A phase I/II study to evaluate the tolerability and efficacy of BMS-813160 (CCR2/5 inhibitor) with nivolumab and gemcitabine and nab-paclitaxel in borderline resectable and locally advanced pancreatic ductal adenocarcinoma (PDAC)

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Study Drug(s): BMS-813160
Nivolumab
Gemcitabine (Gemzar)
Nab-paclitaxel (Abraxane)
IND #: 139562
ClinicalTrials.gov #: NCT03496662

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Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

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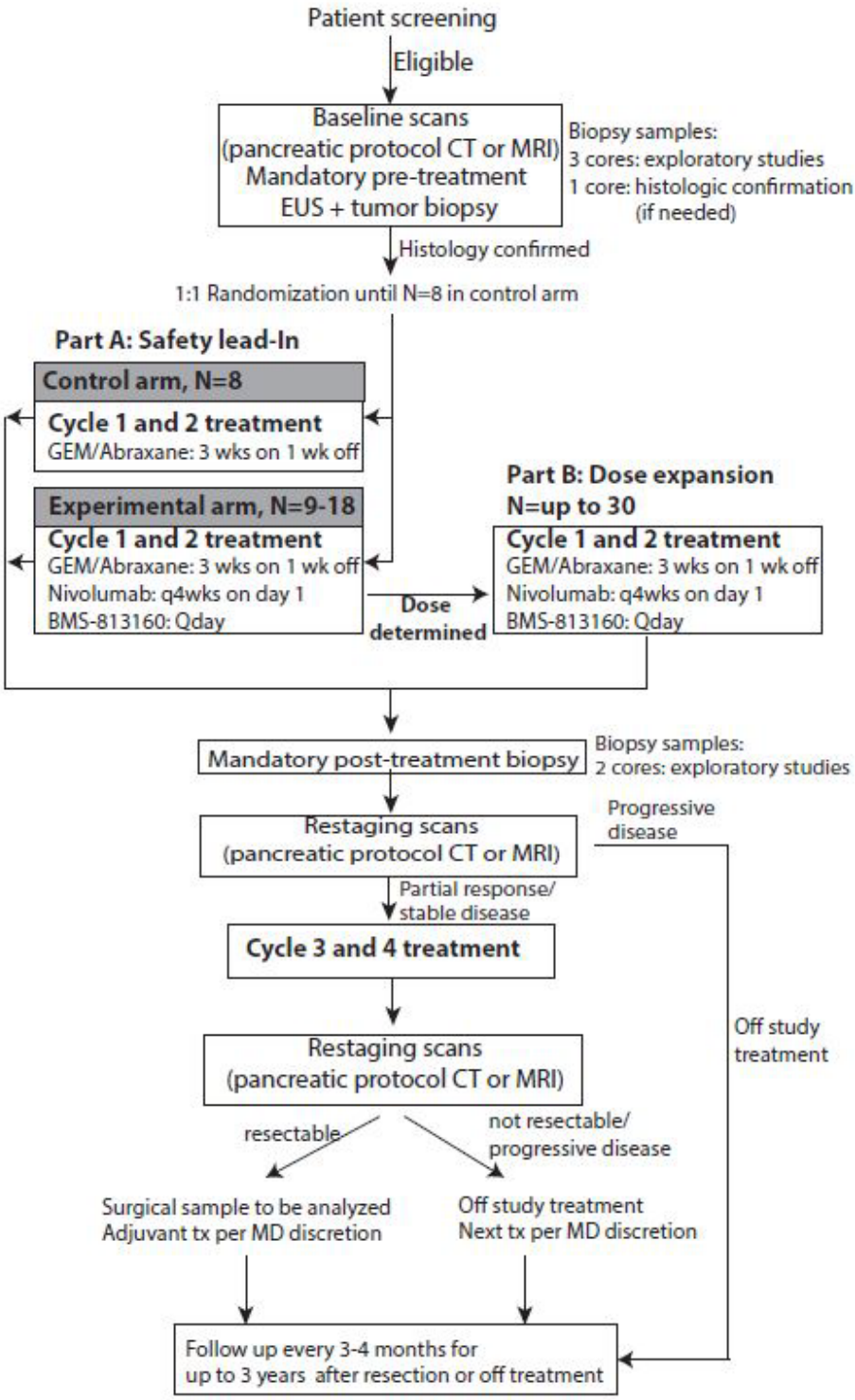
SCHEMA



Part A: Safety Lead-In (Each cycle = 28 days)						
Arm (by randomization)	**BMS-813160 (D1-28)**		**Nivolumab (D1)**	**Chemotherapy (D1, 8, 15)**		
	Dose Level	**Dose**		**Dose Level**	**Gemcitabine**	**Nab-paclitaxel**
Experimental (n=9-18)	0 (starting)	300 mg BID	480 mg	0 (starting)	1000 mg/m^2	125 mg/m^2
	-1	150 mg BID	480 mg	-1	800 mg/m^2	100 mg/m^2
	-2	150 mg QD	480 mg	-2	600 mg/m^2	75 mg/m^2
Control (n=8)	N/A	N/A	N/A	0 (starting)	1000 mg/m^2	125 mg/m^2
	N/A	N/A	N/A	-1	800 mg/m^2	100 mg/m^2
	N/A	N/A	N/A	-2	600 mg/m^2	75 mg/m^2
Part B: Dose Expansion (Each cycle = 28 days)						
Dose expansion (N=30*)		Per Part A	480 mg		Per Part A	

Dose modifications must be made based on toxicities attributed to BMS-813160 or chemotherapy, or both.
G-CSF not allowed for Cycles 1-2
* Total of 30 patients includes patients started on and stayed on MTD on experimental arm in Part A

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
CAF	Cancer-associated fibroblast
CBC	Complete blood count
CTL	Cytotoxic T lymphocyte
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose limiting toxicity
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HCC	Hepatocellular carcinoma
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IM	Inflammatory monocyte
IND	Investigational New Drug
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NSAID	Non-steroidal anti-inflammatory drug
OHRP	Office of Human Research Protections
ORR	Overall response rate
OS	Overall survival
PB	Peripheral blood
PD	Pharmacodynamic
PD	Progressive disease
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PI	Principal investigator

PR	Partial response
QASMC	Quality Assurance and Safety Monitoring Committee
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
SAE	Serious adverse event
SCC	Siteman Cancer Center
SD	Stable disease
TAM	Tumor-associated macrophage
TME	Tumor microenvironment
UPN	Unique patient number
WUSM	Washington University School of Medicine

Table of Contents

1 BACKGROUND AND RATIONALE

1.1 Pancreatic Ductal Adenocarcinoma (PDAC)

The prognosis for patients with pancreatic ductal adenocarcinoma (PDAC) is dismal, with a 5-year overall survival rate of 8%[1]. According to the American Cancer Society, an estimated 53,670 new cases and 43,090 deaths will occur in the US in 2017. Notably, PDAC is projected to be the 2nd leading cause of cancer-related death by 2020[1]. Due to a lack of early warning symptoms and effective screening tools, 85-90% of PDAC patients are diagnosed at advanced stages when chemotherapy is the only treatment option. The two current FDA-approved chemotherapy regimens, FOLFIRINOX and gemcitabine/Nab-paclitaxel, have improved the median survival of patients with advanced PDAC from about 6.7 months to 11.1 months and 8.5 months, respectively[2], but at the price of significant toxicities. Escalating the strength of chemotherapy is unlikely to be tolerated, evidenced by a dearth of new, stronger chemotherapy regimens now being tested in clinical trials[2]. Disappointingly, the therapeutic breakthroughs by immune checkpoint blockade in other cancer types, such as melanoma, non-small cell lung cancer, and bladder cancer, have not yet materialized for PDAC patients[3]. These challenges are at the forefront of efforts to improve the effectiveness of chemotherapy and immunotherapy by overcoming the molecular mechanisms that drive the refractory nature of PDAC.

1.2 BMS-813160

Immunotherapy has emerged as a promising therapeutic modality in cancer treatment. Approaches that have shown success in the clinic include immune checkpoint blockade, use of chimeric-antigen receptor T cell therapy, instillation of cytotoxic anti-tumor T cells and immunostimulatory antibodies. Despite promising results in other cancer types, immune-based treatments have not been successful in PDAC. PDAC tumors are characterized by a profound desmoplastic tumor microenvironment (TME)[4]. Major components of this TME include a dense fibrotic matrix deposited by cancer-associated fibroblasts (CAFs), and significant infiltration of various subsets of immunosuppressive myeloid cells, vascular cells, and nerve cells[5-7]. Targeting the immunosuppressive myeloid cells has recently emerged as a promising approach, with multiple strategies now being developed and tested. Blocking the CCL2-CCR2 and CCL5-CCR2 axes that drive the function of immunosuppressive myeloid cell function are two examples of these approaches. Progression of PDAC is accompanied by increased abundance of various chemokines including CCL2 and CCL5, which draw and reprograms circulatory myeloid cells and regulatory T cells into deterring anti-tumor T cells[8,9]. CCL2 is secreted by tumors and recruits CCR2 positive inflammatory monocytes from the bone marrow to the TME where they transform to immuno-suppressive tumor associated macrophages (TAM) and prevent effective anti-tumor immunity[10-12]. Previous studies have shown that the ratio of bone marrow to blood inflammatory monocytes is prognostic and inhibition of this axis showed responses in preclinical tumor models[11,12]. Since tumors leverage the CCL2-CCR2 and CCL5-CCR5 axis to promote tumor growth through Tregs and TAM, blocking of this axis may be able to overcome the immunosuppressive TME and promote effective anti-tumor immunity.

BMS-813160 (developed by Bristol-Myers Squibb) is an equipotent dual antagonist of CCR2 and CCR5 that binds potently to both receptors and exhibits potent dual inhibition of in vitro receptor-mediated functions, including chemotaxis, calcium flux, non-hydrolyzable guanosine triphosphate analog (guanosine 5'-3-O- [thio]triphosphate) [GTP-γS] exchange, and Mac-1 (integrin β) [CD11b] upregulation, as well as CCR5 phosphorylation and internalization induced by ligand interaction. BMS-813160 is a full and reversible antagonist of both receptors and blocks CCR2- and CCR5-dependent functions in response to all known ligands. BMS-813160 is also at least 800-fold selective against a panel of other chemokine receptors (C-C chemokine receptor 1 [CCR1], C-C chemokine receptor 4 [CCR4], C-X-C chemokine receptor 2 [CXCR2], C-X-C chemokine receptor 3 [CXCR3], and C-X-C chemokine receptor 5 [CXCR5]) and a panel of G protein-coupled receptors (GPCRs)/transporters (21 targets).

In CCR2 PD models, BMS-813160 significantly reduced blood monocytes in human CCR2 knock-in (hCCR2 KI) mice and increased serum levels of monocyte chemotactic protein (MCP)-1 (ligand for CCR2) in hCCR2 KI mice and in monkeys at doses providing plasma concentrations that are greater than or equal to the CCR2 binding concentration at which 90% inhibition is observed (IC90). The compound also reduced blood monocytes in monkeys although the reduction was not statistically significant due to inter-animal variability. These data support the use of these 2 measurements, serum MCP-1 and absolute monocyte count, as CCR2 PD biomarkers in studies of BMS-813160. In CCR5 homeostatic models in the mouse, preliminary studies show that BMS-813160 robustly inhibited ex vivo-stimulated whole blood (WB) CD11b upregulation at doses providing plasma concentrations that are greater than or equal to the mouse CCR5 binding / CD11b IC90. When tested in naïve monkeys for its effect on CCR5 phosphorylation with or without ex vivo stimulation and CCR5 internalization with ex vivo stimulus, BMS-813160 significantly inhibited phosphorylation and internalization at plasma concentrations greater than or equal to the IC90 of CCR5. When studied in 48-hour thioglycollate (TG) peritonitis model using hCCR2 KI mice, BMS-813160 substantially reduced monocyte/macrophage influx into the peritoneal cavity, providing an estimated in vivo free plasma concentration required to yield 50% of the maximal response (EC50) value of 4.9 nM, which correlated well with the in vitro binding IC50 of 5.8 nM (mouse binding to human peripheral blood mononuclear cells [hPBMCs]). Maximal inhibition of monocyte/macrophage infiltration was achieved with approximately 98% receptor occupancy.

