Winship Cancer Institute of Emory University

Phase II trial of Nivolumab and Metformin in patients with treatment refractory MSS metastatic Colorectal Cancer

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Supplied Agent(s): Nivolumab, BMS
Other Agent(s): Metformin ER, commercial, funding supplied by BMS

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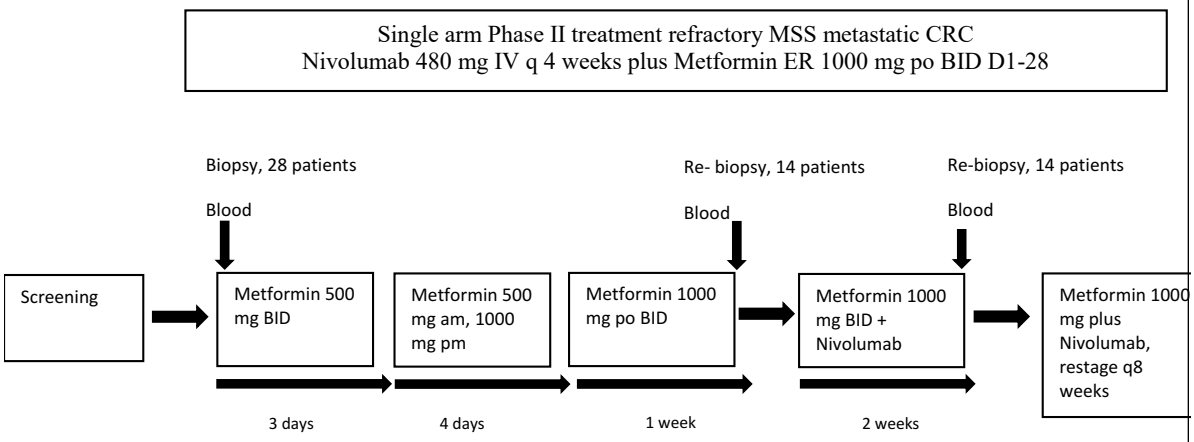
LIST OF ABBREVIATIONS

AE	adverse event/experience
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BP	blood pressure
CFR	Code of Federal Regulations
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
D5W	dextrose 5% in water
DEHP	di(2-ethylhexyl) phthalate
DCR	disease control rate
dL	Deciliter
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GI	Gastrointestinal
HIPAA	Health Insurance Portability Act
HIV	human immunodeficiency virus
HR	Heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
LC-MS/MS	liquid chromatography-mass spectrometry / mass spectrometry
LDH	lactate dehydrogenase
LMW	Low molecular weight
MDSC	Myeloid-derived suppressive cells
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram

MRI	magnetic resonance imaging
MSI-high	microsatellite instable-high
MSS	microsatellite stable
NCI	National Cancer Institute
PFS	Progression-free survival
PICCS	Peripherally-inserted central catheters
PK	Pharmacokinetic
PR	partial response
PVC	polyvinyl chloride
ORR	objective response rate
OS	overall survival
QT	cardiac interval from start of Q wave to end of T wave
RDC	remote data capture
RR	respiration rate
SD	stable disease
UGT	uridine-diphosphoglucuronosyltransferases
ULN	upper limit of normal
VADs	Vascular access devices
WHO	World Health Organization

1. STUDY SYNOPSIS

Title of Study: Phase II trial of Nivolumab and Metformin in patients with treatment refractory MSS metastatic Colorectal Cancer
Study Centers: Emory University Winship Cancer Institute
Study Phase: Phase II
Objectives: **Primary Objective:** ▪ The primary endpoint of this study is to Evaluate the effect of metformin in combination with nivolumab on the overall response rate (ORR) (Primary Objective) as assessed by RECIST.1.1 **Secondary Objectives:** ▪ To determine the effect of the metformin and nivolumab combination on clinical (PFS, OS) outcomes and biochemical (CEA) response. ▪ To compare the effect metformin and nivolumab combination on **immune and metabolic biomarkers in the tumor microenvironment and systemic circulation** (pre and post treatment paired biopsies required).
Trial Design/Methodology: Single arm phase II study. 28 patients with previously treated (previously treated with fluoropyrimidine, oxaliplatin, irinotecan and EGFR inhibitor – if RAS wildtype) metastatic CRC will be started on metformin and nivolumab combination. **Treatment** 1. Patients will start taking metformin 500 mg po BID for 3 days, then 500 mg am and 1000 mg pm for 4 days, then 1000 mg po bid for 1 week. Patients of the study will get paired biopsies as outlined in study calendar. 2. If a patient cannot tolerate metformin 1000 mg po BID the patient will resume the metformin dose which was tolerable 3. After 2 weeks of metformin only therapy (lead-in period) patients will start nivolumab 480 mg IV q4 weeks and continue metformin 1000 mg PO BID (or the tolerated dose of Metformin). 4. Restaging scans will be performed at the end of cycle 2, then every 8 weeks for 2 years. 5. **Correlative assays** will include- immune profiling of TILs and circulating lymphocytes, plasma cytokine levels and metabolic biomarkers. These will be performed at baseline at baseline, cycle 1 day 1, cycle 1 day 15, Cycle 3 Day 1and at progression **Treatment regimen and trial diagram:**



