure. To address this we plan to perform in depth immunological analysis of patient blood and tumor samples. This study incorporates serial tissues samples pre-treatment, during therapy and at progression (optional). The design of this study allows us to compare immune mechanisms pre-, on- to post-therapy.

Tumor PD-L1 expression has been linked to response rates of PD-1 checkpoint blockade [29]. Additionally, little is known about how the pattern of expression (i.e., tumor cells vs. infiltrating immune cells) affects response. Data presented at ASCO and SITC meetings indicate that durvalumab monotherapy response rates in NSCLC are 27% in PD-L1 positive tumors and 5% in PD-L1 negative tumors. TILs and a T-cell inflamed phenotype have been linked with response to CTLA-4 checkpoint blockade in melanoma [30, 31]. Exclusion of T-cells in the tumor microenvironment has also been linked with lack of response to checkpoint inhibition [32] with down-regulation of CCL4 mediated dendritic cell recruitment as one potential mechanism [32]. Whether PD-L1 expression or the presence of TILs is important for response to IDO inhibitors is unknown.

Mutational burden and antigenic load are thought to represent a surrogate for tumor antigenicity and have been linked with response to checkpoint blockade in NSCLC [34]. Whether mutational load is true indicator of tumor antigenicity and how this correlates with response to IDO inhibitors is unknown. To address this we plan to perform in depth immunological analysis of patient blood and tumor samples. We will evaluate immunologic changes systemically and in the tumor and tumor microenvironment within patient's pre to post therapy and across the cohort of patients to identify predictive biomarkers and elucidate the mechanistic immunologic effects of therapy.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

1. To obtain the safety and tolerability of BMS-986205 in combination with nivolumab in unresectable / metastatic HCC in the first or second line setting using CTCAE V5.0 criteria.
2. To determine efficacy as defined by objective response rate (ORR) of BMS-986205 in combination with nivolumab in unresectable / metastatic HCC in the first or second line setting using RECIST (version 1.1).

2.2 Secondary Objectives (Phase II)

1. To determine disease control rate (DCR), duration of response (DOR), progression free survival (PFS), and overall survival (OS) by RECIST 1.1 and ORR using immune RECIST (iRECIST) of BMS-986205 in combination with Nivolumab in unresectable HCC.
2. To further evaluate safety of BMS-986205 in combination with Nivolumab in unresectable HCC.

2.3 Correlative Objectives

1. To analyze serial blood samples for serum cytokine and tryptophan / kynurenine levels, and to quantify the number, function, and gene expression of peripheral blood mononuclear cells (PBMCs).
2. To evaluate serial tumor tissue biopsies for tumor infiltrating immune cell subsets, expression of immune regulatory proteins including IDO1 and PD-L1, gene expression signatures, and mutational load.
3. To evaluate pre-treatment stool samples for microbiome signatures
4. To explore potential biomarkers

3.0 STUDY DESIGN

This is a phase I/II study using a Simon optimal two stage design for efficacy of BMS-986205 in combination with nivolumab as illustrated in the schema. For the phase I portion the primary endpoint is to determine safety profile of BMS-986205 in two dose levels with nivolumab in unresectable HCC using CTCAE V5.0 criteria. For the phase II portion the primary endpoints are safety and toxicity and the objective response rate using the using RECIST criteria. Exploratory endpoints include disease control rate (DCR), duration of response (DOR), ORR using iRECIST, progression free survival (PFS), overall survival (OS), and correlative studies.

For phase I dose escalation, up to two dose levels of BMS-986205 will be evaluated: 50 mg daily and 100mg daily. These two dose levels were selected based on the clinical data described above. We have chosen 50 mg daily as the starting dose level given the existing safety data for this dose and the safe use of this dose in use with other immunotherapy combinations. The dose of BMS-986205 will be escalated to 100 mg daily if 0 of the first 3 patients experience a dose limiting toxicity (DLT) at 50 mg BMS-986205. Three additional patients will be added to receive 50 mg BMS-986205 if 1 of the first 3 patients experiences a DLT. The dose of BMS-986205 will be escalated to 100 mg daily if no more than one of six patients experience a DLT at 50 mg BMS-986205.The expansion phase will be conducted after MTD is reached, which will be defined as no more than one of six patients develops a DLT at 50 mg or 100 mg of BMS-986205 daily with nivolumab. If BMS-986205 50mg daily is not tolerated the study will be halted and modified after discussion with the principal investigator (PI) and BMS. The 6 patients at the maximum tolerated dose in the phase I portion treated at MTD will count towards the 17 patients needed in the phase II expansion cohort. The phase II cohort will be run as a Simon two-stage design to allow for early trial stoppage for futility. We designate an ORR as defined by RECIST criteria of 5% as not worthy of further investigation and of 25% as worthy of further investigation. In the first stage 9 patients will be accrued and at least 1 response must be observed within 6 months of treatment (or longer at PI discretion) to continue the trial (n1=9, r1=0) (see study schema). BMS-986205 will be administered orally daily and nivolumab will be administered intravenously until disease progression.

Toxicity will be assessed using the NCI CTCAE, version 5.0 unless otherwise specified. A DLT is defined (See section 5.6) as any of the following that occur during the 56-day DLT period.

If subjects cannot receive 75% of intended dose of BMS-986205 for reasons other than toxicity and did not experience a DLT, they will be replaced for DLT assessment. Subjects treated at MTD will be monitored for chronic toxicity for 3 months to determine a recommended Phase 2 dose (RP2D).

4.0 SUBJECT SELECTION

4.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry.

1. Men and women ≥18 years of age at the time of study entry.
2. Willing and able to provide written informed consent for the trial.
3. Life expectancy >12 weeks.
4. Histologically or imaging confirmed hepatocellular carcinoma (mixed hepatocellular/cholangiocarcinoma or fibrolamellar subtypes are excluded).
5. Have disease that is not amenable for curative treatment approach.
6. Have measurable disease based on RECIST v1.1.
7. ≥1 liver lesions accessible for core biopsy that was either not previously treated by liver-directed therapy or progressed following liver-directed therapy.
8. Child-Pugh score of A.
9. ECOG performance status of 0 or 1.
10. Adequate hematology parameters:
    a. Absolute neutrophil count (ANC) ≥ 1000 cell/mm^3
    b. Platelet count ≥ 50,000/mm^3
    c. Hemoglobin (Hgb) ≥ 8 g/dL
11. Acceptable blood chemistry levels:
    a. AST/SGOT, ALT/SGPT ≤ 5 x upper limit of normal (ULN)
    b. Total bilirubin ≤ 2 ULN
    c. Creatinine ≤ 2 x ULN
12. Subjects with active hepatitis B virus (Hep B) are allowed if antiviral therapy for hepatitis B has been given for >8 weeks and viral load is <100 IU/ml prior to first dose of trial treatment. Subjects with untreated hepatitis C virus (HCV) are allowed.
13. Willingness to undergo mandatory pre-treatment biopsy (unless there is adequate archival tumor specimen available) and mandatory on-treatment biopsy.

14. Criterion modified per Amendment v4.0.

    a. 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 24 hr prior to planned treatment initiation.

    b. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception (Appendix 9) for the duration of treatment with study treatment(s) plus 5 months post-treatment completion (i.e., 30 days [duration of ovulatory cycle] plus the time required for nivolumab to undergo approximately 5 half-lives).

    c. 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 (i.e., 90 days [duration of sperm turnover] plus the time required for nivolumab to undergo approximately 5 half-lives). In addition, male participants must be willing to refrain from sperm donation during this time.

    d. Males who are sexually active with WOCBP must agree to use a latex or synthetic condom during sexual activity (see Appendix 4) 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.

    e. 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 not considered highly effective methods of contraception for participants receiving BMS-986205 in this study who are WOCBP.

15. Ability to adhere to the study visit schedule and other protocol requirements.

16. Participants must be able to swallow pills intact.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

1. Received more than 1 prior systemic HCC-related therapy or currently receiving HCC-related systemic treatment or participating in a clinical trial and receiving study therapy.

2. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

3. Known diagnosis of immunodeficiency or active autoimmune disease or requiring systemic steroid equivalent of prednisone ≥ 10 mg/day or any immunosuppressive therapies ≤7 days of before the first dose of the study.

4. Active bacterial, viral (except Hepatitis B and C - see Inclusion Criterion 12), or fungal infection(s) requiring systemic therapy, defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, anti-viral therapy, anti-fungal therapy, and/or other treatment.

5. Active pneumonitis or history of interstitial lung disease (ILD) / pneumonitis requiring steroids.

6. Clinically significant ascites.

7. Hepatic encephalopathy.

8. Any significant medical condition including additional malignancies, laboratory abnormalities, or psychiatric illness that would prevent the subject from participating and adhering to study related procedures.

9. Live attenuated vaccine ≤30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

10. Use of strong inhibitor / inducer of CYP3A4 or CYP1A2.

11. Known history of surgery or medical condition that may affect drug absorption, per investigator discretion.

12. Participants with a history of G6PD deficiency or other congenital or autoimmune hemolytic disorders. All participants will be screened for G6PD deficiency prior to

enrollment using quantitative or qualitative G6PD assay results to suggest underlying G6PD deficiency.

13. 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 enrollment using blood methemoglobin > ULN, assessed in an arterial or venous blood sample or by co oximetry.
14. Subjects with screening QTc interval > 480 ms.
15. Liver directed therapy ≤4 weeks before the first dose of study.
16. History of esophageal or gastric variceal bleeding within 3 months of study enrollment.
17. Treatment with botanical preparations (e.g., herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to enrollment.
18. Prior history of serotonin syndrome.
19. Prior treatment with BMS-986205 or any other IDO1 inhibitors.
20. Women who are breastfeeding.
21. History or presence of hypersensitivity or idiosyncratic reaction to methylene blue.
22. History of allergy or hypersensitivity to any study treatment components, specifically to that of BMS-986205.
23. Participants who have had major surgery requiring general anesthesia or significant trauma who have not recovered per physician determination for at least 14 days prior to enrollment.
24. Participants who have had major surgery requiring general anesthesia or significant trauma who have not recovered per physician determination for at least 14 days prior to enrollment.
25. Participants with uncontrolled adrenal insufficiency.

4.3 Inclusion of Women, Minorities, and Other Underrepresented Populations

Recruitment is open to all minorities and both genders. Although distributions may vary by disease type, our recruitment procedures have been developed to enroll patients who are representative of the respective target population.

5.0 DOSAGE AND ADMINISTRATION

5.1 Study Drug Administration

BMS-986205 is administered orally once day; dosing will vary 50 mg or 100 mg according to each cohort (see schema). BMS-986205 is recommended to be taken within 30 minutes after a meal. Nivolumab 240 mg is administered intravenously every 14 days (1 cycle = 14 days).

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.

5.2 Dose Modification and Management of Toxicity

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Sections 4) and close monitoring (as indicated below and in the study calendar). Refer to section 5.5.

5.3 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies as well as the nonclinical/clinical data from other studies were taken into account.