BMS-813160 was previously evaluated and found to be relatively safe and well tolerated in both healthy participant studies and in participants with diabetic kidney disease (DKD). To date, BMS-813160 has been studied in 4 clinical trials. Altogether, 167 participants have received at least one dose of BMS-813160 (108 healthy participants and 59 participants with diabetic kidney disease). In the single ascending dose study, BMS-813160 was safe after single dose administrations up to 2000 mg in healthy participants (NCT01049165). There were no deaths, serious adverse events (SAEs) or discontinuations due to AEs. All reported AEs were mild in intensity. At the 2000 mg dose there was an increased incidence of CNS-related AEs (dizziness and euphoric mood). Dizziness occurred in 5 participants (7.1%), all receiving BMS-813160, and all but 1 was considered

by the investigator to be related to study drug (n = 1 each in the 150 mg and 1200 mg groups, and n = 3 in the 2000 mg group). There were 2 participants in the 2000 mg BMS-813160 group and 1 participant in the placebo group who had AEs of euphoria. Multiple doses of BMS-813160 were safe and generally well tolerated in healthy participants across the dose range of 10 to 300 mg QD (N=24) and 300 to 900 mg BID (N=18) for 14 days. There were no deaths, SAEs, or discontinuations due to AEs in this study. AEs were reported by 17 (40.5%) participants receiving any dose of BMS-813160 and in 3 (21.4%) participants receiving placebo. There was no apparent dose relationship with respect to AEs. One AE of headache in a participant receiving BMS-813160 10 mg QD was considered moderate in intensity. All other AEs were considered to be mild in intensity. There were concentration-dependent increases in QRS and PR intervals and HR at 600 mg BID and 900 mg BID, without any ECG-related AEs or clinical sequalae. The increases in PR (mean < 16 msec at peak), QRS (mean < ~10 msec at peak), and HR (< ~10 bpm at peak) were not considered clinically significant. Concentration-response assessment showed no QTc prolongation. BMS-813160 was generally safe and well-tolerated when administered for 12 weeks.

1.3 Nivolumab (Opdivo)

Nivolumab is a fully human, immunoglobulin G4 (IgG4) [kappa] isotype monoclonal antibody that binds to PD-1 with nanomolar affinity (dissociation constant [Kd], 3.06 nM) and a high degree of specificity. Nivolumab blocks binding of PD-1 to its ligands PD-L1 and PD-L2. Nonclinical in vitro testing of nivolumab demonstrated that binding to PD-1 results in enhanced T-cell proliferation and release of interferon gamma (IFNγ) in vitro in mixed lymphocyte reaction and cytomegalovirus assays. Nivolumb is now approved as second line treatment for sorafenib-resistant hepatocellular carcinoma (HCC) and microsatellite-instability-high (MSI-H) colorectal cancer (CRC).

Combination clinical toxicology studies with BMS-813160 and nivolumab is now being evaluated in clinical trial (NCT03184870) for advanced PDAC and CRC. Side effects of nivolumab are similar to other anti-PD-1 antibodies and include pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies). There is no relationship between the incidence, severity, or causality of AEs and the nivolumab dose level.

Nivolumab 480 mg every 4 weeks (Q4W) is currently under active clinical evaluation across multiple tumor types (NCT03184870). Using a PPK model, nivolumab 480 mg Q4W is predicted to provide average steady-state concentrations (Cavgss) similar to nivolumab 3 mg/kg Q2W. Nivolumab 480 mg Q4W is predicted to provide greater (approximately 40%) Cmaxss and lower (approximately 20%) trough steady-state concentrations (Cminss). Nivolumab has been shown to be safe and well tolerated up to doses of 10 mg/kg Q2W and has not demonstrated a clear dose response or exposure-response safety relationship. Based on these safety findings, the predicted Cmaxss at 480 mg Q4W is not considered to put patients at increased risk for AEs. The approved doses of

3 mg/kg Q2W and 240 mg Q2W have shown survival benefit across multiple tumor types compared to respective standards of care. Nivolumab exposure was not a predictor of survival in exposure response efficacy analyses conducted for multiple tumor types.

Clinical evaluation of 480mg Q4W is ongoing; as such, summaries of safety information, PK, and immunogenicity are not currently available.

1.4 Summary of common or significant side effects for each agent

BMS-813160: Headache, dizziness, diarrhea, abnormal liver function, impaired wound healing, EKG changes (mild prolongation of QRS and PR at > 600mg BID was observed but not considered clinically-significant. Not expected to occur at 300mg BID as proposed in our study).

Nivolumab: infusion reaction, fatigue, diarrhea, immune-related toxicities including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatitis, encephalitis.

Gemcitabine: infusion reaction, nausea/vomiting, anorexia, flu-like symptoms, fatigue, peripheral edema, myelosuppression, abnormal liver function, abnormal kidney function, hemolytic uremic syndrome, pneumonitis, capillary leak syndrome, posterior reversible encephalopathy syndrome.

Nab-paclitaxel: infusion reaction, hypersensitivity, nausea/vomiting, fatigue, peripheral edema, peripheral/sensory neuropathy, abnormal liver function, abnormal kidney function, myelosuppression, pneumonitis, abnormal EKG, alopecia, rash, anorexia.

Overlapping toxicities: Pneumonitis, abnormal liver function, abnormal kidney function, EKG changes, myelosuppression.

Additional potential toxicities: We expect the majority of the acute side effects to be cause by chemotherapy. However, the combination of BMS-813160, nivolumab, gemcitabine and nab-paclitaxel may increase the risk for fatigue, diarrhea, pneumonitis and abnormal liver function based on overlapping toxicities. These will be monitored for during each clinical visit and dose-adjustments will be performed per protocol.

1.5 Study Rationale

The development of new clinical approaches that are effective against pancreatic ductal adenocarcinoma (PDAC) is a significant unmet medical need. One promising way to improve outcomes for patients with PDAC is to alter the tumor immune microenvironment to support therapeutic responses. Acute immune responses involving $CD8^+$ cytotoxic T lymphocytes (CTLs) and/or natural killer cells can effectively restrain tumor development and progression. Indeed, the few durable responses to therapy observed in PDAC are often associated with maintenance of the anti-tumor CTL activity that kills remnant tumor cells following therapy[5,13]. Unfortunately, to date, immunotherapy has struggled to achieve significant clinical benefit when used as a single therapeutic agent in PDAC[3]. This is likely

due to the presence of an immunosuppressive tumor microenvironment. Critical drivers of this immunosuppressive microenvironment are tumor-infiltrating inflammatory monocytes (IMs), tumor-associated macrophages (TAMs), and immature granulocytes[14-17]. In addition to instigating immune suppression, these tumor-infiltrating leukocytes impart resistance to cytotoxic therapies and promote metastatic dissemination[18-20]. Thus, high numbers of these cells correlate with early metastatic relapse and poor PDAC survival[5,21-23]. Therefore, approaches that reprogram the tumor microenvironment to potentiate protective anti-tumor immunity hold significant therapeutic potential.

We and other groups have demonstrated that mobilization and tumor infiltration of IMs and TAMs can promote tumor growth, dissemination, local immunosuppression, and resistance to cytotoxic therapy[5,18,23-25]. Signaling through C-C chemokine receptor type 2 (CCR2) is critical for the mobilization of IMs and their recruitment to inflamed tissues. Our recently published reports clearly illustrate that blockade of IM recruitment using CCR2 inhibitors (CCR2i), slows tumor progression, improves responses to chemotherapy, and prevents metastasis in mouse models of PDAC[5,23]. Based on these data, we initiated an early phase clinical trial targeting the CCR2 signaling pathway in patients with locally advanced PDAC. In this trial (NCT01413022), we have observed a remarkable 48.5% response rate in the 33 patients treated with CCR2i + FOLFIRINOX. This regimen was also well tolerated. Observed clinical responses correlate with a marked reduction in $CCR2^+$ IMs and TAMs in patient tumor tissue. In contrast, CCR2i + FOLFIRINOX significantly increased effector T cell infiltration and anti-tumor cytokines, suggesting that CCR2 inhibition overcomes the suppressive tumor microenvironment. Paralleling these clinical data, our published preclinical studies found that CCR2 blockade reinitiates anti-tumor responses by $CD8^+$ CTLs[5,23]. Intriguingly, we have discovered that CCR2 blockade in both human patients and mouse models leads to the up-regulation of T cell checkpoint pathways, including programmed cell death-1 (PD1) and its ligands (PDL1 and PDL2). In addition, additional targeting of CCL5-CCR5 should further blunt regulatory T cell response thereby further boast the function of cytotoxic T cells[9]. These data suggest that we might find unique therapeutic synergy between dual CCR2/5 inhibition and PD1 antagonists that could be harnessed to generate durable anti-tumor immunity and improved patient survival.

1.6 Correlative Studies Background

Studying immune infiltrates of pre- and post-treatment PDAC tumor is critical in informing the efficacy of tested regimen and potential resistance mechanisms. In this study, all enrolled patients will receive restaging radiographic scans after every 2 cycles of treatment to determine disease status. Treatment response will be defined by RECIST 1.1 criteria. Objective response rate (ORR) is defined as partial response plus complete response. Resectability will be assessed by the local treating oncologists, surgeons, and radiologists. Because this study enrolled patients with borderline resectable or locally advanced PDAC, endoscopic ultrasound-guided tumor biopsies will be performed at two different time points: less than 2 weeks before Cycle 1 Day 1 of treatment (pre-treatment), and within 2 weeks after Cycle 2 Day 15 of treatment (post-treatment).

Exploratory studies will be performed on the paired biopsied samples and include the following:

1. Peripheral and intra-tumoral CCR2 monocytes. Analyses of PB and tumor will be performed using flow cytometry as published[23]. We are particularly interested in changes in the number of IMs, which were predictive of survival in our published data[23].

2. Analyses of antigen-specific T lymphocytes in the periphery. Alterations in peripheral lymphocyte frequency will be determined with flow cytometry. To assess T lymphocyte functionality in PB, we will evaluate proliferation and cytokine profiles following polyclonal and/or PMA activation *ex vivo*. We will compare polyclonal activation of total PB (including IMs) to isolated $CD4^+$ and $CD8^+$ T cells. We will also examine the responsiveness of T lymphocytes to three common PDAC antigens, including mesothelin[26,27], MUC1[28], and CEA[29] using peptide stimulation of PBMCs, followed by ELISPOT[30] and MHC Dextramers responsiveness (IMMUDEX). Results will be compared to the non-tumor antigen responses to CMV. Analyses will be performed using a BD LSRFortessa-X20 (up to 20-color analysis). Based on the observed reprogramming of the tumor microenvironment[10], we anticipate that the proposed regimen will improve T cell responsiveness and/or cytokine production in response to tumor-specific antigens. If this is not observed, we will conclude that CCR2 blockade affects the activity of T cells in the tumor microenvironment rather than regulating systemic immune suppression.

3. Changes in the tumor immune microenvironment that facilitate T cell responses. We have developed techniques to routinely run both gene expression and flow cytometry on very limited amounts of tissue from EUS-guided FNAs or core biopsies. To assess changes in the tumor microenvironment, we will employ these techniques on samples from both clinical trials to assess how these therapies alter both the cellular immune infiltrate and the tumor cytokine microenvironment.

3a Cellular immune infiltrate: Using pre- and post-treatment core biopsies, we will directly assess how CCR2i therapies alter tumor-infiltrating immune populations using high-density flow cytometry. We have optimized these protocols to assess T cells, myeloid cells, and DC subsets and activation markers in three 15-color flow cytometry. Using this we fill focus on three questions:

1. How does CCR2i-based therapy impact the number, activation, proliferation, and checkpoint expression of tumor-infiltrating T cells?
2. How does CCR2i-based therapy alter the spectrum of tumor-infiltrating myeloid cells, including monocytes, macrophages, and granulocytes?
3. How does CCR2i-based therapy impact the number and phenotype of tumor-infiltrating antigen-presenting cells, such as dendritic cells and macrophages?
4. Does CCR2i-based therapy lead to the upregulation of checkpoint or other molecules of immunotherapeutic opportunity (such as LAG3 on T cells or CD40 on innate immune cells)?