Number of Subjects:

28 patients

Duration of treatment:

The treatment will be continued until progression of disease, unacceptable toxicity or consent withdrawal for 2 years

Main criteria for inclusion:

- Age ≥18 years old
- Histological diagnosis of treatment refractory colorectal adenocarcinoma with measurable disease
- Prior treatment with 5 Fluorouracil, oxaliplatin and irinotecan containing chemotherapy (needs to be treated with anti-EGFR agent if extended RAS wild type)
- ECOG 0 or 1
- Adequate organ and hematologic function
- Microsatellite stable tumor
- No metformin use in the last 3 months

Main criteria for exclusion:

- MSI status
- Autoimmune conditions that may require systemic steroids or other immunosuppressive treatments
- Pregnancy or breast feeding

Investigational product and administration:

Nivolumab will be provided intravenously and metformin will be provided in tablet form. Eligible subjects will receive nivolumab 480 mg IV every 4 weeks and metformin 1000 mg po BID according to the study design.

Control therapy, dose and administration: N/A

Efficacy evaluation/Endpoints:

Primary Endpoint: ORR
Secondary Endpoints: To determine PFS, OS, and biochemical response (CEA), immune and metabolic biomarkers in tumor microenvironment and systemic circulation (pre and post research biopsy required)

Safety evaluation/Endpoints:

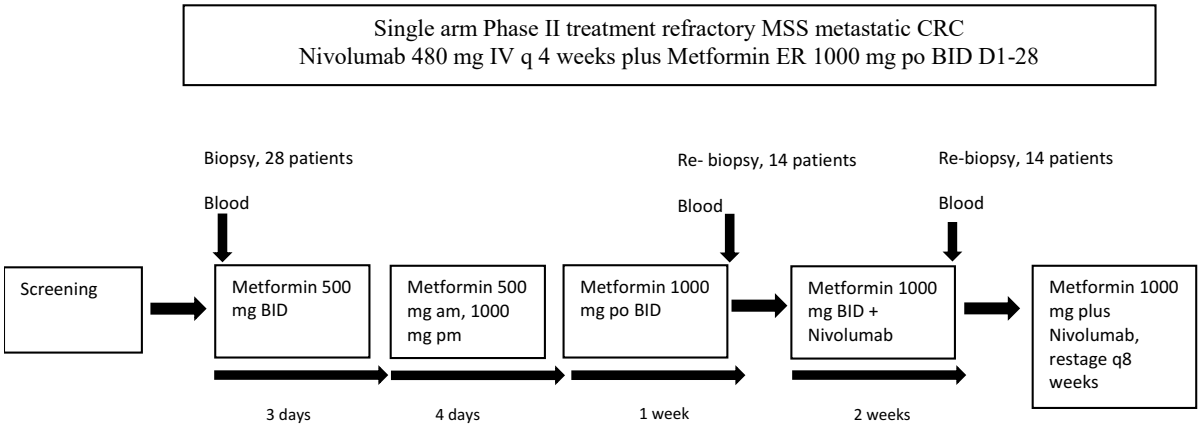
NCI Common Toxicity Criteria Version 4.0

Rationale for number of subjects: **Primary objective is to determine the overall response rate**. Historically ORR with single agent nivolumab in CRC is <5% and metformin and nivolumab combination will have ORR of 15%. Simon's MinMax two stage design is employed for the study with power of 80% and alpha of 0.1. If there is 1 response in first 18 patients in the first stage of the study, then it will proceed with second stage to enroll total of 28 patients. If there are 3 or more responders out of the 28 patients then it would be positive study. This will enable us to evaluate clinical endpoints (ORR, CEA, RFS, OS) as well as evaluate the impact on immune biomarkers.