5.4 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE V5.0. Patients will be assessed for safety (including laboratory values) according to the Study Calendar. Patients will be followed for protocol-related toxicity for 100 days following the last dose of study treatment or until receipt of another anticancer therapy, whichever comes first. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Study Calendar for the list and timing of study assessments). **All serious adverse events (SAEs) will be reported in an expedited fashion**. In addition, the investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment–related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

5.5 Management of Adverse Events from Immunotherapy

5.5.1 Dose Delay BMS-986205 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
    - Hepatic events should be managed as detailed in Section 5.5.3
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

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 (e.g., administrative issues, holidays, etc.), BMS-986205 dosing should continue uninterrupted

If nivolumab dosing is delayed for reasons other than study drug toxicity (e.g., 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.

Tumor assessments for all subjects should continue as per protocol even if study drug dosing is delayed.

5.5.2 Dosage Modification

5.5.2.1 Nivolumab Dose Modifications

No dose modifications for Nivolumab are permitted

5.5.2.2 BMS-986205 Dose Modifications

A dose reduction of BMS-986205 is defined as a change from a 100 mg QD tablet to a 50 mg QD tablet.

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 $\geq$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 interruption 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 PI. For an AE requiring dose modification, BMS-986205 should be interrupted to allow improvement of the AE, even if the AE does not otherwise meet criteria for dose delay.

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

Only one dose reduction is permitted. The participant must discontinue study treatments if a subsequent dose reduction of BMS-986205 is required.

5.5.3 Protocol-Specific Recommendation for Management of Hepatic Events

Subjects with advanced HCC generally have underlying cirrhosis with decreased hepatic function. They may also have a concomitant chronic viral infection. For this study, the upper limits for inclusion were therefore adjusted to account for baseline liver dysfunction. Subjects with AST or ALT elevations within the CTCAE Grade 2 range are allowed to enroll in the study. This requires a protocol-specific approach for the management of hepatic events outlined as follows:

- Both BMS-986205 and nivolumab should be delayed for
  - Grade ≥2 toxicity in subjects with baseline AST or ALT within normal limit,
  - Grade ≥3 toxicity in subjects with baseline AST or ALT within grade 1 toxicity range
  - Drug related increase in AST or ALT at 2x baseline value or when AST or ALT is 8x ULN (whichever is lower) in subjects with baseline AST or ALT in grade 2 toxicity range.
- If AST or ALT levels do not improve with a dose delay of 3 - 5 days or if the levels worsen, initiate steroid therapy at 0.5 - 2 mg/kg/day methylprednisolone or oral equivalent.
- For ALT or AST levels > 8x ULN, initiate steroid therapy promptly at 1 - 2 mg/kg/day methylprednisolone or oral equivalent
- For all subjects initiating steroids, consult the PI within 24 hours after initiation of steroids. Gastroenterology consult is recommended.
- If AST or ALT levels do not improve within 3- 5 days or the levels worsen after the start of steroid therapy, discuss with the PI the possibility of adding mycophenolate mofetil at 1 g BID.
- Tapering of steroids can start once AST or ALT levels have declined by one CTCAE grade. Taper steroids slowly over no less than 1 month.

As outlined in above, nivolumab and BMS-986205 therapy may resume when AST or ALT have returned to patient's baseline unless the criteria for permanent discontinuation are reached. Subjects who require delay of therapy should be re-evaluated weekly or more frequently if clinically indicated. It is recommended to monitor elevations in AST or ALT approximately every 3-5 days until levels peak or begin to decline. Both therapies can be resumed when re-treatment criteria are met. The PI must be consulted prior to resuming nivolumab for all subjects who required steroid intervention. Tumor assessments for all subjects should continue as per protocol even if study drug dosing is delayed.

- For participants with baseline up to 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.
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT >10 x ULN for >2 weeks
  - AST or ALT >15 x ULN irrespective of duration
  - T. Bilirubin >8 x ULN irrespective of duration for subjects with elevated bilirubin at study entry or >5 x ULN for those with normal T bilirubin at entry
- Subjects with AST, ALT, or bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.

5.5.4 Management of Subjects Exhibiting Serotonin Syndrome (SS)

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.

This syndrome has been most closely associated with use of MAOIs, Demerol®, or linezolid; all of these agents are prohibited during the study. Selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. The following procedures will be implemented if subjects exhibit the signs/symptoms of SS described in Table 1, including tremor; hyperreflexia; and spontaneous, ocular, or inducible clonus, together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately discontinue BMS-986205 administration. Administration of other study drugs may continue.
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (e.g., IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists, such as cyproheptadine).

- If subject chooses to withdraw from the study or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.

Table 1. Signs and Symptoms of Serotonin Syndrome

Tremor and hyperreflexia
Spontaneous clonus
Muscle rigidity, temperature > 38°C (100.4°F), and either ocular clonus or inducible clonus
Ocular clonus and either agitation or diaphoresis
Inducible clonus and either agitation or diaphoresis

5.5.5 Treatment of Methemoglobinemia Associated with BMS-986205

5.5.5.1 Detection

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, each treatment cycle, or more frequently if clinically indicated based on symptoms.

5.5.5.2 Treatment

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

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 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.

5.5.6 Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- 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 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.

For participants who have BMS-986205/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.

5.6 Definition of Dose-Limiting Toxicity

Dose limiting toxicities are defined as any of the items listed below which occur during the first 6 weeks.

- Any Grade 2 drug-related uveitis or eye pain that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
- Any Grade 2 drug-related pneumonitis or interstitial lung disease that does not respond to dose delay and systemic steroids in 14 days (radiologic changes may take longer to resolve) or Grade 2 myocarditis of any duration.

- Any Grade 3 or greater nondermatologic, nonhepatic, nonhematologic toxicity will be considered a DLT with the following specific EXCEPTIONS:
    - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
    - Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours and either resolves spontaneously or responds to conventional medical intervention
    - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
    - Isolated Grade 3 fever not associated with hemodynamic compromise (e.g., hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
    - Grade 3 endocrinopathy that is well-controlled by hormone replacement
    - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor)
    - Grade 3 fatigue
    - Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours. Any Grade 4 drug-related adverse event including laboratory abnormalities except Grade 4 leukopenia or neutropenia lasting < 14 days.
- Grade 4 methemoglobin levels ≥ 15 % and Grade ≥ 3 hemolysis (i.e., requiring transfusion or medical intervention such as steroids)
- Any of the following drug-related hepatic function laboratory abnormalities:
    - AST or ALT >10x ULN for > 2 weeks
    - AST or ALT > 15 x ULN irrespective of duration
    - T. Bilirubin >5 x ULN irrespective of duration

If subjects cannot receive 75% of intended dose of BMS-986205 for reasons other than toxicity and did not experience a DLT, they will be replaced for DLT assessment. Subjects treated at MTD will be monitored for chronic toxicity for 3 months to determine a recommended Phase 2 dose (RP2D).

5.7 Treatment Compliance

Subjects will be encouraged to comply with all study-related medications by the Investigator, pharmacist, and research coordinator. Subjects will be given a pill diary to track medication that has been taken. Subjects will bring all bottles of unopened or unused study drug with them to each visit. Unused drug tablets will be counted for compliance and recorded. Treatment compliance of nivolumab will be documented in the electronic medical record.

6.0 TREATMENT DURATION

Patients will complete therapy unless one of the following criteria applies:

- Confirmed Disease progression per iRECIST
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events
- Patient withdrawal from study (patient choice)
- Pregnancy
- Failure of patient to adhere to study requirements
- Physician Discretion
- Study termination
- Patient receives alternative treatment

6.1 Discontinuation Criteria

6.1.1 Discontinuation Due to Disease Progression

Immunotherapeutic agents such as BMS-986205 and nivolumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Immune RECIST will be used for assessment of tumor response for the purposes of managing subjects on study treatment and decision-making for discontinuation of study therapy due to disease progression. PD should be confirmed no earlier than 4 weeks later according to the criteria outlined in Table 2. Subjects who are deemed clinically unstable or who have biopsy proven new metastatic lesions are not required to have repeat imaging for confirmation. This decision will be based on the Investigator's clinical judgment of a subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. At a minimum, subjects must meet the below criteria for continued treatment on study after disease progression is identified at a tumor assessment.

When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the first evidence of disease progression is at the Investigator's discretion based on the clinical status of the subject.

Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- No decline in ECOG performance status.
- Absence of new or worsening symptoms.
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention.

6.1.2 Discontinuation from Study Treatment

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required).
- Additional protocol-specified reasons for discontinuation.

In the case of pregnancy, the investigator must immediately notify the PI of this event. In the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please notify the PI within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the PI must occur.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of BMS-986205. Although there is overlap among the discontinuation

criteria, if discontinuation criteria are met for BMS-986205 but not for nivolumab, treatment with nivolumab may continue if BMS-986205 is discontinued.

If a participant in any of the nivolumab/BMS-986205 combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and BMS-986205 and be taken off the treatment phase of the study.

6.1.3 Discontinuation of BMS-986205

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

- Any event requiring discontinuation of nivolumab as in Section 6.1.2
- Any event requiring more than 1 dose reduction of BMS-986205 (see Section 5.5.2)
- 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 due to toxicity attributable to BMS-986205 and not nivolumab (e.g., methemoglobin, hemolysis, or QTc >500 msec) will result in the discontinuation of BMS-986205 only, and participants may continue treatment with nivolumab after discussion with the PI.
- Any occurrence of serotonin syndrome

6.1.4 BMS-986205 and Nivolumab Discontinuation Due to AEs

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

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
- Any event requiring more than 1 dose reduction of BMS-986205
- 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:
  - Hepatic events should be managed as detailed in Section 5.6.4
  - 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

* 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.

- 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 PI.
- 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 > 10 weeks 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 PI.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the PI 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.

7.0 DURATION OF FOLLOW UP

All patients will be followed for 100 days after the last dose of treatment with the agent under this IND or until all treatment related clinical significant toxicities resolve to baseline or grade ≤ 1. Adverse events with attribution of possible, probable or definite will be reported following guidelines for adverse event reporting and all SAEs will be reported for 100 days after the last dose. Patients will be followed every 3 months per standard of care for PFS and OS until death, loss to follow up, consent withdrawal, or study termination.

8.0 TERMINATION OF TREATMENT AND/OR STUDY PARTICIPATION

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for safety, behavioral or administrative reasons.

The Investigator will make every reasonable effort to keep each patient in the study unless it is in the patient's best interests to discontinue participation. If a patient is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the patient is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all patients are followed up for survival status after the Final Visit.

Patients who discontinue following entry will have relevant information completed and recorded on the CRF. All patients who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any patient should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the IRB and Sponsor (if applicable) The cause of death should be recorded in detail, within 24 hours, on a serious adverse event (SAE) form and reported to institutional, federal and any other appropriate committees and/or sponsors.

9.0 CONCOMITANT AND EXCLUDED THERAPIES

9.1 Concomitant Therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including blood transfusions) administered during the study should be recorded.

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit. 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.

Patients who experience infusion-associated symptoms may be treated symptomatically with antipyretics (ibuprofen preferred), diphenhydramine, and/or famotidine or another H2 receptor antagonist, as per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megastrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy should continue their use, unless prohibited.