3b Tumor cytokine microenvironment: We will analyze gene expression in tumor tissue following pre-amplification using two Taqman-based qRT-PCR arrays. We have designed

these arrays to contain 180 cytokines, immune effector, and checkpoints molecules. These analyses will yield information regarding alterations in the cytokine microenvironment, immunosuppression, and potential new targets for combined immunotherapy.

2 OBJECTIVES

2.1 Primary Objectives

1. Part A: To determine the safety of the combination of BMS-813160 plus nivolumab plus gemcitabine plus nab-paclitaxel.
2. Part B: To determine the objective response rate of patients with locally advanced and borderline-resectable pancreatic ductal adenocarcinoma treated with the combination of BMS-813160 plus nivolumab plus gemcitabine plus nab-paclitaxel.

2.2 Secondary Objectives (Part B)

1. To determine the percentage of patients with locally advanced and borderline resectable pancreatic ductal adenocarcinoma treated with the combination of BMS-813160 plus nivolumab plus gemcitabine plus nab-paclitaxel whose disease becomes resectable after treatment.
2. To determine the progression-free survival (PFS) of patients with locally advanced and borderline resectable pancreatic ductal adenocarcinoma treated with the combination of BMS-813160 plus nivolumab plus gemcitabine plus nab-paclitaxel.
3. To determine the overall survival (OS) of patients with locally advanced and borderline resectable pancreatic ductal adenocarcinoma treated with the combination of BMS-813160 plus nivolumab plus gemcitabine plus nab-paclitaxel.

2.3 Exploratory Objectives (Parts A and B)

1. To determine the prevalence and function of inflammatory monocytes in the peripheral blood and tumor of patients with locally advanced and borderline resectable pancreatic ductal adenocarcinoma before and after treatment with the combination of BMS-813160 plus nivolumab plus gemcitabine plus nab-paclitaxel.
2. To compare the difference in the immune cell infiltration and cytokine expression in the biopsied tumors of patients with locally advanced and borderline resectable pancreatic ductal adenocarcinoma before and after treatment with the combination of BMS-813160 plus nivolumab plus gemcitabine plus nab-paclitaxel.
3. To correlate changes in the immune infiltrate with clinical responses to treatment with the combination of BMS-813160 plus nivolumab plus gemcitabine plus nab-paclitaxel and survival following treatment with that combination.
4. To compare results of inflammatory monocyte, analysis, immune cell infiltration and cytokine expression analysis, and correlation of immune infiltrate with clinical response from patients enrolled to the experimental arm with results of analyses from patients enrolled to the control arm (if feasible and depending on the results).

3 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed locally advanced or borderline resectable pancreatic ductal adenocarcinoma. Patients with clinical suspicion of pancreatic adenocarcinoma can be enrolled for pre-treatment biopsy, and must be histologically confirmed to have adenocarcinoma before being treated on study. Patients with squamous carcinoma, adenosquamous carcinoma or neuroendocrine tumor will be excluded. Tumor Biopsy can be omitted, if deemed by PI and treating physician, that it may incur immediate, excessive health risks to patients. This determination (rationale and discussion with PI and treating physician) should be clearly documented in the screening visit notes.

2. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan or MRI.

3. At least 18 years of age.

4. ECOG performance status ≤ 1 (see Appendix A)

5. Normal bone marrow and organ function as defined below:
   a. Leukocytes ≥ 2,000/mcL
   b. Absolute neutrophil count ≥ 1,500/mcl
   c. Hemoglobin ≥ 8.5 g/dL
   d. Platelets ≥ 100,000/mcl
   e. Total bilirubin ≤ 1.5 x IULN (except participants with Gilbert's Syndrome who must have normal direct bilirubin)
   f. AST(SGOT)/ALT(SGPT) ≤ 3 x IULN
   g. Serum albumin ≥ 3g/dL
   h. Creatinine ≤ 1.5 x IULN OR creatinine clearance ≥ 40 mL/min by Cockcroft-Gault for patients with creatinine levels above institutional normal

6. Women of childbearing potential and men must agree to use at least two forms of contraception (hormonal, barrier method of birth control, abstinence, and must include barrier method) prior to study entry, for the duration of study participation, and through 5 months (for women) or 7 months (for men) after the last dose of treatment on this study. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

7. Able to understand and willing to sign an IRB approved written informed consent document.

8. All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0) or baseline before administration of study

treatment. Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum-based therapy, are permitted to enroll.

3.2 Exclusion Criteria

1. Prior exposure to chemotherapy or radiation for the disease to be treated on this trial not allowed.

2. Previous malignancies (except non-melanoma skin cancers, and *in situ* bladder, gastric, colorectal, endometrial, cervical/dysplasia, melanoma, or breast cancers) unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period. Other active malignancy requiring concurrent intervention

3. Currently receiving any other investigational agents, or exposure to any investigational drug or placebo within 4 weeks of study treatment

4. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to BMS-813160, nivolumab, gemcitabine, paclitaxel, nab-paclitaxel, or other agents used in the study.

5. Prior exposure to anti-PD-1, anti-PD-L1, CCR2/5, or anti-CTLA4 antibodies.

6. Taking immunomodulatory agents (including steroids and NSAIDs). A wash-out period of at least 4 weeks or 5 half-lives, whichever is shorter, is required for patients receiving immunomodulatory agents at the time of enrollment.

   NOTE: daily use of low dose aspirin (e.g. 81 mg PO QD) is not considered an immunomodulatory agent and patients are still eligible for enrollment despite taking such medication at a low dose.

7. Participants with active, known or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study treatment), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll after discussing with the Principal Investigator

8. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study treatment except for adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease. Note:

treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study treatment is permitted.

9. History of allogeneic organ or stem cell transplant.

10. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative pregnancy test within 14 days of study entry and again within 24 hours prior to first treatment.

11. Known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (by PCR).

12. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome. Anti-retroviral agents are known to have potential adverse pharmacokinetic interactions with nivolumab and/or BMS-813160. IN addition, patients not on anti-retroviral agents, regardless of HIV viral load, are at increased risk of lethal infections with marrow-suppressive therapy including chemotherapy. Testing for HIV must be performed at sites mandated by local requirements.

13. Requires continued use of warfarin for anticoagulation and cannot stop warfarin or be safely switched to another anticoagulant.

14. Current or recent (within 3 months of study treatment administration) gastrointestinal disease or conditions that could interfere with the swallowing or absorption of study medication or inability to tolerate oral medication.

15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral anti-bacterial, anti-viral, or anti-fungal therapy ≤ 7 days prior to administration of study medication; immunosuppression; autoimmune conditions; underlying pulmonary disease; or psychiatric illness/social situations that would limit compliance with study requirements.

16. Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity.

17. Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
    a. Myocardial infarction or stroke/transient ischemic attack within the past 6 months
    b. Uncontrolled angina within the past 3 months
    c. Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes)
    d. QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec

e. History of other clinically significant heart disease (e.g. cardiomyopathy, congestive heart failure with NYHA functional classification III-IV, pericarditis, significant pericardial effusion, or myocarditis)

18. Major surgery within 28 days prior to the first study treatment. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

19. Concurrent use of oral or intravenous medications, or food which may interfere with BMS-813160 including any strong inhibitors or inducers of CYP3A4 or P-gp is not allowed (see Appendix C). These include but are not limited to Class I antiarrhythmics (eg, quinidine, procainamide, dysopiramide, lidocaine, phenytoin, mexiletine, tocainide, flecainide, propafenone, moricizine), Grapefruit and Seville oranges.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date

6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5 TREATMENT PLAN

This study will be conducted in two parts. Part A is the dose safety lead-in phase. In Part A, approximately the first 16 patients will be randomized 1:1 to the control arm (where patients will receive chemotherapy only) or the experimental arm (where patients will receive BMS-813160 plus nivolumab plus chemotherapy). Randomization will stop after 8 patients have been deemed evaluable, as defined by having treated in the control arm, have undergone at least 2 cycles of treatment, pre- and post-treatment biopsies, and restaging scan. Therefore, more subjects may be randomized to complete 8 evaluable controls. After 8 evaluable patients have been enrolled and treated on the control arm, subsequent patients will be enrolled only into the experimental arm (up to 18 patients total including the patients previously randomized to the experimental arm) or in the expansion phase if MTD (or recommended phase II dose, RP2D) has been determined. These 8 patients who are enrolled in the control arm will serve as important controls for all analyses including toxicities, response rates and exploratory studies when determining the effect of gemcitabine plus nab-paclitaxel plus BMS-813160 and nivolumab. For patients randomized to the experimental arm, treatment will start at dose level 0 (refer to Section 5.2). Enrollment in the experimental arm will continued until an MTD is determined, which may require up to 18 subjects. Enrollment in the experimental arm will be conducted in the standard 3+3 fashion. For the first 3 subjects, if ≥ 2 subjects experience DLTs, dose de-escalation will be performed, and three new subjects will be enrolled. All patients already on the starting dose will resume treatment after recovery from previous toxicities, or continue on treatment at the new dose-deescalated level. Nine to 18 patients may be needed to determine an MTD if one or more dose de-escalation is warranted.

After the MTD of BMS-813160 and chemotherapy has been determined in Part A (or the RP2D), more patients will be enrolled at that dose level for a total of 30 patients, including the Part A experimental arm patients who were initiated at the MTD and stayed on treatment at that dose level. These patients will all be assessed for efficacy in Part B.

For all patients, a post-treatment biopsy will be performed after 2 cycles of treatment, followed by a restaging scan (pancreatic protocol CT or MRI). Patients who have disease progression per RECIST 1.1 criteria after the first 2 cycles of treatment will discontinue study treatment, and the next treatment option will be decided by the treating physicians. Patients who achieve stable disease, a partial response, or complete response after the first 2 cycles of treatment will continue to receive 2 more cycles of treatment followed by a restaging scan. Patients thought to have pseudo-progression, as evaluated as per Section 6.4, will continue to receive treatment for 2 more cycles. All remaining patients will come off treatment after 4 cycles of treatment. All patients treated on control or experimental arms will be followed up every 3-4 months after surgery or the last treatment on study for the first two years and per the physician's discretion beyond two years. Participants who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose of BMS-813160.

Patients with progressive disease or patients whose disease is not considered resectable after treatment will receive other treatments off study as determined by their treating oncologist. If deemed appropriate, patients may continue to be treated with gemcitabine and/or nab-paclitaxel. Patients whose disease is considered resectable will undergo surgical resection off study (with specimens collected as part of this study).

Treatment beyond radiographic disease progression per initial RECIST v 1.1 may be allowed in select participants after discussion and agreement with the PI and study supporter that the benefit/risk assessment favors continued administration of study treatment. These include: good tolerance of study treatment, stable performance status, treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases). These are considered investigator-assessed clinical benefit and must be clearly documented in clinic notes.

5.1 Agent Administration

BMS-813160 is an oral drug which will be given at the assigned dose twice (or once) daily for patients in Part A assigned to the experimental arm and all patients in Part B. If a patient misses a dose and the next scheduled dose is within the next 8 hours (or within the next 16 hours if being taken once daily), s/he should not make up that dose but simply resume dosing with the next scheduled dose. Therefore, patients should make up for the missed BMS-813160 dose as long as the next scheduled dose is more than 8 hours away (16 hours if once daily). If a patient should vomit within one hour after intake, s/he should make up for that dose as long as the next scheduled dose is more than 8 hours away (16 hours if once daily). Patients will be instructed to bring all unused drug and their medication diary (Appendix B) to each study visit for an assessment of compliance.

Nivolumab will be given as a 30-minute intravenous infusion at a flat dose of 480 mg on Day 1 (+/- 2 days) of each 28-day cycle for patients in Part A assigned to the experimental arm and all patients in Part B.

Gemcitabine will be given as a 30-minute intravenous infusion at the assigned dose (for all patients in Part A) or at the MTD (for all patients in Part B) on Days 1, 8, and 15 of each 28-day cycle. A window of +/- 2 days is allowed for D1, 8, and 15 of treatment, based on blood test results (see Section 6.3) and clinical assessment of patients by treating physicians. On days when both nivolumab and gemcitabine are given, a 30-minute rest is required between nivolumab and gemcitabine.