Statistical methods: Phase II design

Translational Research: Correlative assays will include- immune profiling of TILs and circulating lymphocytes, plasma cytokine levels, and key metabolic biomarkers of relevance to mechanism of metformin action when administered in combination with immunotherapy. Paired biopsies will be obtained in all patients.

2. TRIAL DIAGRAM



3. OBJECTIVES

3.1 Primary Objective and Hypotheses

1. **Objective:** To evaluate the effect of nivolumab and metformin combination on the overall response rate (ORR) as assessed by RECIST 1.1.

   Hypothesis: Metformin will impact the tumor microenvironment and potentiate the anti-tumor effects of nivolumab in patients with treatment refractory, MSS metastatic CRC patients.

3.2 Secondary Objectives and Hypotheses

1. **Objective:** To determine the effect of nivolumab and Metformin combination on clinical outcomes, progression free survival and overall survival, and biochemical response (CEA).

   Hypothesis: Metformin plus nivolumab will affect overall response rate, progression free survival, overall survival.

2. **Objective:** To compare the effect of nivolumab and metformin combination on immune and metabolic biomarkers in the tumor microenvironment and systemic circulation (pre and post treatment paired biopsies required).

   Hypothesis: Metformin plus nivolumab will change the immune profile in the peripheral blood as well as the tumor microenvironment.

4. BACKGROUND AND RATIONALE

4.1 *Study Disease*

Colorectal cancer (CRC) is the third most common cancer in the US and it is estimated to cause more than 50,000 deaths in 2018. [1] Approximately 20% of patients have metastatic CRC at initial presentation who have a 5 year overall survival of 14%. [1] Clear majority of the CRCs develop through chromosomal instability (CIN) pathway and approximately 15% develop from the microsatellite instability (MSI) pathway which results from deficient DNA mismatch repair (MMR). [2] While about 15% of all CRCs are MSI-H, about 4% of metastatic CRCs are MSI-H. [3] Germline mutations in MMR genes such as MLH1, MSH2, MSH6, PMS2 or epigenetic inactivation of MLH1 gene cause deficient MMR. MSI-H CRCs have better stage adjusted prognosis compared to MSS CRCs. [2] Consensus molecular subtype (CMSs) system classifies CRCs into 4 different gene expression-based molecular subtypes: CMS1 (14%, microsatellite unstable with strong immune activation and hypermutated), CMS2 (canonical, 37%, epithelial differentiation, strong WNT and MYC Signaling activation), CMS3 (13%, characterized with metabolic dysregulation and KRAS mutations) and CMS4 (mesenchymal, 23%, phenotype with strong transforming growth factor beta activation, stromal invasion and angiogenesis), an unclassified group with mixed features represent 13% of remaining cases. [4] The immunological signatures of tumor microenvironment (TME) and the molecular subtypes were shown to be correlated. [Becht et al] CMS1 is the most immunogenic subtype of all four subtypes while the CMS4 is the second most immunogenic. [4, 5] Immunotherapy with checkpoint inhibitors has been proven to be very effective in the treatment of metastatic CRC with high level of Microsatellite Instability (MSI-H), but ineffective in Microsatellite Stable (MSS) CRC. [6] Immunotherapy with anti-PD-1 agents is approved only in MSI-H metastatic CRC patients after failure of standard first line systemic chemotherapy. [7] MSI-H tumors respond to check point inhibitors because of high mutational rate, up 20 times higher compared to MSS CRC, as well as significant immune checkpoint expression [5]. At the present time patients with MSI-H status, high expression of neo-antigens and TILs are good candidates for check point inhibition whereas MSS CRC patients lack response to immunotherapy due to opposite tumor features. [5] TME is essential for prognosis and is a viable target for anti-cancer therapy by modulation of the TME composition. Only a small set (4%) of metastatic CRCs would be candidate for anti-PD-1 therapy therefore there is significant unmet need for innovative approaches to combine anti-PD1 therapy with other agents to achieve manipulation of TME of CRCs and sensitize MSS CRCs to anti-PD-1 therapy. For example, by modulating the tumor microenvironment antitumor responses (ORR 17%, 4PR, 5SD) were reported in MSS patients when a checkpoint inhibitor was combined with Cobimetinib in a phase Ib trial based on preclinical data showing increased intratumoral CD8+ T cell infiltration and increased sensitivity to PDL-1 inhibition. [8] The preclinical rationale was also confirmed in this phase Ib trial by showing increased CD8+ T cell infiltration, MHC-I expression and PDL-1 upregulation in serial tumor biopsies on treatment.