9.2 Prohibited Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Concomitant use of strong inhibitors of CYP3A4 and/or CYP1A2 or strong inducers of CYP3A4 and/or CYP1A2 (see Appendix 11)
- Immunosuppressive agents (except used to treat a drug-related AE)

- Immunosuppressive doses of systemic corticosteroids (exceptions: 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 (eg, contrast dye allergy) or for treatment of non-autoimmune conditions [eg, delayed type hypersensitivity reaction caused by a contact allergen] is permitted.)
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, 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 section 9.3.
- Prophylactic antimicrobial therapy
- Any live / attenuated vaccine (e.g. varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

9.3 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 11) 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. See Appendix 11 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 11 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 13 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 14 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 15). Dapsone, topical anesthetics, and antimalarial drugs are the most likely agents, and thus these medications should only be used after discussion with the Principal Investigator.

9.4 Other Restrictions and Precautions

Use caution and monitor for symptoms of serotonin syndrome in participants receiving concurrent serotonergic psychiatric medications and/or tryptophan supplements.

9.5 Permitted Therapy

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 (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed type hypersensitivity reaction caused by a contact allergen) is permitted.

10.0 STUDY CALENDAR

Evaluation	Pre-Treatment		Treatment Cycles	End of Treatment		Post-Treatment	
Treatment Cycle / Title	Screening		Day 1 of Each Cycle[12]	End of Treatment[16]	Safety Visit[17]	Follow Up[18]	Day 100 Visit[19]
Scheduling Window	≤28 days prior to registration	≤14 days prior to registration	± 3 days	± 7 days	± 7 days	± 7 days	± 7 days
History							
Informed Consent	X						
Medical History	X						
Clinical/Laboratory/Assessments							
Physical Exam[1]: height[2], weight, BSA[3], performance status[4]		X	X		X	X	
Vital signs[5]		X	X		X	X	
Adverse Events and Concomitant Medications[10]	X		Continuously				X
Hematology: CBC with differential		X	X		X		
Biochemistry[6]		X	X		X		
AFP, TSH, hepatitis viral load if applicable		X	X[13]				
G6PD[7]		X					
Methemoglobin and Oxygen Saturation[8]		X	X				
HIV, HBV, HCV serology		X					
Pregnancy test if applicable[9]		X	X				
ECG		X		X			
Chest/abdomen/pelvis CT scan (MRI if appropriate)	X[11]		X[14]				
Correlatives							
Correlative Samples: Plasma, Serum, Whole Blood		X[15]	X[15]				
Tumor Tissue		X[15]	X[15]				
Stool sample		X					
Study Treatment Administration							
Nivolumab			X				
BMS-986205			daily				

Evaluation	Pre-Treatment	Treatment Cycles	End of Treatment	Post-Treatment

1. Complete physical examination at screening only; subsequent physical examinations are limited to signs and symptoms of disease or toxicity. Clinical tumor measurements (if applicable).
2. Height is required at Baseline only.
3. BSA should be calculated prior to each dose of treatment.
4. ECOG only.
5. Vital signs: temperature, systolic and diastolic blood pressure, respiratory rate, and pulse.
6. Biochemistry: creatinine (serum), sodium, potassium, total bilirubin, alkaline phosphatase, AST, ALT, albumin, INR
7. Quantitative or qualitative G6PD assay must performed within 28 days prior to enrollment to screen for underlying G6PD deficiency.
8. Methemoglobin levels must be performed within 14 days prior to enrollment, C1D1, each treatment cycle or more frequently if clinically indicated based on symptoms. Methemoglobin levels to be assessed on arterial or venous blood sample or by co-oximetry. Oxygen saturation levels must be measured within 14 days prior to C1D1 and every cycle while on treatment by pulse oximetry at rest.
9. Female subject of child-bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotrophin [hCG]) within 14 days of C1D1, and ≤ 24 hr prior to planned treatment initiation, and prior to each cycle while on treatment. Women with childbearing potential and males must be willing to use adequate birth control on trial and until 5 months for women or 7 months for men after the last of study therapy. Refer to Appendix 9.
10. Baseline symptoms will be documented prior to starting study treatment. SAE will be collected starting from time of consent. Adverse Events collection will begin from the time of first dosing through 100 day post-treatment. Adverse events will be coded as per CTCAE V5.0.
11. ≤ 28 days prior to registration.
12. One cycle consists of 2 weeks.
13. Every other cycle. If TSH >2x ULN, check free T3 and T4.
14. Radiology to be repeated at the following time points (± 7 days): at the end of 8 and 16 weeks, then every 12 weeks, and at End of Treatment. Patients that go off treatment without radiological progression will have scans repeated every 3 months until documented disease progression or start of new therapy.
15. Blood samples for correlative studies will be obtained at the following time points (± 7 days): day 15, day 29, day 57, day 85 and end of treatment. Core biopsy of tumor will be obtained at Baseline (unless there is adequate archival tumor specimen available), day 29 (± 7 days), and End of Treatment (end of treatment biopsy is optional).
16. End of Treatment is at the time the decision is made to take the patient off study treatment.
17. Safety Visit: 28 days after taken off protocol treatment.
18. Follow up: Every 3 months from End of Treatment for survival follow up.
19. 100 day visit for safety follow up.

11.0 STUDY EVALUATIONS

11.1 Screening Phase

The screening phase is defined as the interval between the day the subject signs the inform consent (ICF) and the day of registration. The screen phase will allow a total of 28 days. The subject can re-screen if he/she fails the first screen due to temporary illness.

11.2 Treatment Phase

One cycle of treatment is 14 days in which the subject will receive the combination therapy and the treatment phase is up to a total of 24 months. The subject may stop both therapy at 24 months or continue therapy per treating physicians based on standard of care.

11.3 End of Treatment Visit

The end of treatment visit should be performed when the treating physician decides to permanently discontinue study drug combinations.

11.4 Follow-up Phase

The safety follow up phase is the interval between the end of treatment visit and scheduled safety follow up visit which will occur 28 (±7 days) days after discontinuation of combination therapy. If the subject starts on a new anticancer drug before 28 (±7 days) days after discontinuation of study drugs, the safety follow up visit should be prior to the start of new therapy. If the subject discontinues treatment without disease progression, the subject will be followed every 84 days (12 weeks ±7 days) by imaging to monitor disease status. Once the subject starts a new therapy or has progression of disease, the subject's survival status should be followed with telephone or email until death or withdrawal of consent.

11.5 Efficacy

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [35] as well as iRECIST criteria. Changes in the largest diameter (unidimensional measurement) of the tumor lesions is used in the RECIST criteria. Radiologic assessment is to be repeated at the following time points (+/- 7 days): at the end of 8 and 16 weeks, then every 12 weeks, and at End of Treatment. Patients that go off treatment without radiological progression will have scans repeated every 3 months until documented disease progression or start of new therapy.

11.5.1 Disease Parameters

11.5.1.1 Measurable Disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

11.5.1.2 Measurable Lesions

Lesions that can be accurately measured in at least one dimension with longest diameter 20mm using conventional techniques or 10mm with spiral CT scan.

11.5.1.3 Non-Measurable Lesions

All other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, ascites, pleural/pericardial effusion, cystic lesions, and abdominal masses that are not confirmed and followed by imaging techniques**.**

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, preferably within two weeks of treatment initiation, and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up.

11.5.2 Methods of Measurements

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

11.5.3 Response Criteria

11.5.3.1 Evaluation of Target Lesions by RECIST 1.1

- **Complete Response (CR):** Disappearance of the target lesion
- **Partial Response (PR):** At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
- **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of target lesion, or the appearance of one or more new lesions
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

11.5.3.2 Evaluation of Best Overall Response

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

Table 2. Best Overall Response Evaluation

Best Overall Response Evaluation		
Target Lesion	**New Lesion**	**Overall Response**
CR	No	CR
PR	No	PR
SD	No	SD
PD	Yes or No	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue.

When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

11.5.3.3 Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. For reporting the study outcomes the response rate and confirmed response rate will be made clear. For interval evaluation of response rates during the Simon-two stage study responses do not need to be confirmed for the study to progress. To be assigned the status of confirmed responses must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol. For PD all results should be confirmed as described in section 6.2.

11.5.3.4 Duration of Overall Response

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

11.5.3.5 Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started. The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

11.5.3.6 Objective Response Rate

ORR is defined as the percentage of patients that achieve PR or CR.

11.5.3.7 Disease Control Rate (DCR)

DCR is defined as the percentage of patients that achieve an objective tumor response or have stable disease to therapy.

11.5.3.8 Progression-Free Survival (PFS)

PFS is defined as the duration of time from date of enrollment to time of progression or death, whichever occurs first.

11.5.3.9 Overall Survival (OS)

OS is defined as the duration of time from date of enrollment to death from any cause.

11.5.4 Reporting of Results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration, or failure to complete all prescribed study therapy, does not result in exclusion from the analysis of the response rate. All conclusions should be based on all eligible patients. Sub analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of

treatment, major protocol violations, etc.). The reasons for excluding patients from the analysis should be clearly reported.

11.6 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry, coagulation parameters, urinalysis and the regular monitoring of vital signs, and physical condition as shown in corresponding tables. For details on AE collection and reporting, refer to the Safety section in the protocol.

12.0 CORRELATIVES

One of the major shortcomings of immunotherapy trials has been the lack of in depth correlative studies to help identify the mechanism of action of these therapies, identify biomarkers of response, and provide a foundation for further improving these approaches. To address this we plan to perform in depth immunological analysis of patient blood and tumor samples. Pre- and post-treatment blood and tumor biopsies (when available) will be obtained as outlined in the study calendar. Briefly, blood and tumor samples will be collected as detailed in the study calendar. Optional blood and tumor biopsies can be obtained at progression. Participation in the correlative studies is mandatory unless waived by the study principal investigator due to safety concerns or other reasons. Archival tumor blocks will also be collected when available. We will evaluate immunologic changes systemically and in the tumor and tumor microenvironment within patient's pre to post therapy and across the cohort of patients to identify predictive biomarkers and elucidate the mechanistic immunologic effects of therapy. For further details, refer to Appendix 4. Correlative studies will include (in order of priority):

12.1 Blood

- FACS for quantification, immunophenotyping, and functional assessment of PBMCs
- Evaluation of immune related gene signatures by RNAseq and/or Nanostring
- Whole exome sequencing (as normal tissue baseline for determining mutational burden and neoantigen load of tumors)
- Ex Vivo evaluation of T cell function by in vitro stimulation studies and metabolic status by seahorse analysis
- Evaluation of systemic plasma tryptophan to kynurenine ratios
- Luminex evaluation of plasma for systemic cytokine / chemokine signatures
- T-cell receptor (TCR) deep sequencing to determine clonal expansion and diversity of T-cells in the systemic circulation
- Other studies as deemed feasible and informative by the principal investigator

12.2 Tissue

- Multi-plexed IHC/IF to determine expression of markers including PD-1, PD-L1, CD8, CD4, IDO1, Ki-67, Granzyme b and FOXP3
- Evaluation of immune related gene signatures by RNAseq and/or Nanostring
- T-cell receptor (TCR) deep sequencing to determine clonal expansion and diversity of T-cells in the tumor microenvironment
- Evaluating mutational burden and neoantigen load of tumors using RNAseq and WES data
- Flow cytometry and ex-vivo analysis of T-cells from fresh tumor biopsies
- Other studies as deemed feasible and informative by the principal investigator

12.3 Stool

- Stool microbiome analysis

A comprehensive analysis of tumor, blood, and stool samples will provide valuable insight into potential biomarkers and into the mechanism of action of our combined therapy.