Nab-paclitaxel will be given as a 30-40-minute intravenous infusion at the assigned dose (for all patients in Part A) or at the MTD (for all patients in part B) on Days 1, 8, and 15 of each 28-day cycle. A window of +/- 2 days is allowed for D1, 8, and 15 of treatment, based on blood test results (see Section 6.3) and clinical assessment of patients by treating physicians.

5.2 Dose De-Escalation Schema – Part A

Part A: Safety Lead-In (Each cycle = 28 days)						
Arm (by randomization)	**BMS-813160 (D1-28)**		**Nivolumab (D1)**	**Chemotherapy (D1, 8, 15)**		
	Dose Level	**Dose**		**Dose Level**	**Gemcitabine**	**Nab-paclitaxel**
Experimental (n=9-18)	0 (starting)	300 mg BID	480 mg	0 (starting)	1000 mg/m^2	125 mg/m^2
	-1	150 mg BID	480 mg	-1	800 mg/m^2	100 mg/m^2
	-2	150 mg QD	480 mg	-2	600 mg/m^2	75 mg/m^2
Control (n=8)	N/A	N/A	N/A	0 (starting)	1000 mg/m^2	125 mg/m^2
	N/A	N/A	N/A	-1	800 mg/m^2	100 mg/m^2
	N/A	N/A	N/A	-2	600 mg/m^2	75 mg/m^2
Part B: Dose Expansion (Each cycle = 28 days)						
Dose expansion (N=30*)		Per Part A	480 mg		Per Part A	

* Total of 30 patients includes patients started on and stayed on MTD on experimental arm in Part A

5.3 Definition of MTD, DLT, and Dose Escalation Criteria – Part A

5.3.1 Definition of Maximum Tolerated Dose (MTD)

The maximum tolerated dose (MTD) is defined as the dose level at which 2 or less of a 6 treated patients experience dose-limiting toxicity during the first cycle (28 days). Dose de-escalations will proceed until the MTD has been reached. This will be the recommended phase II dose (RP2D) for Part B and any future clinical trials.

5.3.2 Dose Limiting Toxicities (DLTs)

For the purpose of guiding dose regimen, DLTs will be defined based on the incidence, duration, and grade of AEs for which no alternate cause can be identified. Adverse events will be evaluated according to the NCI CTCAE v5.0. The incidence of DLT(s) during the first cycle (28 days) of treatment in Part A (the

DLT evaluation period) will be used. Every attempt must be made to assign relationship to BMS-813160, nivolumab, chemotherapy or to all. Toxicities that are well recognized and expected with the chemotherapy backbone, as determined by treating physician and PI on the study, will not be counted as dose limiting for the entire regimen if the patient is on experimental arm. Also, to meet criteria for dose limiting, AEs have to be related to study treatment and not to disease progression or known common complications from the disease, be clinically relevant, and be a clinically relevant shift from baseline (see Section 6). Consideration will be given to a participant's ability to tolerate the regimen during the safety lead-in phase. Participants experiencing a DLT may be treated at one dose reduction of BMS-813160 and/or chemotherapy as long as they recover from the toxicity and do not meet discontinuation criteria, and as long as it is in the best interest of the participant per the treating physician, and after discussion with the Principal Investigator and Sponsor Participants who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose of BMS-813160.

Continue to monitor all patients for approximately 100 days following discontinuation of the study treatment for late immune-related toxicities that have been associated with immunotherapy products. Consider any such late toxicities in the determination of the maximal tolerated dose and dose schedule to be taken forward into the expansion phase of the study.

Hematologic DLT is defined as any of the following that occur during the first cycle that are attributed as possibly, probably, or definitely related to the study treatment:

- Grade 4 neutropenia (ANC < 500 cells/mm^3) > 7 consecutive days without growth factor support
- Febrile neutropenia of any duration with temperature ≥ 38.5 °C
- Grade 4 anemia regardless of duration
- Grade 2 or above thrombocytopenia (platelets < 75,000/mm^3)

Non-hematologic DLT is defined as any possibly, probably, or definitely related grade 3 or grade 4 non-hematologic toxicity that occurs during the first cycle with the following specific exceptions:

- Grade 3 diarrhea that responds to optimal antidiarrheal therapy
- Grade 3 nausea or vomiting that responds to optimal antiemetic therapy
- Grade 3 prolonged QTc interval on at least two separate ECGs, which are corrected by underlying causes including electrolytes abnormalities or abnormal fluid status, not complicated by adverse clinical experiences and not thought to be related to treatment
- Grade 3 increase in total bilirubin that improves within 48 hours.
- Grade 3 electrolyte or laboratory 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
- Isolated Grade 3 or 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis

Other events that are considered DLTs are:

- Autoimmune hypophysitis (any grade)
- Persistent (>4 weeks) unresolved grade≥3 hepatitis not corrected by interventions including biliary drainage, adjustment of medications and strongly suspected to be related to nivolumab, BMS-8313160 or chemotherapy.
- Pneumonitis (at least grade 2)
  Any toxicity that is possibly, probably, or definitely related to study treatment that results in failure to receive at least approximately 75% of the planned doses of BMS-813160 during Cycle 1 (e.g. failure to complete at least 21 days of treatment in a continuous 28-day regimen) despite maximal supportive care measures is also considered a DLT.

5.3.3 Dose De-escalation Criteria

Dose de-escalations will proceed as follows after the occurrence of dose-limiting toxicity (DLT). Dose de-escalation of BMS813160 and/or chemotherapy should be conducted separately based on consideration of DLTs contributed individually by these agents (see Section 6).

Number of Patients with DLT at a Given Dose Level	**De-Escalation Decision Rule**
0 out of 3	Stop de-escalation. This is defined as RP2D.
1 out of 3	Treat 3 more patients at the dose level. • If 0 of these 3 experiences DLT, then stop de-escalation. • If 1 or more experience DLT, then proceed to the next dose level.
>=2 out 3	Treat 3 new patients at the next dose level.

5.4 Toxicity, Response, and DLT Evaluations

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 100-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment due to treatment related adverse events(s) prior to completion of Cycle 2 and have not had any disease assessment.

A patient is evaluable for DLT assessment only if enrolled to the experimental arm during Part A of the study and only during Cycle 1 of treatment. If the patient is not able to be treated on Day 1 of Cycle 2, then s/he is still considered in Cycle 1 active treatment and

will continue to be evaluated for DLT. Once the patient has been treated in Cycle 2, s/he will no longer be evaluated for DLTs in all subsequent cycles.

5.5 Part B – Dose Expansion

After the MTD is determined in Part A, additional patients will be enrolled in Part B to reach a total of 30 patients treated at the MTD dose level (including part A)

5.6 General Concomitant Medication and Supportive Care Guidelines

Supportive care will be administered as per routine practice. This typically will include loperamide as needed for diarrhea, and antiemetic medication for symptoms of nausea or emesis. Intravenous fluid support will be provided at the discretion of the treating physician for patients who experience significant nausea, emesis, or diarrhea. For grade 3 or greater skin toxicity, dermatology consult is recommended. Oral antibiotics (such as minocycline or doxycycline should be considered at any sign of rash. Topical cleomycin should also be considered at the first sign of rash.

Prohibited and/or restricted medications taken prior to study treatment administration in the study are described below. Medications taken within 4 weeks prior to study treatment administration must be recorded on the CRF.

- In vitro, the metabolism of BMS-813160 was primarily mediated via cytochrome P450(CYP) 3A4, with some contribution from CYP3A5, and BMS-813160 was also a substrate for P-glycoprotein (P-gp). Based on these results, the potential exists for drug-drug interaction if BMS-813160 is co-administered with inhibitors or inducers of CYP3A or P-gp. Therefore, use of any oral or intravenous strong inhibitors or inducers of CYP3A4 or P-gp is not allowed, but topical use is allowed (see Appendix C).
- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and should not be consumed while on study.
- Caution is warranted with concomitant use of MATE1 substrates with a narrow therapeutic index (see Appendix D).
- Exposure to any investigational drug or placebo within 4 weeks of study treatment
- administration.
- Class I antiarrhythmics (eg, quinidine, procainamide, dysopiramide, lidocaine, phenytoin, mexiletine, tocainide, flecainide, propafenone, moricizine).
- In limited circumstances (eg, life threatening illness) the use of the above medications may be permitted.

5.7 Women of Childbearing Potential (WOCBP)

Women of childbearing potential are defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation). 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. Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. 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. WOCBP are required to have a negative pregnancy test within 14 days prior to the first day of study treatment, within 24 hours prior to first treatment, and every 4 weeks while on treatment

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.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 5 months (for women) or 7 months (for men) following the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 3 months after the last dose of study treatment, the investigator must be notified in order to facilitate outcome follow-up.

5.8 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for a total of 4 cycles or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.9 Duration of Follow-up

Patients will be followed every 3 to 4 months after being off treatment for 3 years or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, or up to 100 days after the last dose, whichever is later. Patients that did not undergo surgery may be contacted via phone for follow-up assessments.

6 DOSE DELAYS/DOSE MODIFICATIONS

Participants will be monitored continuously for AEs while on study therapy. Participants will be instructed to notify their physician for any and all AEs. Dose modifications in this section for chemotherapy are meant as a general guidance. Modifications should be applied by the investigator's judgment. In case of an AE relationship assignment to chemotherapy alone, dose modifications for chemotherapy alone are allowed. In case of doubt, both chemotherapy and BMS-813160 doses should be modified. Also, in case of assignment of AE relationship to BMS-813160 alone, dose reduction for chemotherapy is not mandated. Specific algorithms for the management of immune-related AEs are provided in Appendix E and are applicable to immune-related AEs for all immuno-oncology study treatment combinations. For chemotherapy agents, the package insert and local standard of care rules for dose reduction should also be applied.

For an AE requiring dose modification, BMS-813160, chemotherapy, and/or nivolumab should be interrupted to allow recovery from the AE. Re-initiation of study treatment cannot occur until the AE decreases to ≤ Grade 1 or baseline assessment. In case of delayed recovery to ≤ Grade 1 or baseline from treatment-related AEs that result in a delay of treatment for > 28 days, the participant

will not receive additional protocol-related therapy and will be removed from study unless discussed and agreed upon by the Investigator that it is in the best interest of the participant to receive additional therapy with BMS-813160 and/or other study treatments.

6.1 Dose Modifications for BMS-813160

Please refer to Section 5 for study drug administration guidelines.

Dose Level	BMS-813160
0 (starting)	300 mg BID
-1	150 mg BID
-2	150 mg QD

- New onset of QTcF intervals > 500 msec or prolongation > 50 msec over baseline, new onset QRS intervals > 140 msec, new onset bundle branch block or symptomatic bradycardia, Type 2 second or third-degree heart block will require dose interruption and restarting at one dose level lower. Any electrolyte abnormalities should be corrected and ECG should be repeated with cardiology consultation if clinically indicated.
- Grade 3 non-hematologic toxicity or Grade 4 non-hematologic toxicity attributed to BMS-813160 will require immediate discontinuation until recovery to baseline. BMS-813160 will then be resumed at one dose level reduction.
- Any Grade 3 laboratory only abnormalities without clinical manifestations or electrolyte abnormalities that may be managed with supplementation can be managed with dose delay and do not automatically need dose modification.
- Participants who hold BMS-813160 for 7 days or fewer for reasons other than drug toxicity will skip those days and continue on BMS-813160 treatment for the rest of the cycle.
- Participants who hold BMS-813160 for more than 7 days or for drug toxicity will hold treatment for the remainder of the cycle and start at a reduced dose for the next cycle.
- Participants who hold BMS-813160 for more than 7 days due to events deemed unlikely or not related to BMS-813160 may resume BMS-813160 at the same dose level after discussion with the PI and when it is deemed safe to resume treatment by the treating physician. Missed doses will be skipped.
- If chemotherapy or nivolumab is delayed due to toxicity attributable to chemotherapy or nivolumab alone or due to scheduling issues, participants can continue on BMS-813160 alone. Participants who need a dose reduction for toxicity attributable to BMS-813160 will continue on the reduced dose of BMS-813160 for the remainder of the study.
- If a participant needs more than 2 dose reductions of BMS-813160 for toxicity, the participant will be taken off BMS-813160 and nivolumab, but can continue chemotherapy if it is determined to be in the participant's best interest as per the treating investigator.
- If a participant is off BMS-813160 for more than 28 days, the participant will permanently discontinue treatment and be taken off study, unless it is determined to be in the participant's best interest as per the treating investigator.