4.2 Investigational Agents

4.2.1
Nivolumab in CRC:

Immune checkpoint expression as programmed death 1 (PD-1) or cytotoxic T-lymphocyte-associated antigen (CTLA-4) by tumor cells is one of the major immune evasion mechanisms. [3, 9] PD-1, a member or B7/CD28 costimulatory receptor family, down regulates T-cell activation by binding to its receptors programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PDL-2). Nivolumab is a fully humanized monoclonal IGG4 anti-PD-1 inhibitor which is currently approved for MSI-H CRC after progression on systemic chemotherapy.
Nivolumab was studied as a single agent at doses of 0.3-10 mg/kg in the first phase I study in 39 patients with advanced solid tumors, 1/14 CRC patients achieved durable complete response (CR), no maximum tolerated dose was determined. [10] That patient had MSI-H positive CRC. In the following phase Ib study with single agent Nivolumab at a dose of 0.1-10 mg/kg IV in 296 patients with treatment refractory solid tumors none of the 19 CRC patients had objective response. Of note these patients included predominantly MSS CRCs. [11]

CheckMate 142 Phase II study of single agent Nivolumab 3 mg/kg IV every 2 weeks in 74 treatment refractory MSI-H CRC patients revealed 31.1% objective response rate (ORR), 3% complete response (CR) and 69% disease control rate (DCR) for 12 weeks or longer at a median follow up of 12 months. [12] More updated results of the same study at median follow up of 21 months revealed 34% ORR, 9% CR, and 62% DCR. [13] The response rates did not differ between Tumor expression of PD-Ll≥ 1% and <1% in the same study. CheckMate142 trial currently has multiple arms with Nivolumab combined with other agents.

Most commonly reported grade 3 or 4 adverse events in CheckMate142 study included elevated lipase (8%) elevated amylase (3%); and rest of grade 3 or 4 adverse events included fatigue (1%), diarrhea (1%), maculopapular rash (1%), increased alanine aminotransferase (1%), stomatitis (1%), abdominal pain (1%), increased creatinine (1%), decreased lymphocyte count (1%), colitis (1%), acute kidney injury (1%), adrenal insufficiency (1%), esophagitis (1%), increased gamma-glutamyltransferase (1%), gastritis (1%), pain (1%) No treatment related deaths were reported.

Please refer to the Investigator's Brochure for additional information for preclinical activity, toxicology and potential adverse effects.

4.2.2
Metformin in CRC:
Metformin is a biguanide and decreases liver glucose production and increases insulin sensitivity. It is the first line therapy and most commonly prescribed antidiabetic agent for diabetes mellitus type II. It has favorable safety profile, weight neutral effects, low risk of hypoglycemia and low cost. [14] Immediate release (IR) and extended release formulations (ER) exist and extended release formulation provides better tolerability especially lower gastrointestinal adverse events as well as improved patient adherence. ER formulation provides gradual release of the drug into upper GI tract although it provides similar drug exposure at the same daily total dose as immediate release formulation. [14] Maximum plasma concentration of IR Metformin is reached at 2-3 hours and 7 hours for ER Metformin. [15] ER tablets cannot be crashed or chewed and should be swallowed whole in order to maintain slow drug release. The most common adverse events were reported as following in a 16-week, randomized, double-blind, placebo-controlled study in patients with type II diabetes: upper respiratory tract

infection (15%), diarrhea (12.9%), nausea/vomiting (8.2%), musculoskeletal pain (7.6%), headache (7.1%), influenza (6.6%), dyspepsia/heartburn (5.3%), abdominal pain (5.1%), sinus abnormality (3.7%), dizziness (3.4%), hypertension (3.1%), urinary tract infection (3.1%).That particular study included 5 different treatment regimens including Metformin ER 1000 mg po twice daily.

Please refer to the Investigator's Brochure for additional information for preclinical activity, toxicology and potential adverse effects.