Blood samples will be separated into PBMCs and plasma and stored at -80°C for batched analysis. PBMCs will be stained for FACS analysis using well characterized antibodies against markers such as CD45, CD3, CD4, CD8, FOXP3, Granzyme B, Interferon gamma, tumor necrosis factor (TNF) alpha, PD-1, PD-L1 etc. Results will be analyzed using a BD Fortessa multi-color flow cytometer and Flowjo software. An aliquot of PBMCs will also be set aside for RNA isolation and batched analysis of gene expression. An aliquot of PBMCs at baseline blood draw will also be set aside for DNA extraction for WES. To determine if certain clones of T cells are preferentially expanding after therapy, an aliquot of PBMCs will also be used for TCR deep sequencing. Plasma will be evaluated for systemic cytokine and chemokine signatures using Luminex technology. Markers will include IL-2, IL-6, IL-10, IL-12p70, GM-CSF (granulocyte-macrophage colony-stimulating factor), TNF alpha, IFN (interferon) gamma, CXCL10 (C-X-C motif chemokine 10), RANTES (regulated on activation, normal T cell expressed and secreted), MIP1 (Macrophage Inflammatory Protein) alpha, MIP1 beta, TGF-beta and others. Systemic tryptophan and kynurenine levels will also be evaluated.

Tissue biopsies will be formalin fixed and paraffin embedded using standard protocols. Tissue will be analyzed by multi-plexed IHC/IF staining for markers including PD-1, PD-L1, CD8, CD4, IDO, Ki-67, Granzyme b and FOXP3. An aliquot of tumor tissue will be stored in RNA later for batched analysis of gene expression signatures and TCR deep sequencing. If sufficient tissue is available an aliquot will be freshly processed to evaluate T cell function and metabolic status. Pre-treatment stool samples will be collected to analyze the gut microbiome

13.0 DRUG INFORMATION

13.1 BMS-986205

13.1.1 Dosing and Administration

BMS-986205 will be dispensed once every 28 days and administered at 50-100mg orally, daily throughout the study period. Subjects will take their dose of BMS-986205 once a day around the same time during the day. Subjects should take the tablet with 240 ml/8 ounces of water following a meal.

13.1.2 Formulation, Packaging, and Handling

BMS-986205-04 Film-coated Tablet, 100 mg (30 tablets per bottle): BMS-986205-04 tablet 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.

BMS-986205-04 Film-coated Tablet, 50 mg (30 tablets per bottle): BMS-986205-04 tablet is a beige, 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® beige color dispersion. The tablets are supplied in tightly-closed high-density polyethylene bottles with child-resistant closures containing a desiccant.

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.

For complete details on drug preparation, administration, storage conditions, clinical pharmacology, pharmacokinetics, and known precautions and adverse reactions please see the BMS-986205 IB.

13.1.3 Preparation

No preparation is required for BMS-986205-04 capsules or tablets.

13.1.4 Ordering / How Supplied

BMS-986205 will be supplied by BMS at no cost to study patients.

13.1.5 Accountability, Handling and Disposal

Responsibility for drug accountability is on the investigator and the assigned pharmacist or designee. Drug supply will be disposed of according to institutional standard operating

procedure. Accurate records of all investigational product received at and dispensed from the study site should be recorded on the Drug Log.

13.2 Nivolumab

13.2.1 Dosing and Administration

Patients should be administered nivolumab 240 mg as an in intravenous infusion over 30 minutes every 2 weeks (± 1 day for cycles 1 to 3 and ± 3 days for subsequent cycles). For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop acute symptoms.

13.2.2 Formulation, Packaging, and Handling

Nivolumab will be supplied by Bristol-Myers Squibb and labeled appropriately as investigational material for this study. Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody. Nivolumab vials must be stored in the refrigerator at 2-8°C, protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. The product does not contain a preservative, and as such after preparation, nivolumab should be used immediately. If not used immediately, nivolumab infusions should be stored at room temperature (20-25°C) and room light for no more than 4 hours from time of preparation. This includes room temperature storage of infusion in IV container and time for administration of infusion. Alternatively, nivolumab infusion can be stored under refrigeration at 2 to 8oC (36-46°F) for no more than 24 hours from the time of infusion preparation and protected from light. The infusion should not be frozen.

Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For complete details on drug preparation, administration, storage conditions, clinical pharmacology, pharmacokinetics, and known precautions and adverse reactions please see the Nivolumab IB.

13.2.3 Preparation

Preparation of nivolumab should be performed by trained personnel in accordance with package insert and good practices rules, especially with respect to asepsis. The required volume of nivolumab should be withdrawn and transferred into an intravenous container. Nivolumab should be then be diluted with either 9 mg/mL (0.9%) sodium chloride solution for injection, USP or 50 mg/mL (5%) dextrose solution for injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. Diluted solution should be mixed by gentle

inversion, but should not be shaken. Partially used or empty vials of nivolumab should be discarded.

13.2.4 Ordering / How Supplied

Nivolumab will be supplied by BMS at no cost to study patients.

13.2.5 Accountability, Handling and Disposal

Responsibility for drug accountability is on the investigator and the assigned pharmacist or designee. Drug supply will be disposed of according to institutional standard operating procedures. Accurate records of all investigational product received at and dispensed from the study site should be recorded on the Drug Log.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design and Overview of Primary and Secondary Endpoints

This is a phase I/II study using a Simon optimal two-stage design for efficacy of BMS-986205 in combination with nivolumab. In the phase I portion, we will treat patients following 3+3 standard design with dose escalation in BMS-986205 along with fixed dose of nivolumab. BMS-986205 dose level 1 will be 50mg and dose level 2 will be 100mg. 3 patients will be treated with BMS-986205 at dose level 1 of 50mg along with fixed dose of nivolumab. If no patient experiences a DLT at dose level 1, we will add 3 patients will be treated at a dose of 100 mg of BMS-986205 with fixed dose of nivolumab. If 1 of 3 patients has a DLT at DL1, we will add 3 patients at a dose of 50 mg. If $\leq$1 of 6 patients has a DLT at 50mg of BMS-986205, 3 patients will be treated at 100 mg. Maximum tolerated dose will be defined as $\leq$1 of 6 patients at DL1 or DL2 experiencing a DLT. After identifying the MTD, the phase II expansion phase will be initiated with 3 additional patients at the MTD. A maximum total of 17 patients at MTD will be treated on trial including 6 patients treated during phase I portion at MTD. An interim efficacy analysis will be done after 9 patients (including the 6 patients in phase I portion) have been treated. If at least 1 patient out of the 9 initial patients treated at MTD achieves a response, we will accrue 8 more patients at the MTD. If at least 3 of the 17 patients treated at MTD achieve a response, we will deem the treatment worthy of further study, provided the safety profile is acceptable.

14.2 Sample Size Estimation /Accrual Rate

The Simon optimal 2 stage design described above provides 80% power to detect the difference between an acceptable response rate by RECIST of 25% vs. an unacceptable rate of 5% at the 0.05 level (1-sided). The estimated time to accrue 23 patients is 24 months, at approximately 1 patient per month.

14.3 Evaluation of Efficacy

The ORR will be estimated as the proportion of participants who experience an objective response, along with its exact 95% confidence interval; the disease control rate will be analyzed similarly. DOR, PFS, and OS will be analyzed using Kaplan-Meier methods; medians and 95% confidence intervals will be computed.

14.4 Evaluation of Safety

DLTs, adverse events, serious adverse events, and clinical laboratory values outside normal limits will be listed for each patient and summarized by body system and dose level in frequency tables.

15.0 SAFETY REPORTING OF ADVERSE EVENTS

15.1 Adverse Events

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

15.1.1 Severity of Adverse Events

The severity of an AE is graded as follows:

Grade 1 (Mild):	The event causes discomfort that affects normal daily activities.
Grade 2 (Moderate):	The event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Grade 3 (Severe):	The event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Grade 4 (Life-threatening):	The patient was at risk of death at the time of the event.
Grade 5 (Fatal):	The event caused death.

15.1.2 Causality (Attribution) of Adverse Events

The investigator is to assess the causal relation of all AEs (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

Related: The AE is clearly related to use of the investigational product.

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

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

15.1.3 Serious Adverse Events

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

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

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

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days after discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

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

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.

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

The following hospitalizations will not be considered SAEs:

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

15.1.4 Adverse Events of Special Interest

15.1.4.1 What is considered an adverse event of special interest?

Adverse events of special interest (AESI) 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

15.1.4.2 Reporting Timeframe

These AESI, whether related or not related to study drug, must be reported to BMS or designee within 24 hours of awareness of the event. These AESI are medically important events and are therefore considered SAEs. The reporting system for SAEs should be used (See Section 15.2).

15.1.4.3 Diagnostic Scoring Criteria

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. 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 AESI.

15.1.5 Non-Serious Adverse Event

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

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

15.1.5.1 Non-Serious Adverse Event Collection and Reporting

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

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

15.1.6 Laboratory Test Abnormalities

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

The following laboratory abnormalities should be documented and reported appropriately:

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

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

15.1.7 Pregnancy

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

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

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

15.1.8 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 (section 15.2).

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.

15.1.9 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.

15.1.10 Other Safety Considerations

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

15.2 Procedures for Reporting Adverse Events

15.2.1 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), BMS in accordance with CFR 312.32 (IND Safety Reports).

15.2.2 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins at initiation of study treatment and ends 100 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

15.2.3 Procedures for SAE Reporting

15.2.3.1 Initial and Follow up Reports

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 MedWatch or approved site SAE form.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: +1 609-818-3804

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

1. MedWatch or
2. BMS Pregnancy Surveillance Form or,
3. Approved site SAE 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 / 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

15.2.3.2 Additional Reporting Requirements for IND Holders

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 312.32.

Sponsor-investigators of studies conducted under an IND are required to report all serious, unexpected, and related adverse events directly to the FDA on a MedWatch Form FDA 3500A within 7 (if fatal or life-threatening) or 15 calendar days of first awareness, as described below.

Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction
- Serious
- Unexpected

The Sponsor-Investigator will notify the FDA according to the following timelines:

- within **7 calendar days** of any unexpected fatal or life-threatening adverse event with possible relationship to study drug;
- Within **15 calendar days** of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

FDA fax number for IND Safety Reports:
(800) FDA-0178 or (800) 332-0178

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report to the FDA. For adverse events that are either serious but don't meet the criteria for expedited reporting or are not serious, the FDA will be notified at the time of the IND Annual Report.

MedWatch Form FDA 3500A Reporting Guidelines

In addition to completing appropriate demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch Form FDA 3500A:

- Treatment regimen (dosing, frequency, combination therapy)
- Protocol description (include number if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive diagnostic and laboratory results
- Investigator's assessment of the relationship of the SAE to each investigational product and suspect medication

Follow-up information:

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch Form FDA 3500A and submitting it as follow-up
- Adding supplementary summary information and submitting it as follow-up with the original MedWatch Form FDA 3500A
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e., DOB, initials, subject number), protocol description and number, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted

15.2.3.3 Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Office of Clinical Research (OCR) policies. The UC Davis IRB can be reached at (916) 703-9151.