6.2 Dose Modifications for Nivolumab

No dose modifications allowed. Doses can be delayed for side effects. Nivolumab will be withheld for drug-related toxicities and severe or life-threatening AEs as per the table below.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

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 the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

- Any Grade 4 drug-related adverse event 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 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, 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 BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 4 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor Investigator.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 4 weeks, the Sponsor Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

6.3 Dose Modifications for Gemcitabine and Nab-Paclitaxel

Dose Level	**Gemcitabine**	**Nab-Paclitaxel**
0 (starting)	1000 mg/m^2	125 mg/m^2
-1	800 mg/m^2	100 mg/m^2
-2	600 mg/m^2	75 mg/m^2
If additional dose reduction required	At PI's discretion	

Dose Modifications for Hematological Toxicity

Cycle Day	ANC (cells/mm3)		Platelet count (cells/mm3)	Dosing Adjustment
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	< 1000 [a, b]	OR	< 75,000 [a, b]	Withhold doses [1, 4]
Day 15 if Day 8 doses were reduced or given without modification	< 1000 [a, b]	OR	< 75,000 [a, b]	Withhold doses [1, 4]
Day 15 if Day 8 doses were withheld	≥ 1000	OR	≥ 75,000	Treat with 1 dose level reduction from Day 1
	< 1000 [a, b]	OR	< 75,000 [a, b]	Withhold doses [1, 5]

1. Doses held during a cycle (i.e. D8 or D15) will not be made up.
    a. If ANC < 500 with C1, re-check CBC within 7 days. If ANC < 500 for 7 days or longer, consult with PI and Treating MD to determine if DLT was met (per Section 5.3.2)
    b. If platelets < 75,000 with C1, may be DLT. Consult with PI and Treating MD to determine if DLT was met (per Section 5.3.2)
2. Grade 3-4 Febrile Neutropenia at any point in the cycle (defined as temperature > 101°F with a neutrophil count of < 1000 cells/ml), hold dosing until fever resolution and ANC > 1500 and resume at next lower dose level.
3. Recurrent Grade 3-4 Febrile Neutropenia at any point in the cycle 1 or 2, hold dosing until fever resolution and ANC > 1500 and resume at next lower dose level.
4. Upon recovery of platelets ≥ 75,000 and ANC ≥ 1000, dose reduce 1 level at next scheduled visit
5. Upon recovery of platelets ≥ 75,000 and ANC ≥ 1000, dose reduce 2 levels at next scheduled visit

Dose Modifications for Other Treatment-Related Non-Hematological Toxicities

Adverse Drug Reaction	Gemcitabine	Nab-Paclitaxel
Peripheral neuropathy (Grade 2)	No dose reduction	Dose reduction allowed PI discretion
Peripheral neuropathy (Grade 3 or 4)	No dose reduction	Withhold until improves to ≤ grade 1; resume at next lower dose level
Cutaneous toxicity (Grade 2 or 3)	Reduce to next lower dose level; discontinue treatment if grade 2 or 3 toxicity persists	
Gastrointestinal toxicity (Grade 3 mucositis or diarrhea)	Withhold until improves to ≤ grade 1; resume at next lower dose level	
Unexplained dyspnea or other evidence of severe pulmonary toxicity	Discontinue	No dose reduction
Grade 3 or 4 hepatic toxicity	Dose Modification at PI or Tx MD Discretion. If attributed to Gemcitabine, and not recovered to G1 after 4 weeks, permanently discontinue	Do not administer to patients with total bilirubin > 1.5 x IULN or AST > 10 x IULN
Hemolytic-Uremic Syndrome	Discontinue	No dose reduction
Capillary Leak Syndrome	Discontinue	No dose reduction
Posterior Reversible Encephalopathy Syndrome	Discontinue	No dose reduction
Other grade 3 or 4 non-hematological toxicity (except nausea or vomiting)	Withhold or reduce by one dose level either one or both drugs after discussion with PI	
Grade 3 or 4 nausea and vomiting	If strongly attributed to chemotherapy, dose reduction at PI's discretion upon resolution to G1 or baseline	

6.4 Treatment Beyond Progression

Pseudoprogression is a possibility for patients who experience actual clinical benefit from immunotherapies despite initial radiographic progression (see Section 12). Therefore, participants will be permitted to continue treatment beyond initial RECIST v1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/scan should be performed at the next scheduled scan to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued

study treatment. If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the study calendar. For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Study treatment should be discontinued permanently upon documentation of further progression. The tumor burden volume from time of initial progression should be used as the reference baseline for comparison with the post progression assessment.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

7 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix F for definitions and Appendix G for a grid of reporting timelines.

Adverse events will be tracked from the time of consent until the date of surgery, or 100 days after the last dose of treatment on study if patients do not go for surgery. Patients that did not undergo surgery may be contacted via phone for follow-up assessments. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Adverse events related to off-study, non-protocol related therapy

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1. Reporting requirements for secondary site study teams participating in Washington University-coordinated research may also be found in Section 7.2.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Washington University Sponsor-Investigator (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submissions to QASMC must include the myIRB form and any supporting documentation sent with the form.

For events that occur at secondary sites, the Washington University Sponsor-Investigator (or designee) is required to notify the QASMC within 10 days of Washington University notification via email to qasmc@wustl.edu. Submission to QASMC must include either the myIRB form and supporting documentation or (if not submitted to myIRB) the date of occurrence, description of the event, whether the event is described in the currently IRB approved materials, the event outcome, determination of relatedness, whether currently enrolled participants will be notified, and whether the informed consent document and/or any study procedures will be modified as a result of this event.

7.1.3 Reporting to Bristol Myers Squibb

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of 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 (eg, 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.

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 FDA 3500a MedWatch SAE form.

Pregnancies must be reported and submitted to BMS on a MedWatch SAE form.

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 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.

7.1.3.1 Reconciliation

The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and 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.

7.1.3.2 Early Asset every 3 month AE reporting

Adverse Events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month.

The Adverse Event information required to be sent to BMS is noted in an attached 'Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan' which describes the method of collection and submission to BMS via the mailbox: MG-RD-GPVE-PHARMACOVIGILANCE@bms.com

When the file is submitted to BMS, it must be noted the file contains:

- All Non-serious Adverse Events (only adverse events not previously submitted to BMS within the 3 months).

7.1.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University principal investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix Ffor definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix F) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix F) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
  - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.1.5 Reporting to Secondary Sites

The Washington University Sponsor-Investigator (or designee) will notify the research team at each secondary site of all unanticipated problems involving risks to participants or others that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the Sponsor-Investigator or designee of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable. Refer to section 16.0 (Multicenter Management) for more information.

7.2 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University Sponsor-Investigator and designee of all serious adverse events (as described in APPENDIX F and G) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report using FDA Form 3500a (MedWatch) form and Washington University's Cover Sheet (APPENDIX H). A formal written report must be sent to the Washington University Sponsor-Investigator and designee within 4 **calendar days** (for fatal or life-threatening suspected adverse reactions**) or 11 calendar days (for serious unexpected suspected adverse reactions)** of the occurrence of the event or notification of the secondary site's PI of the event

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA and Bristol Myers Squibb as needed.

Washington University pre-approval of all protocol exceptions must be obtained prior to implementing the change. Local IRB approval must be obtained as per local guidelines. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

8 PHARMACEUTICAL INFORMATION

8.1 BMS-813160

8.1.1 BMS-813160 Description

Molecular Formula: $C_{25}H_{40}N_8O_2$
Molecular Weight: 484.64

8.1.2 Clinical Pharmacology

Inhibition of the CCR2 receptor with BMS-813160 impedes the ability of MCP-1 to bind to the CCR2 receptor and internalize to activate subsequent signaling pathways within the cell. As this internalization of MCP-1 is the main mechanism of MCP-1 clearance from the circulation, inhibition of this association and internalization would lead to increases in MCP-1 in circulation. Therefore, if BMS-813160 effectively binds to and inhibits the CCR2 receptor, MCP-1 levels in the plasma would increase.

8.1.3 Pharmacokinetics and Drug Metabolism

- The t½ of BMS-813160 in dose groups that had a well characterized terminal phase was approximately 12 to 18 hours, which may be amenable for QD dosing.
- Renal excretion (%UR) of BMS-813160 generally increased and CLT/F generally decreased with increasing dose, suggesting a dose-related increase in the oral bioavailability of BMS-813160.
- A total of 81.5% of the administered radiolabeled dose was recovered as [14C]: the majority in feces (58.7%) and the remaining amount in urine (22.8%).
- BMS-813160 was the predominant drug-related component in the plasma, and BMS-939429 was a prominent metabolite, accounting for 53% and 30% of total [14C]. The parent drug, together with selected metabolites that were quantified with an exploratory LC-MS/MS assay, comprised approximately 87% of the circulating radioactivity.

8.1.4 Supplier(s)

BMS-813160 will be supplied by Bristol Myers Squibb. 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.

8.1.5 Dosage Form and Preparation

BMS-813160 is available in 150-mg strength capsules for oral administration.

8.1.6 Storage and Stability

BMS-813160 capsules should be stored between 2°C and 25°C (35.6°F and 77°F) in a tightly closed container.

8.1.7 Administration

To be taken by mouth on a daily basis as described in Section 5.1.

8.1.8 Special Handling Instructions

None.

8.2 Nivolumab (Opdivo)

8.2.1 Nivolumab Description

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with:

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent
- BRAF V600 mutation positive unresectable or metastatic melanoma, as a single agent
- Unresectable or metastatic melanoma, in combination with ipilimumab
- Metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy
- Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin
- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy

It is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

8.2.2 Clinical Pharmacology

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human

immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

8.2.3 Pharmacokinetics and Drug Metabolism

The pharmacokinetics (PK) of nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

8.2.4 Supplier(s)

Nivolumab will be supplied by Bristol Myers Squibb. 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.

8.2.5 Dosage Form and Preparation

Nivolumab is available as a 40 mg/4 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) solution in a single-use vial. Each kit will contain 1 40mg vial and 2 100mg vials. As Nivolumab is administered fixed dose at 480mg, each patient will be dispensed 2 kits per dose to achieve the 480mg target.

- Withdraw the required volume of nivolumab and transfer into an intravenous container.
- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.

8.2.6 Storage and Stability

The product does not contain a preservative.

After preparation, store the nivolumab infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze, Protect from Light

8.2.7 Administration

Administer the infusion over 30 minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

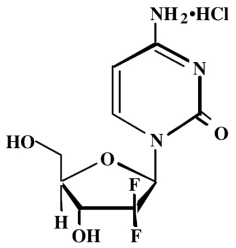
Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

8.3 Gemcitabine (Gemzar)

8.3.1 Gemcitabine Description

Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer). The structural formula is as follows:



The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4 \cdot HCl$. It has a molecular weight of 299.66.

8.3.2 Clinical Pharmacology

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible

for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

8.3.3 Pharmacokinetics and Drug Metabolism

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m^2/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2'-deoxy-2',2'-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

8.3.4 Supplier(s)

Gemcitabine will be given as per routine care from commercial supply.

8.3.5 Dosage Form and Preparation

Gemcitabine for injection, USP, is available in sterile single-use vials individually packaged in a carton containing: 200 mg white to off-white lyophilized powder in a 10-mL size sterile single use vial or 1 g white to off-white lyophilized powder in a 50-mL size sterile single use vial.

8.3.6 Storage and Stability

Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature 20°C to 25°C and that allows for excursions between 15°C and 30°C.

8.3.7 Administration

Gemcitabine should be given as an intravenous infusion over the course of 30 minutes.

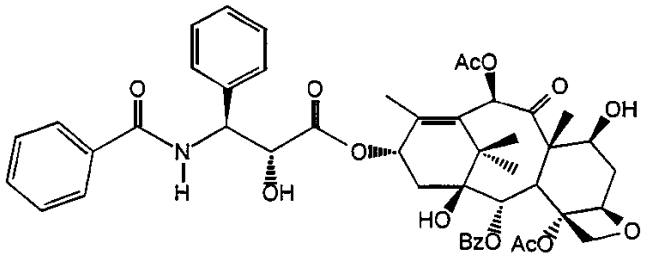
8.3.8 Special Handling Instructions

No special handling instructions.