15.2.4 Reconciliation

The Sponsor-Investigator will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Reconciliation will be done at the end of study prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

16.0 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

16.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

16.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to BMS

before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to BMS. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

16.3 Study Documentation

The required documents include, but are not limited to the following: IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators.

16.4 Informed Consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

Fertile men and women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study.

Refer to Appendix 9.

If there is any question that the patient will not reliably comply, they should not be entered in the study.

In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location at participating institutions. Copies of the signed and dated Informed Consent document will be provided to the study participant and a copy will be stored in the patient's electronic medical record at the participating institution.

16.5 Discontinuation of Study Support

BMS reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

16.6 Amendments to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by BMS and the investigator before implementation. Any protocol amendment requires approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to BMS.

16.7 Patient Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCD OCR or at the participating institutions. Medical records of patients will be maintained in strict confidence according to legal requirements. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

16.8 Protocol Deviations

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Comprehensive Cancer Center OCR policies.

16.9 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to BMS. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to BMS.

16.10 Quality Assurance

Quality assurance audits of select patients and source documents may be conducted by the Quality Assurance and/or Data Safety Committees at participating institutions or UC Davis Comprehensive Cancer Center as outlined in the UC Davis Comprehensive Cancer Center Data and Safety Monitoring plan.

17.0 OVERSIGHT AND MONITOROING

17.1 Data and Safety Monitoring

In addition to the requirements for adverse event reporting as outlined in Section 7.0, this protocol is also subject to the UC Davis Comprehensive Cancer Center's (UCDCCC) Data and Safety Monitoring Plan. The UCDCCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data and Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Comprehensive Cancer Center (UCDCCC) Office of Clinical Research (OCR) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI) and clinical research coordinator meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable.

According to the UCDCCC Data and Safety Monitoring Plan, any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCCC Data and Safety Monitoring Committee and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCCC SRC determines if a UCDCCC Data and Safety Monitoring Board (DSMB) is required. If required, the Data and Safety Monitoring Committee will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

The Research Monitor is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

17.2 Investigator Monitoring Guidelines

Investigators will conduct continuous review of patient safety. Patients will be monitored bi-weekly during the study. All patients on active treatment will be discussed at weekly conferences that are held at the University of California Davis. Per Cancer Center guidelines, a trial cannot proceed to the next dose level until a DLT meeting is conducted to comprehensively review all toxicity data and approve the dose de-escalation. The discussion will include for each dose level: the number of patients, significant toxicities as described in the protocol, doses adjustments, and responses observed.

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19.0 APPENDICES

Appendix 1: ECOG Performance Status Scale

ECOG Grade	ECOG Status*
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

*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 2: Study Registration

Once signed, informed consent has been obtained; patients will be entered on study. To register a patient, the study coordinator must complete the Eligibility Checklist. The study coordinator will register the patient onto the study and assign a unique patient number.

Appendix 3: Data Submission Schedule

All data will be collected using UC Davis data collection forms. Any and all source documentation should be maintained.

Appendix 4: Molecular Correlative Sample Handling

Specimen Submission for Correlative Studies:
Participation in these molecular correlative studies is mandatory. With the patient's consent, tissue and blood specimens will be submitted as outlined below. Samples will be de-identified and coded with a new patient ID number to protect patient's identity.

A specimen submission form should be filled out for each specimen obtained. All specimens must be labeled with protocol number, site identification, patient registration number, date of specimen collection, and number of cells (for PBMCs) or weight of tissue (for tissue biopsies). Correlative studies will be performed at UC Davis or samples will be shipped in a de-identified manner to other institutions / companies for analysis.

For correlative studies the following samples should be collected:

- Peripheral blood samples obtained per study calendar
- Fresh tumor biopsy per study calendar. Optional biopsy at progression.
- Stool sample collected pre-treatment.

Correlative studies will include (in order of priority):

Blood

- FACS for quantification, immunophenotyping, and functional assessment of PBMCs
- Evaluation of immune related gene signatures by RNAseq and/or Nanostring
- Whole exome sequencing (as normal tissue baseline for determining mutational burden and neoantigen load of tumors)
- Ex Vivo evaluation of T cell function by in vitro stimulation studies and metabolic status by seahorse analysis
- Evaluation of systemic plasma tryptophan to kynurenine ratios
- Luminex evaluation of plasma for systemic cytokine / chemokine signatures
- T-cell receptor (TCR) deep sequencing to determine clonal expansion and diversity of T-cells in the systemic circulation
- Other studies as deemed feasible and informative by the principal investigator

Tissue

- Multi-plexed IHC/IF to determine expression of markers including PD-1, PD-L1, CD8, CD4, IDO, Ki-67, Granzyme b and FOXP3

- Evaluation of immune related gene signatures by RNAseq and/or Nanostring
- T-cell receptor (TCR) deep sequencing to determine clonal expansion and diversity of T-cells in the tumor microenvironment
- Identification of tumor neo-antigens by RNA deep sequencing in conjunction with peripheral blood WES data.
- Flow cytometry and ex-vivo analysis of T-cells from fresh tumor biopsies
- Other studies as deemed feasible and informative by the principal investigator

Stool

- Evaluation of stool microbiome

1.0 Peripheral Blood

1.1 Blood Collection

Blood specimens will be collected from each patient as indicated in the study calendar**. ~30ml should be collected into lavender top EDTA tubes for the first blood draw and ~20ml should be collected into lavender top EDTA tubes for subsequent blood draws.** It is important that each tube be filled to 5ml to ensure sufficient specimens for the planned analyses. It is important that a blood specimen be obtained at the time the patient is removed from protocol treatment or if the patient's disease progresses.

1.2 Blood Specimen Processing and handling – lavender top EDTA tubes

~30 mls will be collected from each patient at each time point. If possible five tubes should be collected for the first pre-treatment draw and 4 tubes thereafter. Each lavender-top (EDTA) tube should be inverted several times, placed on wet ice, and delivered to the appropriate lab for processing. Every effort should be made to process blood samples within 1 hour of collection. Samples should be processed in sterile fashion.

The tube should be centrifuged as soon as possible at approximately 1,000-1,500 rpm (400 x g) for 10 minutes. The Plasma layer should be removed and kept on ice (see 1.2.1). PBMCs should be separated using sterile and endotoxin free Ficoll density gradient solution. The peripheral blood mononuclear cells (PBMCs) should be removed and pooled. The PBMC layer should be resuspended in three times the volume of cold sterile PBS. Cells should be counted using a hemocytometer and the total cell number should be noted. The expected yield is 1-2 million cells per ml of blood.

For the first pretreatment blood draw, the PBMCs collected from 5 lavender top tubes will be divided into three aliquots. Roughly 60% of the cells should be cryopreserved for future analysis. The second aliquot consisting of roughly 20% of the cells will be placed in RNAlater

and snap frozen with liquid nitrogen and stored at -70 to -80°C for future RNA extraction. The third aliquot consisting of the last 20% of cells will be snap frozen in liquid nitrogen and stored at -70 to -80°C for future DNA extraction. If there are more than 20 x 10^6 viable cells the RNA and DNA extraction aliquots should be limited to a total of 5 x 10^6 cells each and the additional cells should be cryopreserved thus deviating from the 3:1:1 aliquoting.

For the subsequent blood draws the PBMCs collected in 20 mls will be divides into two aliquots. Roughly 75% of the cells should be cryopreserved and roughly 25% should be placed in RNA later. **DNA extraction is performed only for the pre-treatment sample and not for subsequent samples.** If there are more than 15 x 10^6 viable cells the RNA later aliquot should be limited to a total of 5 x 10^6 cells and the additional cells should be cryopreserved thus deviating from the 3:1 aliquoting.

1.2.1 Blood plasma

The removed plasma layers should be pooled and centrifuged at 1000 x g for 10 minutes to clarify the plasma. The plasma should then be placed in up to eight 0.5 ml aliquots in labeled cryotubes. Any additional plasma can be discarded. The plasma will be frozen (snap frozen with liquid nitrogen if possible) and stored at -70 to -80°C.

1.2.2 Cryopreservation

After counting, PBS washed PBMCs should be divided into aliquots of 5 million cells and spun down at approximately 1,000-1,500 rpm (400 x g) for 10 minutes. Each aliquot should be resuspended in 1ml of cold sterile CryoStor CS10 freeze media (catalog number 07930, STEMCELL technologies) which contains 10% DMSO. Each 1ml aliquot should be placed in a cryopreservation tube and the lid should be tightly secured. Tubes should be placed into a "Mr. Frosty" or other slow freeze container and placed into a -70 to -80°C freezer for 12-24 hours. Tubes should then be transferred to and stored in vapor phase liquid nitrogen (-135°C). In a batched manner tubes should be shipped overnight in liquid nitrogen to UC Davis at the indicated address.

1.2.3 RNA later

After counting, PBS washed PBMCs should be spun down at approximately 1,000-1,500 rpm (400 x g) for 10 minutes. The cell pellet should be re-suspended in 1ml of RNAlater solution and allowed to sit at room temperature for 30 minutes then snap frozen in liquid nitrogen and stored at -70 to -80°C.

1.2.3 Snap frozen for DNA extraction

This specimen will be collected from the pre-treatment blood draw only. After counting, PBS washed PBMCs should be spun down at approximately 1,000-1,500 rpm (400 x g) for 10 minutes. The cell pellet should be immediately snap frozen in liquid nitrogen and stored at -70 to -80°C.

1.3 Peripheral Blood Analysis

1.3.1 Plasma

Plasma samples will be stored at UC Davis for batched analysis. Plasma will be interrogated for chemokine and cytokine levels using the luminex platform as well as

1.3.2 Cryopreserved samples

Cryopreserved samples will be stored at UC Davis for batched analysis. Samples will be thawed and stained with fluorophore-conjugated antibodies against CD4, CD8, CD25, CD62L, CD45RA, CD127, ICOS, PD-1, PD-L1, FoxP3, CD3, CD56, CD16, CD83, TIM-3, Ki-67, CD19, CD20, CD33, CD15, CD11b, HLA-DR and others. Stained cells will be interrogated by flow cytometry and results analyzed using FlowJo software. PBMCs will also be evaluated ex vivo for T cell function by in vitro stimulation studies and metabolic status by seahorse analysis

1.3.3 RNAlater samples

Cells in RNA later will be stored at UC Davis for batched analysis. Samples will be thawed and RNA will be extracted. The transcriptome will be analyzed by RNA deep sequencing (RNAseq) using the Illumina HiSeq platform or nanostring. Targeted RT-PCR will be used to validate genes of interest identified by RNAseq or nanostring. TCR deep sequencing data will also be obtained from the RNAseq.

2.4.5 Snap frozen samples

Snap frozen cell pellets will be stored at UC Davis for batched analysis. Samples will be thawed and genomic DNA will be extracted. Whole exome sequencing will be performed using the Illumina HiSeq platform.

2.0 Fresh tumor biopsy

2.1 Tumor biopsy collection

Fresh tumor biopsy is collected pre-treatment and at end of cycle 2. Optional biopsy can be obtained at progression. Tumor biopsies should be collected by core needle biopsy using 18 gauge needle and number of passes deemed safe with a goal of 4 cores. The same lesions should be targeted for all fresh tissue biopsies.

2.2 Tumor biopsy processing and handling

On site at the time of the biopsy tumor tissues should be aliquoted into two or three portions. The top priority assay is IHC/IF and biopsy samples should be placed in formalin fixative and later embedded into FFPE blocks. In general samples should be placed in fixative at a 10:1 ratio and fixed for at least 48 hours but thicker tissue samples may require longer fixation.

If sufficient tissue is available (which there generally should be if more than one biopsy pass has been undertaken) then no less than 10mg and but preferably 20 - 50mg of tumor tissue should be placed in 1ml of RNAlater for 30 minutes at room temperature then snap frozen in liquid nitrogen and stored at -70 to -80°C.

If sufficient tissue is available (at least one entire core) it should be placed in RPMI, place on ice, and taken immediately to the UC Davis Laboratory of Cancer Immunology for processing and flow cytometry.

2.3 Tumor biopsy analysis

FFPE tissue biopsy blocks will be collected and stored at UC Davis. Tissues will be sectioned, prepared, and mounted for IHC/IF using standard procedures. When possible, IHC/IF should be performed within two weeks of slide sectioning. Biopsy samples will be stained by multi-plex IHC/IF at UC Davis or collaborating laboratories to immunologically profile the tumor microenvironment. Markers examined will include CD3, CD8, CD4, FoxP3, Ki-67, PD-1 and PD-L1.

Tissue in RNA later will be stored at UC Davis for batched analysis. Samples will be thawed and RNA will be extracted. The transcriptome will be analyzed by RNAseq using the Illumina HiSeq platform. Targeted RT-PCR will be used to validate genes of interest identified by RNAseq. TCR deep sequencing data will also be obtained from the RNAseq. RNAseq data will also be used in conjunction with PBMC WES to identify putative neoantigens.

Tissue in RPMI will be processed into a single cell suspension and evaluated by flow cytometry and ex-vivo analysis of T-cells from fresh tumor biopsies.

3.0 Stool

A stool sample will be collected from patients pre-treatment. Samples will be collected at home using a provided take home stool collection kit. Samples should be returned to UC Davis within 24 hours of collection and will be snap frozen in liquid nitrogen and stored at -70 to -80°C.

Appendix 5: Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance
- with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

a) In the event of a suspected anaphylactic reaction during drug administration, the following procedures should be performed:

b) Stop the study drug administration.

c) Apply a tourniquet proximal to the injection site to slow systemic absorption of drug. Do not obstruct arterial flow in the limb.

d) Maintain an adequate airway.

e) Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.

f) Continue to observe the patient and document observations.

Appendix 6: Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. 1964. pp. 50-64.

Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . “Transection of the oesophagus for bleeding oesophageal varices”. *The British journal of surgery*, 1973;60: 646-9.

Appendix 7: Pill Diaries

Patient Name: _____ **Medical Record #**: _____

Cycle#: _____ **Start Date**: _____**Dose**: _____

Instructions to Patients: In the table below, please provide time and date of each dose taken. If a dose is missed, please leave blank and confirm with study coordinator upon return of pill diary.

BMS-986205 – Daily

BMS-986205 is an oral tablet that should be taken daily every day throughout the study period. BMS-986205 should be taken with 240 ml (8 ounces) of water following a meal.

Day	1	2	3	4	5	6	7
	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:
Day	**8**	**9**	**10**	**11**	**12**	**13**	**14**
	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:	_____ Time: _____ Date:

Patient Signature: _____ Date: _____

Date Returned	# of pills left	Collector's Initials	Returned to Pharmacy
			Yes or N/A

Appendix 8: Instructions on Taking BMS-986205

BMS-986205 is a tablet and should be taken orally (by mouth). You will take these at home as instructed by the study staff. BMS-986205 tablets should be stored at room temperature.

You should take the prescribed number of BMS-986205 tablet(s) one time a day (approximately 24 hours apart), around the same time during the day. BMS-986205 is recommended to be taken within 30 minutes after a meal.

Tablets should be taken with 240 ml (8 ounces) of water following a meal. You should not consume grapefruit, grapefruit juice, or Seville oranges while on study. All other types of oranges are acceptable to eat.

If a dose is missed for more than 12 hours, do not take the tablet until the next scheduled dose (i.e., next day). Do not take a double dose of study drug to make up for a missed dose. Missed doses should be recorded on the pill diary.

If you vomit after taking the dose, you should not repeat the dose. You should contact your study doctor and resume dosing at the time of the next scheduled dose (i.e., next day).

On the day before your next study clinic visit, please provide the date and time of your dose on the last page of the pill diary.

Appendix 9: 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 not considered highly effective 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 BMS-986205 IDO: Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
Not in Arms which include BMS-986205 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 BMS-986205 IDO. Implantable progestogen-only hormonal contraception associated with inhibition of ovulation b **Not in Arms which include BMS-986205 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 10. 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.
- 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 the Pregnancy Surveillance Form-Quick Reference Guide.

Appendix 10: Adverse Event Management Algorithms

These general guidelines constitute guidance to the investigator and may be supplemented by discussion with the Principal Investigator. The guidance applies to all immune-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.

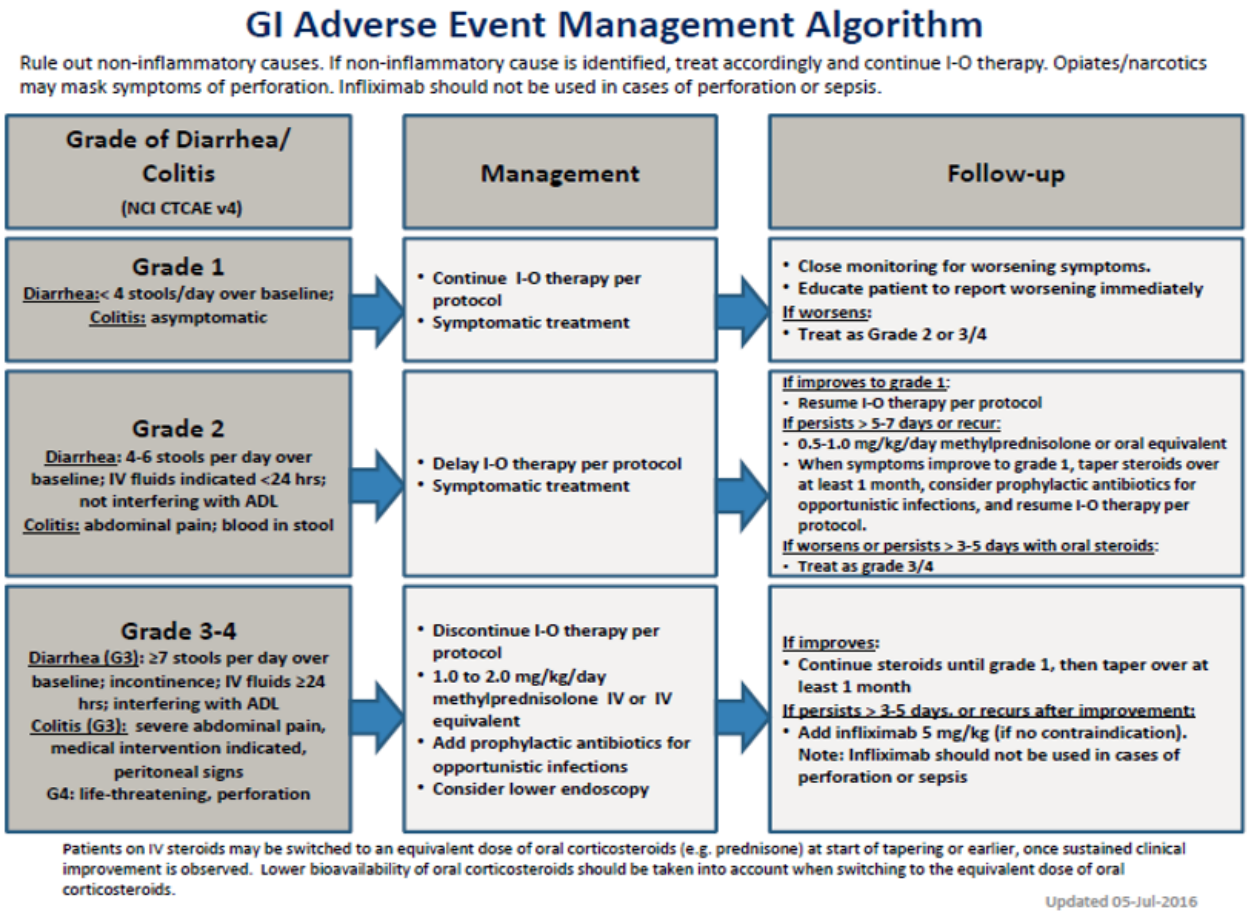
Corticosteroids are a primary therapy for immune-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

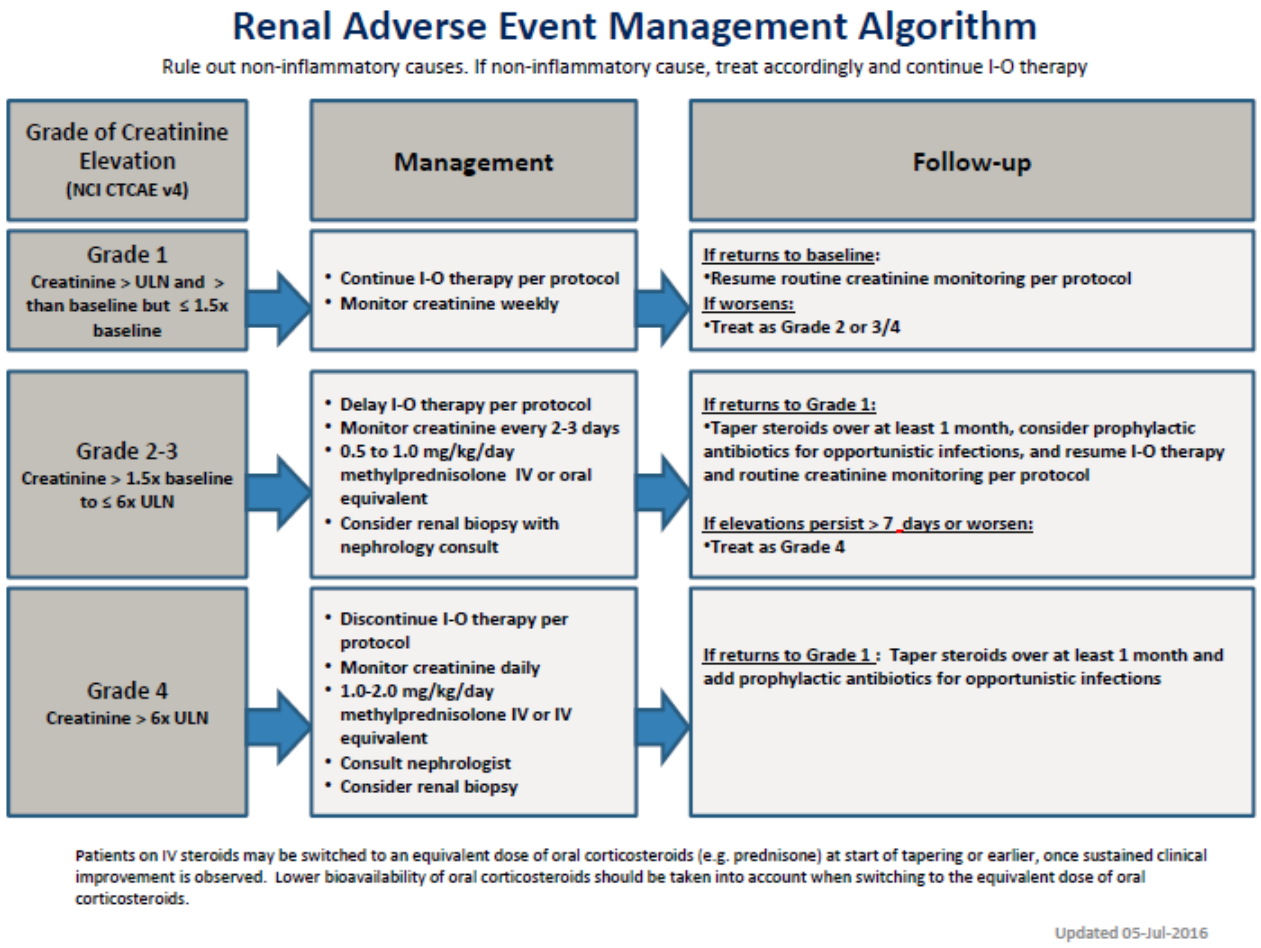
The frequency and severity of the related adverse event covered by these algorithms will depend on the immune-oncology agent or regimen being used.