8.4 Nab-Paclitaxel (Abraxane)

8.4.1 Nab-Paclitaxel Description

Nab-paclitaxel is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. The active agent is paclitaxel, a microtubule inhibitor. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine. Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216-217°C.

8.4.2 Clinical Pharmacology

Nab-paclitaxel is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

8.4.3 Pharmacokinetics and Drug Metabolism

Following intravenous administration of nab-paclitaxel, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was approximately 27 hours.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6αhydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the

concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

8.4.4 Supplier(s)

Nab-paclitaxel will be given as per routine care from commercial supply.

8.4.5 Dosage Form and Preparation

It is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20mL of 0.9% sodium chloride injection, USP prior to intravenous infusion. Each single use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter of reconstituted suspension contains 5 mg paclitaxel.

8.4.6 Storage and Stability

Store the vials in original cartons at 20°C to 25°C. Retain the original package to protect from bright light.

8.4.7 Administration

Nab-paclitaxel should be given as an intravenous infusion over the course of 30 to 40 minutes.

8.4.8 Special Handling Instructions

No special handling instructions.

9 CORRELATIVE STUDIES

9.1 Tumor Biopsy

9.1.1 Collection of Specimens

Collection of tumor core biopsies at the following time points is required:

- Pre-treatment
- End of C2
- End of treatment for patients who progress or otherwise do not go to surgery
- Surgery for patients who do go to surgery

A total of three core biopsies (with a 22-gauge needle) will be taken at each time point from each patient.

Tumor Biopsy can be omitted, if deemed by PI and treating physician, that it may incur immediate, excessive health risks to patients. This determination (rationale and discussion with PI and treating physician) should be clearly documented in visit notes.

9.1.2 Handling of Specimens

Both cores are to be cut in half with the top portion placed in 10% formalin buffered in PBS and the bottom portion snap frozen in liquid nitrogen. Follow the processing instructions in the lab manual.

9.1.3 Shipping of Specimens

Ship snap frozen specimens on dry ice and samples in ethanol on cold packs, Monday through Thursday only, via FedEx to:

Dr. David DeNardo
Washington University School of Medicine
425 S. Euclid Ave.
Campus Box 8069
St. Louis, MO 63110

9.2 Peripheral Blood

9.2.1 Collection of Specimens

Four heparinized green-top tubes each containing 8-10mL of blood will be collected at the following time points:

- Cycle 1 Day 1 before treatment begins
- after 2 cycles of treatment +/- 3 days of mandatory tumor biopsy
- End of treatment for patients who progress or otherwise do not go to surgery
- no more than 24 hours prior to time of surgery (if applicable)

9.2.2 Handling of Specimens

Mix all blood tubes and process promptly (within 1 hour) upon receipt. Follow the processing instructions in the lab manual.

9.2.3 Shipping of Specimens

Specimens will be collected by CRA and hand-delivered to the following labs:

Dr. David DeNardo

Washington University School of Medicine
425 S. Euclid Ave.
Campus Box 8069
St. Louis, MO 63110

10 STUDY CALENDAR

Screening/baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done no more than 4 weeks prior to the start of the protocol therapy. There is a +/- 2-day window for D1, D8, and D15 of treatment, all laboratory assessments, and +/- 7-day window for radiographic assessments and research tumor biopsies. All lab evaluations will be reviewed with regard to dosing timeframe on D1, D8, D15.

	Screening	**Pre-Tx**	**Each 28-day cycle[2]**			**End of C2**	**End of C4**	**End of tx**	**Surgery[5]**	**Follow-up[9]**
			D1	**D8**	**D15**					
Informed consent	X									
Physical exam, ECOG PS	X		X	X (D8 or D15)						
CBC plus differential[13]	X		X	X	X					
CMP[14]	X		X	X	X					
CA19-9 or CEA	X		X							
Pregnancy test[1]	X	X[11]	X							
CT or MRI	X					X[4]	X			X
EKG	X		X							
Randomization[3]		X								
BMS-813160			Taken daily[6]							
Nivolumab			X[6]							
Gemcitabine			X	X	X					
Nab-paclitaxel			X	X	X					
Research tumor biopsy		X[15]				X[15]		X[7,15]	X[15]	
Research blood draw			X[8]			X		X[7]	X[12]	
AE assessment		X---------- X[10]								
Progression and survival										X

1. Women of childbearing potential only
2. Total of up to 4 cycles
3. Part A patients only
4. Patients who progress will discontinue treatment at this point, while patients who achieve SD, PR, or CR will receive 2 more cycles of treatment
5. Patients whose disease is considered resectable will undergo resection and come off treatment (with specimens collected as part of this study)
6. To patients randomized to the experimental group in Part A and all patients in Part B
7. For patients who progress or otherwise do not go to surgery
8. Before treatment C1D1 only
9. Q3-4Mo after whipple/EOT tumor collection for the first two years after surgery or until progression, whichever happens first
10. For patient proceeding to surgery (i.e .Whipple) at end of study treatment, collect until date of surgery. For patients that do no undergo surgery, collect for 100 days after last day of treatment. Patient may be contacted by phone for these post study treatment follow-up assessments.
11. No more than 24 hours prior to the start of treatment
12. Up to 24 hours prior to surgery
13. CBC is WBC, Hb, Hct, Plt, MCV, RDW, differential includes neutrophil, lymphocyte, monocyte percentage and absolute counts

14. CMP is albumin, BUN, calcium, bicarbonate, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein, ALT, AST, and ALP
15. Tumor Biopsy can be omitted, if deemed by PI and treating physician, that it may incur immediate, excessive health risks to patients. This determination (rationale and discussion with PI and treating physician) should be clearly documented in visit notes.

11 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Research Tissue Form	Pre-treatment, end of C2, EOT / surgery
Research Blood Form	C1D1, end of C2, surgery
Follow Up Form	Every 3-4 months after whipple/EOT tumor collection for the first two years after surgery and per physician's discretion afterwards
Tumor Measurement Form	Baseline, end of C2, end of C4
MedWatch Form	See Section 7.0 for reporting requirements

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

11.1 AE Reporting in the EDC

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

12 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

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) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

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

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

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

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

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

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

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should

also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

New lesions: New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

12.3 Methods for Evaluation of Measurable Disease

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 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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific

MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

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

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

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

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

12.4.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

12.4.4 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

12.4.5 Progression-Free Survival

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

12.4.6 Response Review

It is strongly recommended that all responses be reviewed by an expert independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

13 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this

trial to review toxicity data. A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

Until such a time as the first secondary site enrolls its first patient, a semi-annual DSM report to be prepared by the study team will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after study activation at Washington University (if at least one patient has been enrolled) or one year after study activation (if no patients have been enrolled at the six-month mark).

The DSM report will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). The DSMB must meet at least every six months beginning six months after enrollment of the first patient at a secondary site and no more than one month prior to the due date of the DSM report to QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site, and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites and separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMB charter.

The study principal investigator and coordinator will monitor for all serious and non-serious adverse events on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

14 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

15 STATISTICAL CONSIDERATIONS

15.1 Part A

Data on the tolerability and toxicity of the combination therapy will be collected for each subject, including frequency, type, and severity of adverse events. Based on the treatment plan (Section 5.0), 16 patients are randomized to 1:1 to control or experimental arm through block randomization without stratification factors. After 8 evaluable patients have been enrolled and treated on the control arm, subsequent patients are enrolled only into the experimental arm. Up to 18 patients will be enrolled on experimental arm to determine an MTD. Due to small sample sizes and dose heterogeneity, no statistical tests of hypotheses are planned specifically for this part of the study, but patients who receive MTD will be included in Part B for final analyses including ORR, PFS, OS and exploratory studies.

15.2 Part B

Part B will be conducted subsequently to determine if there is a sufficiently high objective response rate (ORR) to warrant further studies.

15.2.1 Sample size calculation

The primary endpoint is ORR and the secondary endpoints include PFS and OS. The sample size calculation is based on the primary endpoint only. The objective response rate (ORR) of Gem/Abraxane in the MPACT study was 23%[31] and the disease control rate (DCR) was 48%.. There is interest in pursuing future studies if the DCR is greater than 75%. A Simon optimal 2-stage design will test the null hypothesis that the true disease control rate (DCR) is less than or equal to 48% versus the alternative hypothesis that it exceeds 48% at the type I error rate of 5%. In the first stage, 9 patients will be accrued. If the study continues, 19 additional patients will be accrued. This design will have at least 80% power to reject the null hypothesis when the true DCR is 75%.

The patients treated at the MTD in part A will be included in this expansion cohort.

15.2.2 Stopping rule

If 5 or fewer DCRs are observed out of these 9 patients, the study will be stopped. Otherwise, an additional 19 patients will be enrolled in the second stage. If 18 or more DCRs are observed out of these 28 patients, we would conclude that preliminary evidence for efficacy exists.

15.3 Statistical analysis

Descriptive statistics will be used to summarize demographic and clinical characteristics, as well as the trial results, i.e., statistics for continuous variables may include means, medians, ranges and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. All data will be evaluated as observed, and no imputation method for missing values will be used. The primary endpoint ORR and toxicity rates, and associated 95% confidence intervals, will be calculated assuming a binomial distribution of the number of subjects responding or experiencing toxicity. Due

to the possibility of enrollment stopping early based on response, these empirical rates may not be exactly unbiased, nor may the confidence intervals achieve exactly the correct coverage. These statistical summaries are useful descriptive statistics, however, and will still be calculated. The Kaplan-Meier method will be used to calculate the probability of OS and PFS. OS is defined as days from date of treatment to date of death within 3 years after surgical resection. Patients alive or lost to follow-up are censored at the last treatment on study or 3 years after surgical resection, regardless of subsequent treatment received. PFS is defined as the days from the date of treatment and death or progression, which occurs first. Patients alive without progression or lost to follow-up are censored at the last follow-up. For exploratory endpoints, investigations will use Wilcoxon signed-tests and paired t-tests to compare the difference of continuous variables before and after treatment, and Fisher's exact tests to compare binary response.

16 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: BMS-813160 Cycle: _____ Pt #: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _____mg (___capsules) of BMS813160 _____ daily.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forget to take your dose at the right time, you should make up for the missed BMS-813160 dose as long as the next scheduled dose is more than ___ hours away. If you should vomit within one hour after intake, you should make up for that dose as long as the next scheduled dose is more than ___ hours away and you see intact capsule. If your next scheduled dose is less than ___ hours away, do not take that dose. Restart it with the next dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?		Comments
		AM dose	PM dose	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
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25				
26				
27				
28				

APPENDIX C: CYP3A4 and P-GP 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

Please note these are not exhaustive lists. **Only intravenous and oral therapy for strong CYP3A4 inhibitors such as ketoconazole are contraindicated. Topical use of CYP3A4 inhibitors is allowed.**

CYP Enzymes	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

CYP Enzymes	Strong Inducers	Moderate Inducers	Weak Inducers
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, Echinacea, pioglitazone, prednisone, rufinamide

Transporter	Inhibitors
P-gp	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil

APPENDIX D: MATE Substrates Guidance

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

Transporter	Substrates
MATE	Metformin, cisplatin, oxaliplatin, ganciclovir, acyclovir, procainamide, captopril, quinine