Refer to nivolumab Investigator's Brochure for additional information.

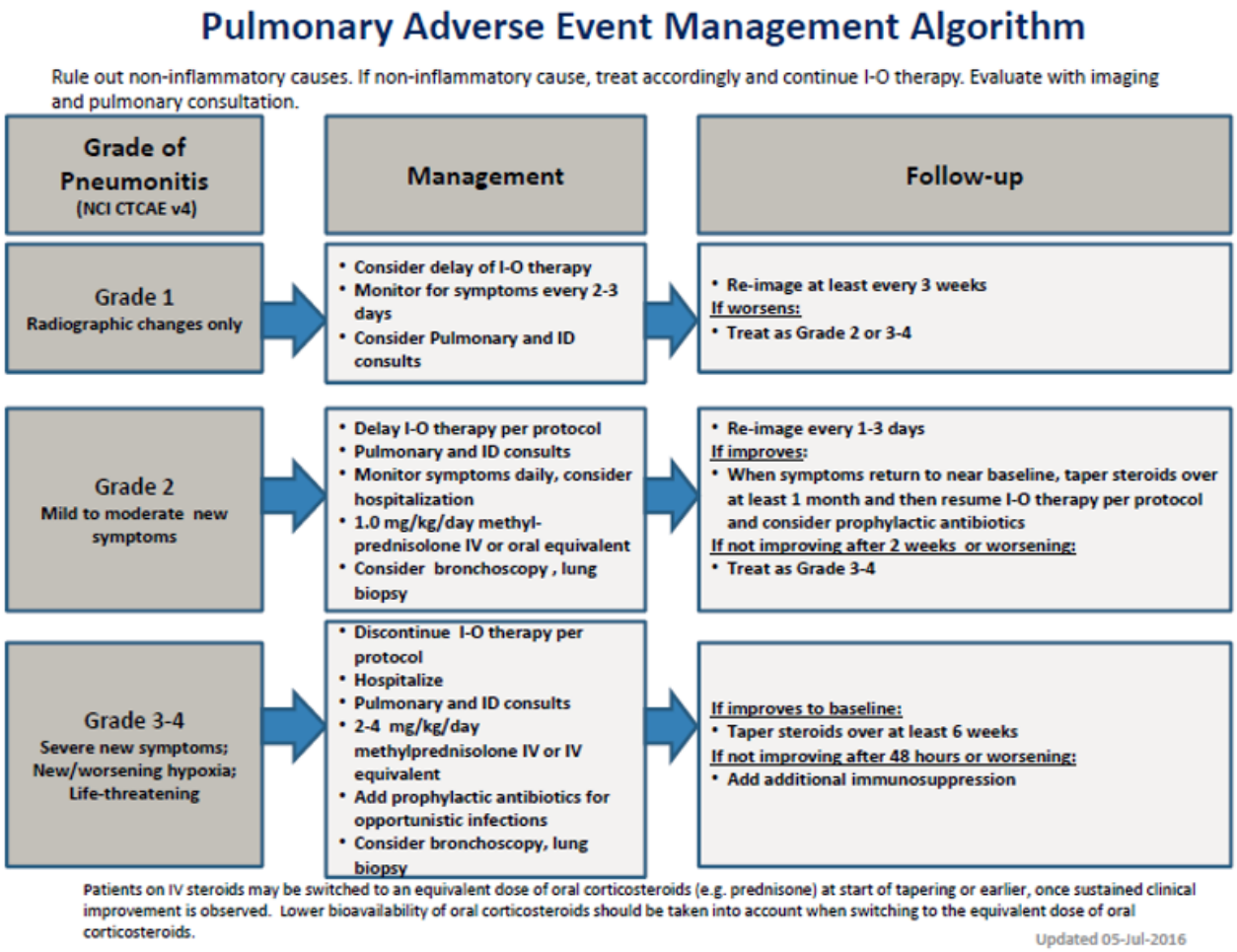
GI Adverse Event Management Algorithm



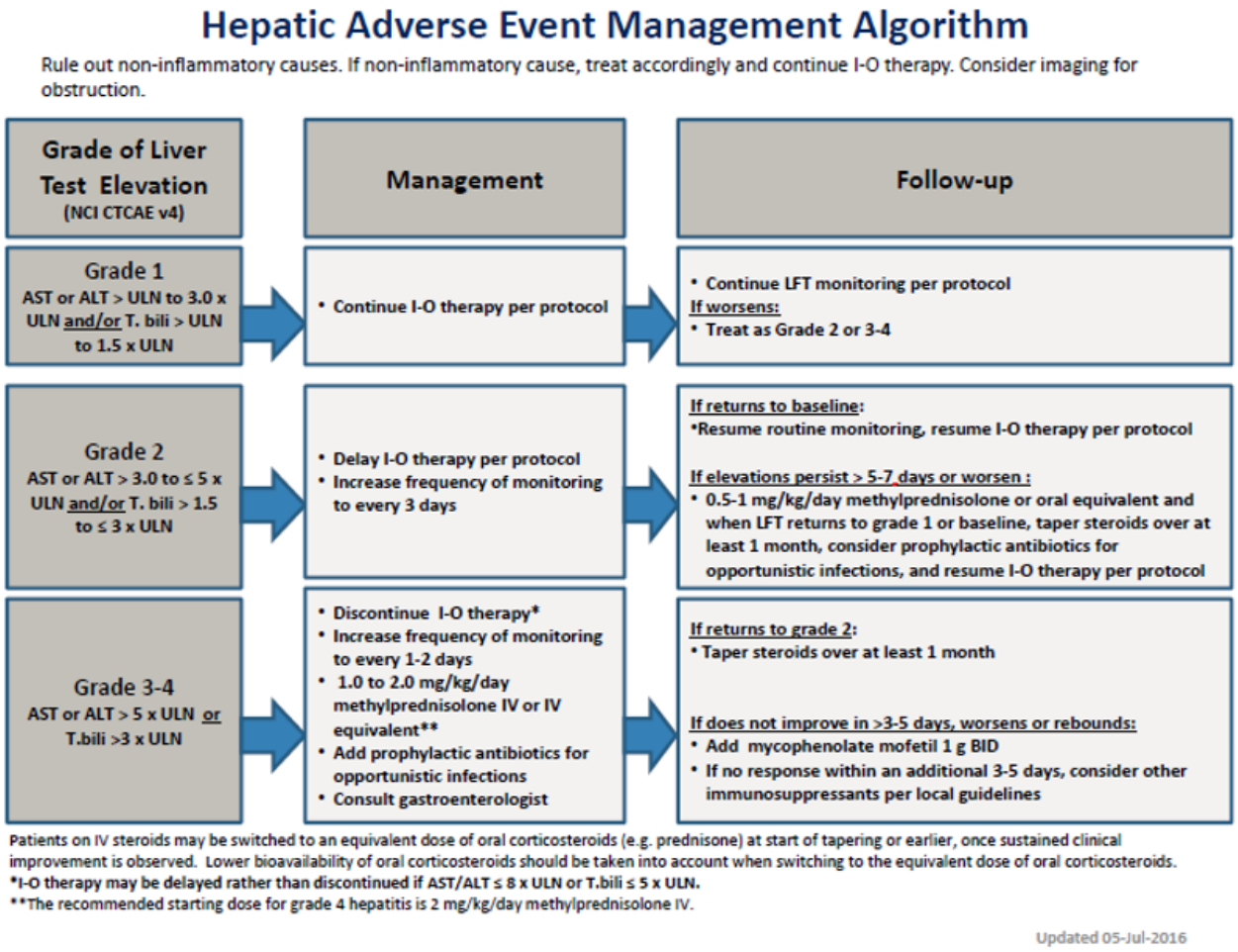
Renal Adverse Event Management Algorithm