APPENDIX E: Nivolumab Management Algorithms

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

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

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

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

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

GI Adverse Event Management Algorithm

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

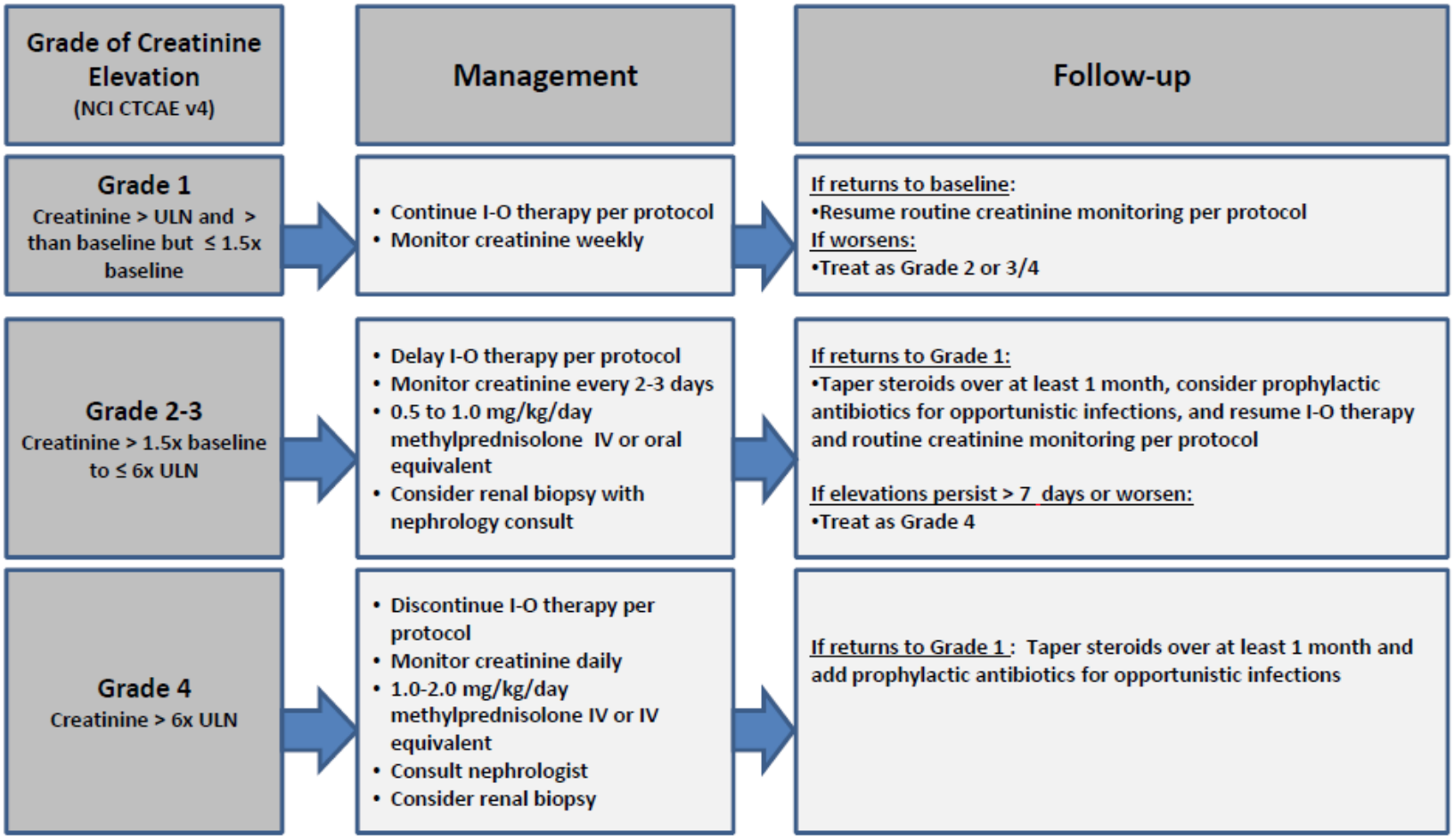
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat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

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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