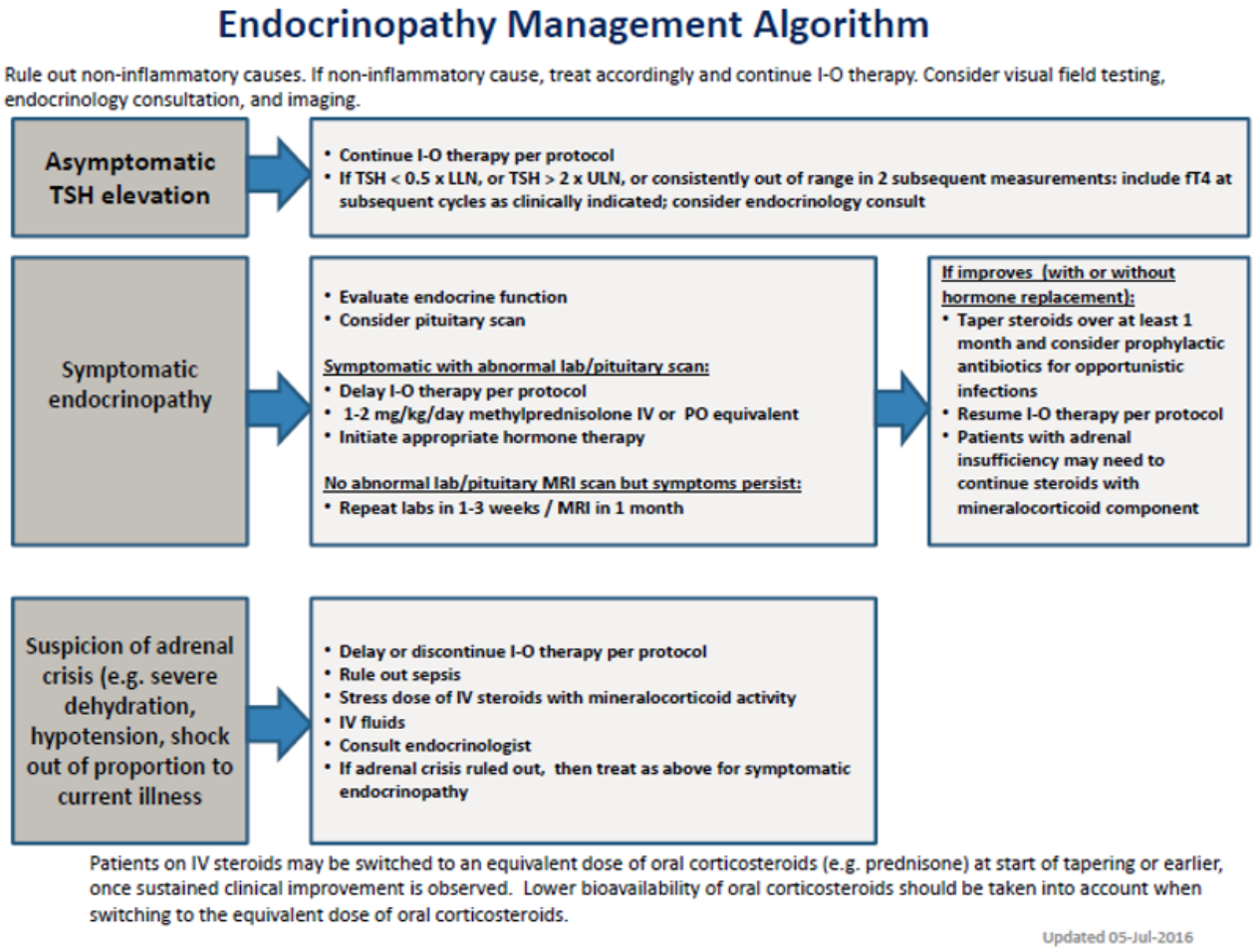
Pulmonary Adverse Event Management Algorithm



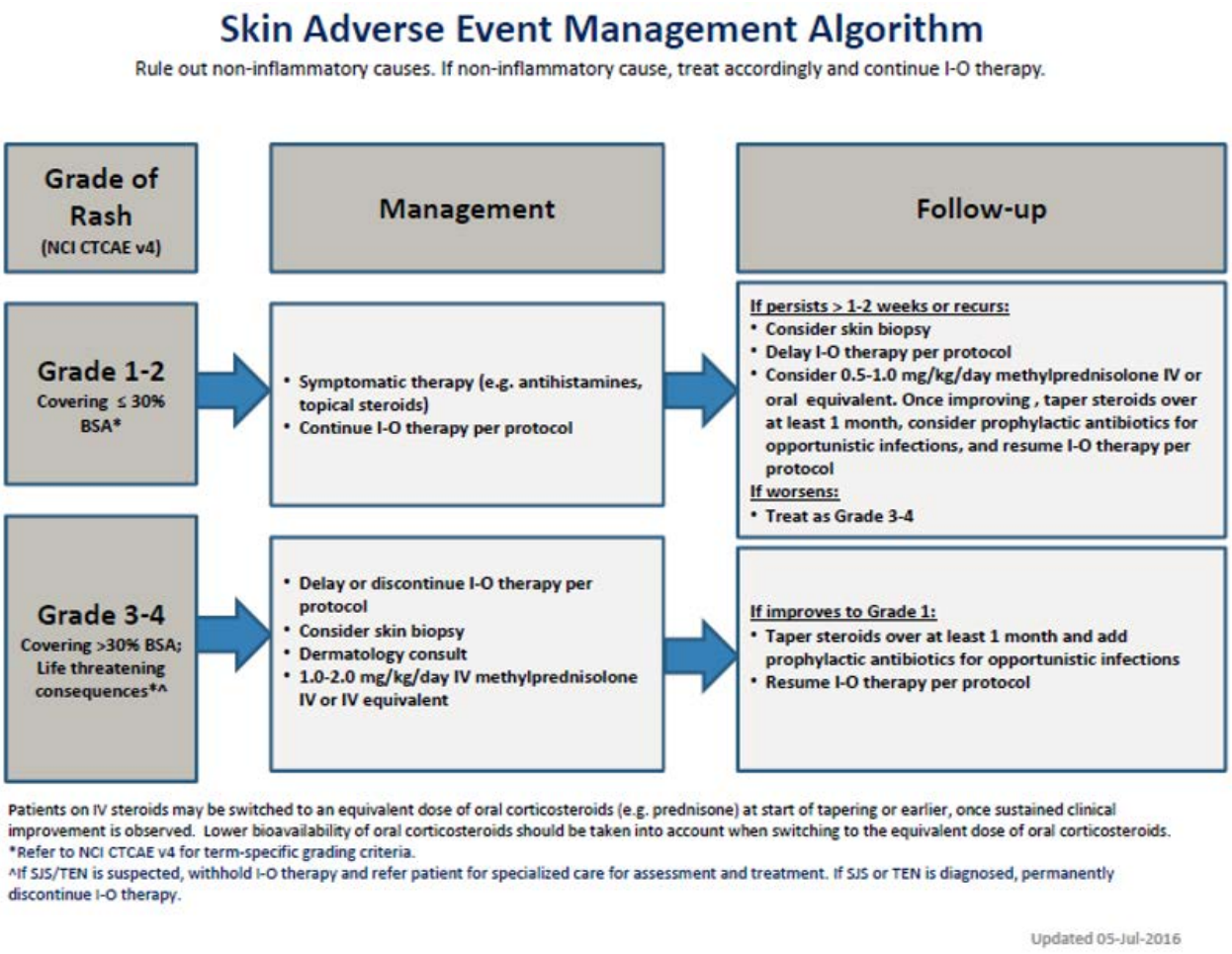
Hepatic Adverse Event Management Algorithm



Endocrinopathy Management Algorithm



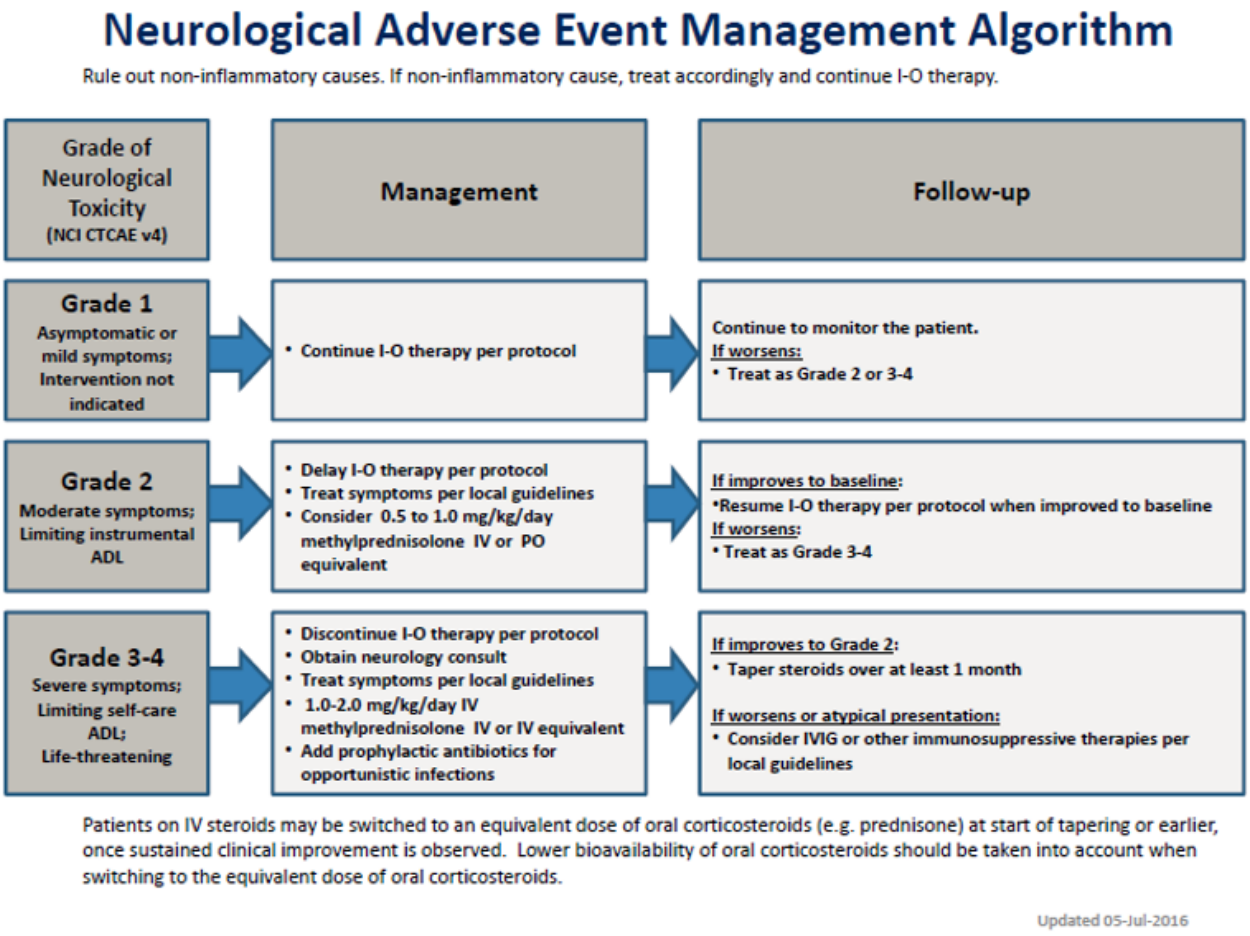
Skin Adverse Event Management Algorithm



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

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm



Appendix 11: 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 A 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 A 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 A 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 12: Immune RECIST Criteria

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 1: **Comparison of RECIST 1.1 and iRECIST**

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category*
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same. *Previously identified in assessment immediately before this timepoint. "i" indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumours.

Source: Lancet Oncol. 2017 Mar;18(3):e143-e152.

Appendix 13: Medications Associated with QT Prolongation

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 14: 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 A 4: 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 15: Agents Known to Cause Methemoglobinemia

Acetanilid	Naphthoquinone
p-Amino salicylic acid	Naphthalene
Aniline, aniline dyes	Nitrites
Benzene derivatives	Amyl nitrite
Clofazimine	Farryl nitrite
Chlorates	Sodium nitrite
Chloroquine	Nitroglycerin
Dapsone	Nitric oxide
Local anesthetic agents	Nitrobenzene
Benzocaine	Paraquat
Lidocaine	Phenacetin
Prilocaine	Phenazopyridine
Menadione	Primaquine
Metoclopramide	Rasburicase
Methylene blue*	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 16: 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			$0{\cdot}7–1{\cdot}499 \times 10^9\ L^{-1}$	$\geq 1{\cdot}5 \times 10^9\ L^{-1}$		
Eosinophils, if leucocytes $< 4{\cdot}0 \times 10^9\ L^{-1}$			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[a]					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. [a]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.