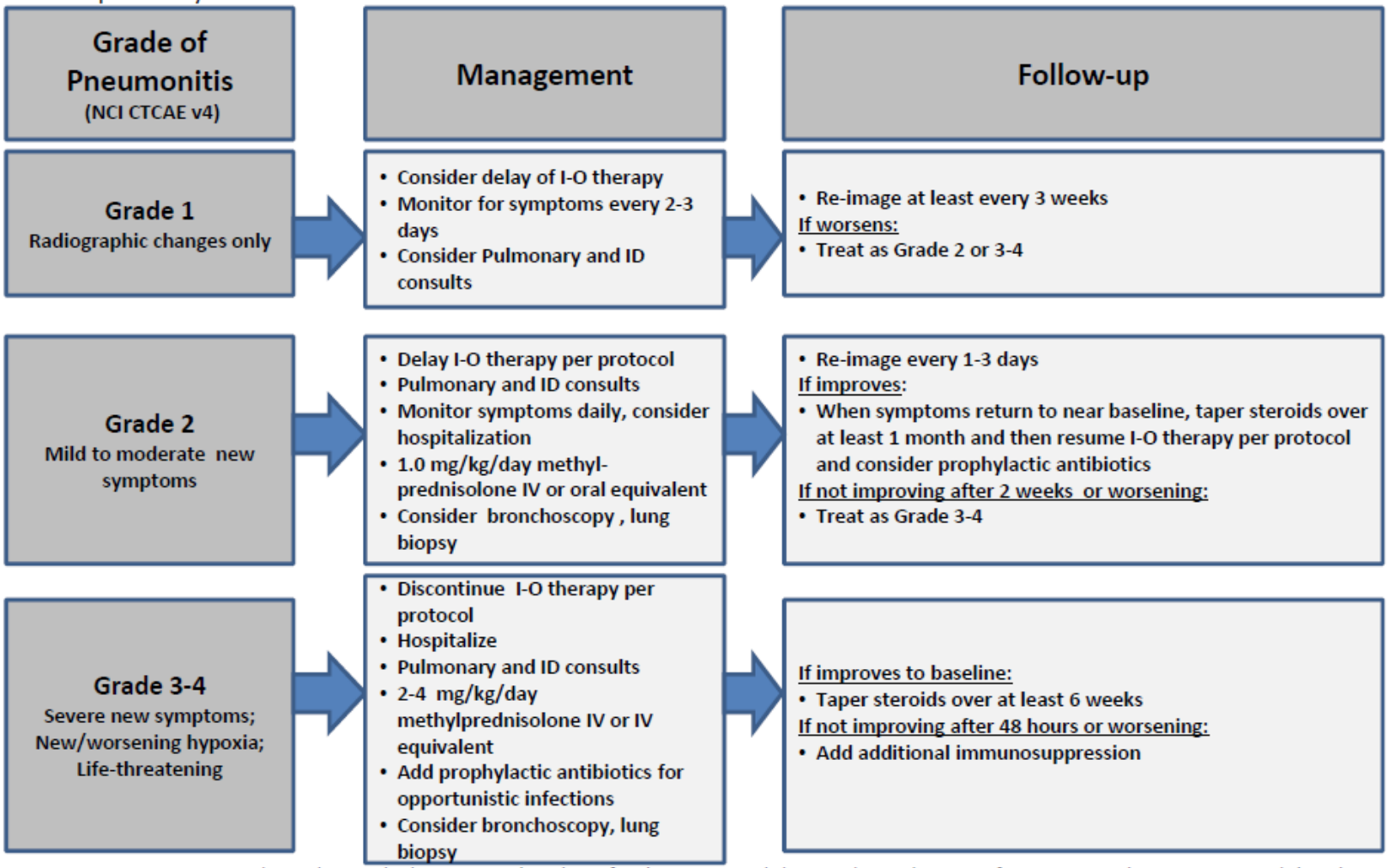


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

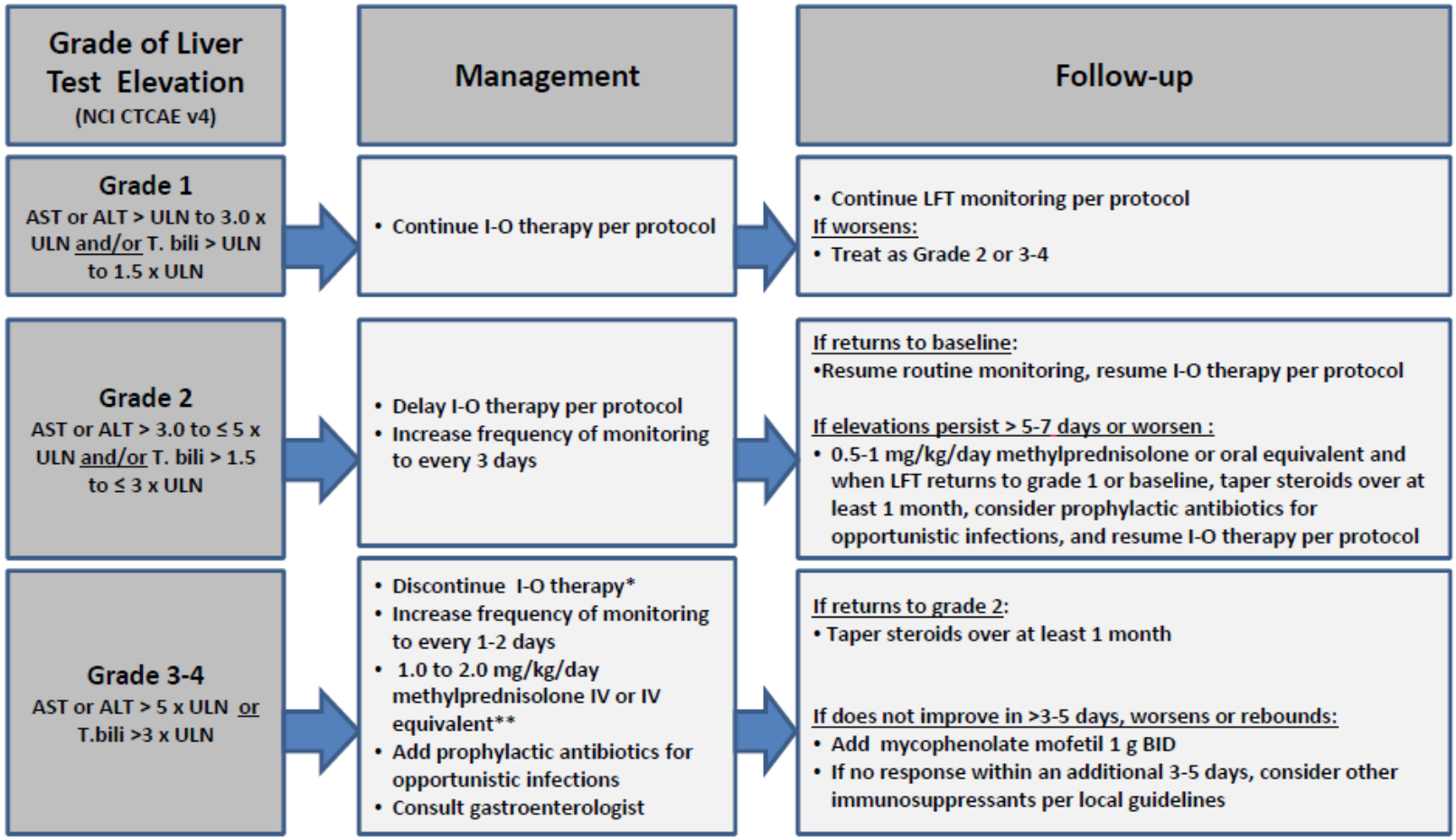


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

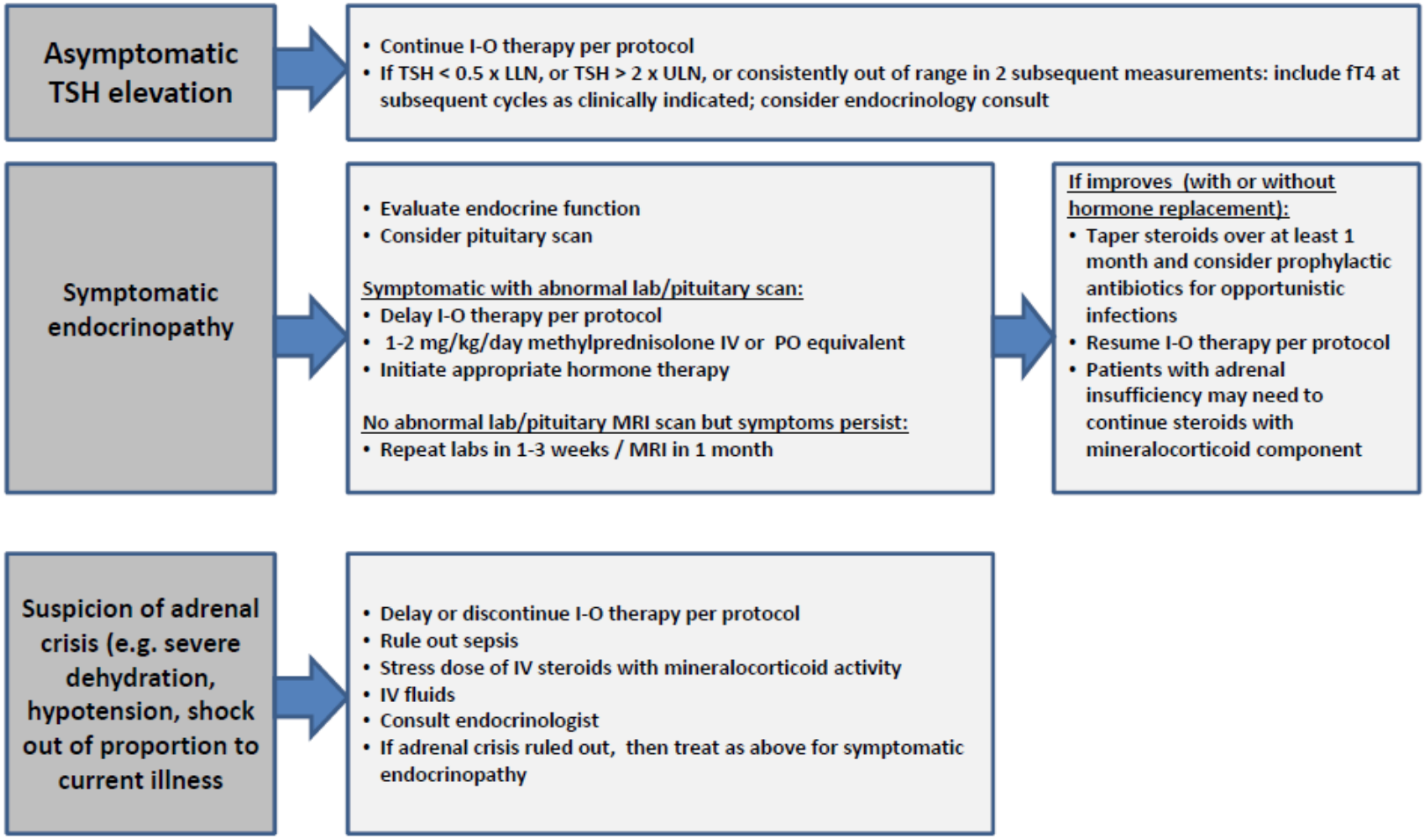
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

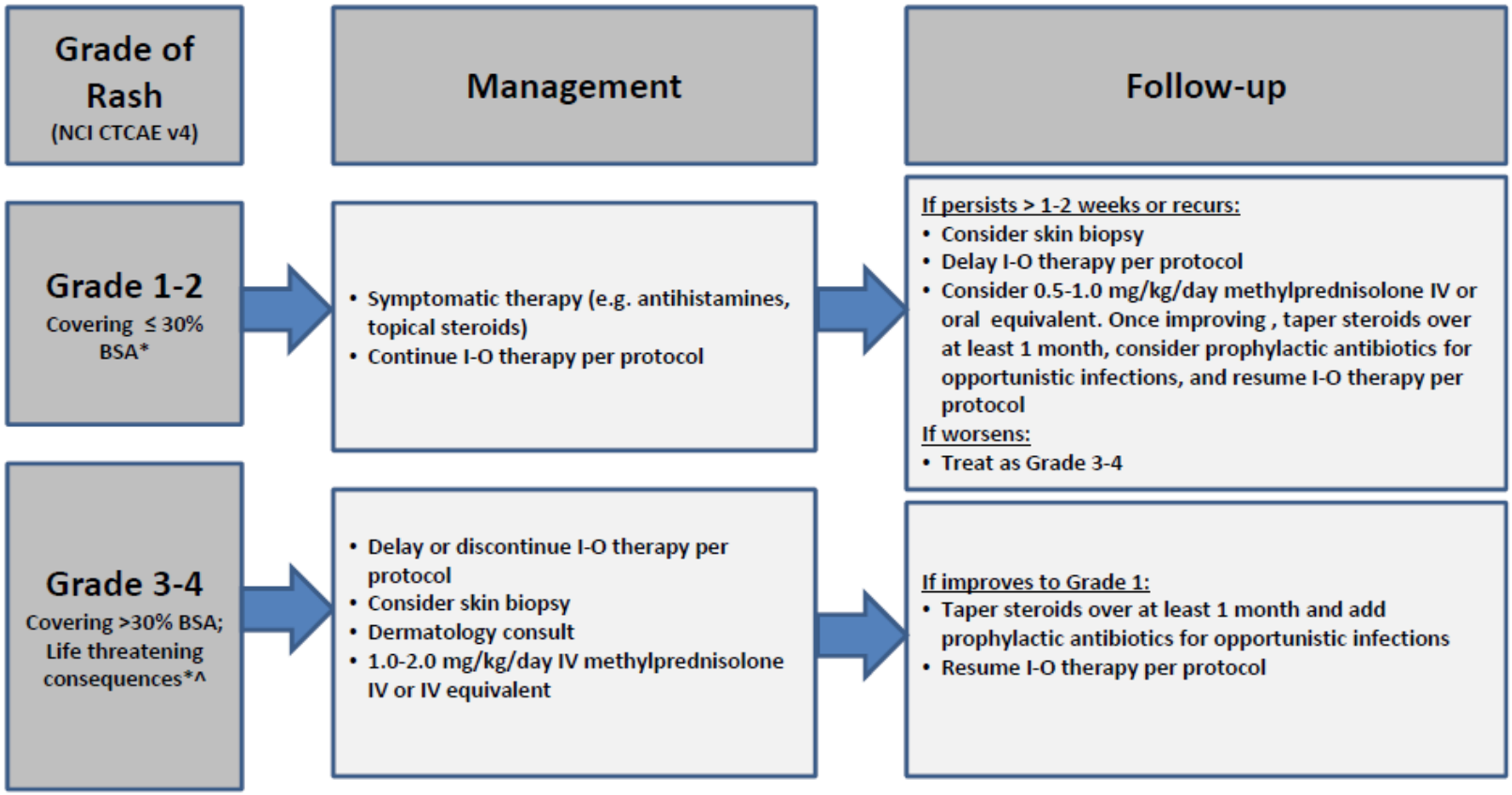


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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

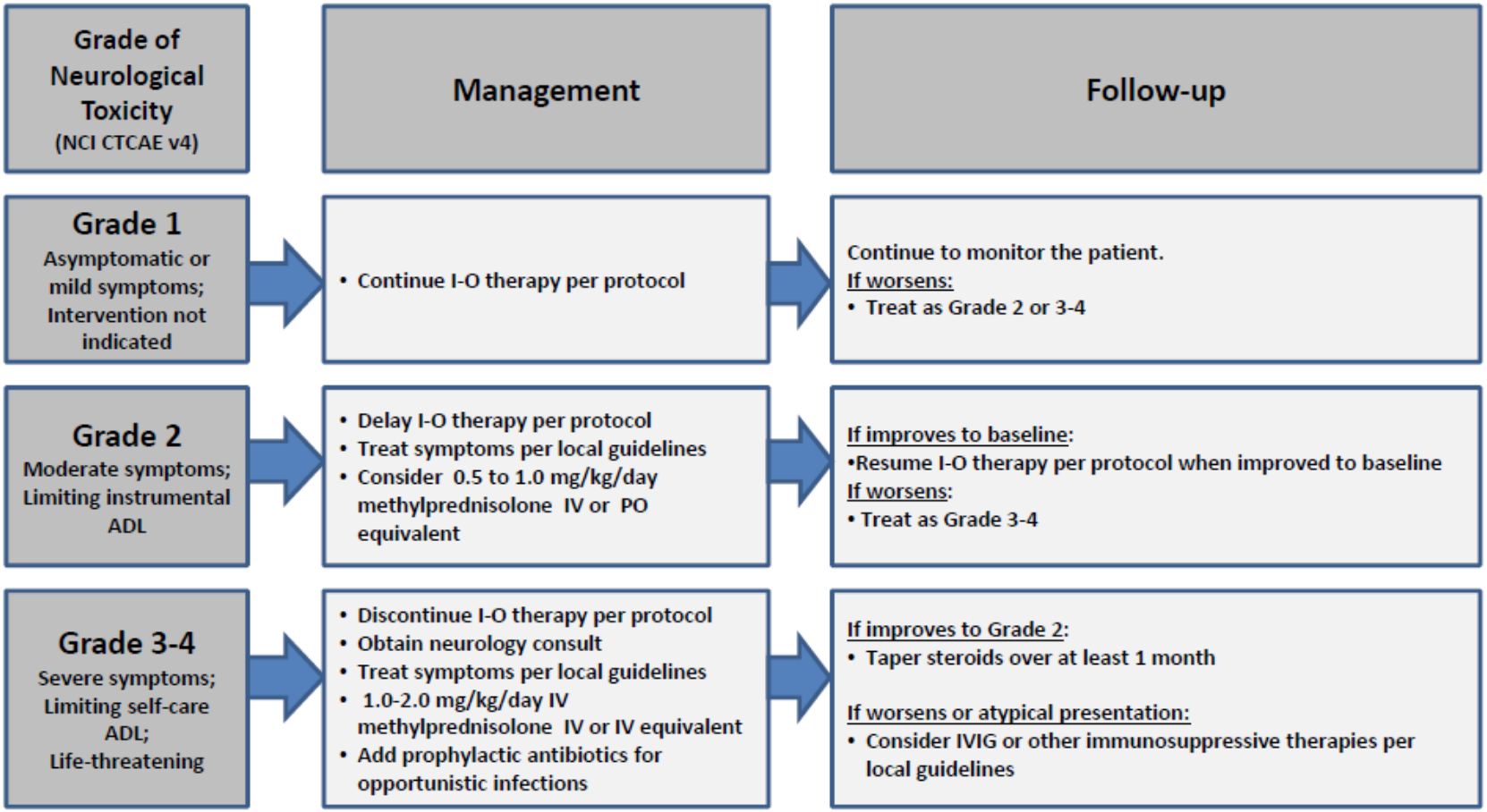


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

APPENDIX F: Definitions for Adverse Event Reporting

A. **Adverse Events (AEs)**

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. **Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction**

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. **Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction**

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death

- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization. The following hospitalizations are not considered SAEs in BMS clinical studies:
    - a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
    - elective surgery, planned prior to signing consent
    - admissions as per protocol for a planned medical/surgical procedure
    - routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
    - medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
    - admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
    - admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. **Protocol Exceptions**

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX G: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Bristol Myers-Squibb**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	Report to BMS within 24 hours \ 1 Business Day of becoming aware of the event
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	Report to BMS within 24 hours \ 1 Business Day of becoming aware of the event
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	
Complaints	If the complaint reveals an unanticipated problem			

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Bristol Myers-Squibb**
	involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			
Pregnancy				Report to BMS within 24 hours \ 1 Business Day of becoming aware of the event

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Bristol Myers-Squibb**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			
Pregnancy				Report to BMS within 24 hours \ 1 Business Day of becoming aware of the event

Expedited Reporting Timelines for Secondary Sites				
Event	**WU (Coordinating Center)**	**Local IRB**	**FDA**	**Bristol Myers-Squibb**
Serious AND unexpected suspected adverse reaction	Report no later than 11 calendar days after it is determined that the information qualifies for reporting.	Report all applicable events to local IRB according to local institutional guidelines.	The research team at Washington University is responsible for reporting all applicable events to the FDA as needed.	The research team at Washington University is responsible for reporting all applicable events to Bristol-Myers-Squibb as needed.
Unexpected fatal or life-threatening suspected adverse reaction	Report no later than 4 calendar days after initial receipt of the information.			
Unanticipated problem involving risk to participants or others	Report no later than 4 calendar days after initial receipt of the information.			
Adverse event or SAE that does not require expedited reporting	As per routine data entry expectations			
Protocol exception	Approval must be obtained prior to implementing the change.			

APPENDIX H: Washington University Serious Adverse Event Reporting Cover Sheet

SAE COVER SHEET- Secondary Site Assessment

Washington University HRPO#:	Sponsor-Investigator:
Subject Initials:	Subject ID:
Treating MD:	Treating Site:
EVENT TERM:	Event Start Date:
EVENT GRADE:	Date of site's first notification:

Treating MD Event Assessment:

Is this event **possibly, probably, or definitely** related study treatment?

☐ Yes ☐ No

If yes, please list which drug (if more than one)_____

Explain _____

_____

_____ _____ _____

Physician's Name **Physician's Signature** **Date**