Several epidemiological studies revealed decreased risk of cancer development and cancer related mortality with use of metformin. A meta-analysis revealed decreased risk of colorectal cancer incidence diabetic patients who are on metformin and improved overall mortality, CRC specific mortality in CRC patients who are on metformin compared to those who are not. [16, 17] In meta-analysis by Meng et al. improved overall survival (OS), HR 0.75; 95% CI 0.65 to 0.87, was reported for metformin users compared to nonusers in patients with CRC and diabetes although no cancer specific survival, HR 0.79, 95% CI 0.58 to 1.08, was detected. [18] Anticancer properties of Metformin were attributed to mTOR inhibition through AMPK pathway activation. [19] The positive therapeutic effects of metformin were shown in colon cancer and lung cancer patients with diabetes on metformin versus other antidiabetic drugs in a single institution retrospective study. [20] In that study colon cancer (104 on metformin, 98 non-metformin) and lung cancer (93 metformin and 87 non-metformin) patients with diabetes were stratified according to being on metformin versus other antidiabetic medications between 1998 and 2012. 94.2% of patients were treated with surgery, 44.2% were treated with chemotherapy, and 14.4% were treated with radiation therapy in colon cancer patients on metformin as opposed to 89.8%, 48% an 18.4% in non-metformin cohort with colon cancer. In the colon cancer group better OS (5.7 versus 4.1 years, p=0.001), better 5-year OS rates (57% vs 37%, p=0.004), rate of CEA decrease (72% versus 47%, p=0.015), less metastasis (23% versus 46%, p=0.001), less number of deaths (48% versus 76%, p<0.001) and less recurrences (4% versus 19%, p=0.002) were seen in the metformin group compared to non-metformin group. Additionally, better 5-year OS rates (29% versus 15%. P=0.023) and OS (3.4 vs 1.8 years, p<0.001) were reported in patients on metformin compared to non-metformin antidiabetic medication group in lung cancer cohort. 48.4% received surgery, 47.3% received chemotherapy, and 40.9% received radiation therapy metformin cohort with lung cancer patients compared to 40.2%, 42.5%, 47.1% in non-metformin cohort, respectively. No clinical staging information was included for either colon cancer or lung cancer patients in this report. In a nationwide population-based study from Taiwan including 47,597 patients with DMII metformin use was associated with lower risk of CRC in a dose dependent manner. [21]

More recently multiple immunomodulatory effects of Metformin have been shown which points to potential synergistic effect of Metformin with anti-PD-1 therapy in CRC. [22, 23]

4.3 Study Rationale

Preclinical studies suggest that metformin, by virtue of its impact on metabolic features in the

tumor microenvironment has distinct immunomodulatory properties that could complement PD-1 blockade and may potentially increase the sensitivity of MSS metastatic CRC patients to PD-1 inhibition. [22, 23] Longer PFS and OS was reported in CRC patients with higher CD8+ T cell and memory T cell infiltration highlighting the potential role of immunomodulation as a mechanism by which metformin elicits its effects.

Immune effects of Metformin in tumor microenvironment:

1. Metformin increased CD8+ tumor infiltrating T cells (TILs) and prevented apoptosis and immune exhaustion of TILs. Metformin prevents apoptosis of CD 8+ tumor infiltrating lymphocytes (TILs) and restored multi-functionality of PD1+, Tim3+ CD8+ TIL by promoting a phenotypic switch of T cells to adopt central memory and effector phenotypes in murine tumor models. [22]
2. Metformin has metabolic properties that favor decreased intratumoral oxygen consumption in vitro and in vivo, while it increased the oxygen consumption by CD 8+ TIL and improved the effector cytokine production by CD8+ TIL in B16 melanoma and MC38 colon adenocarcinoma tumor models. [23]
3. Expression of coinhibitory molecules PD1 and Tim3 was modulated in metformin treated mice compared to controls. [23]
4. The combination of metformin and PD1 inhibitor resulted in improved intratumoral T cell function and increased anti-tumor activity. [23]
5. The metformin and PD-1 inhibitor combination improved antitumor activity and intratumoral T cell function. [23]

Preclinical data strongly suggests that metformin can improve immune exhaustion of TIL and potentiate the effects of immunotherapy. **Based on this preclinical rationale, in this study we propose evaluating the effects of metformin in potentiating the effects of immunotherapy in patients with treatment refractory metastatic MSS CRC patients.**

4.4 Correlative Studies Background

Abundant CD8+ T cell infiltration in the tumor microenvironment is associated with a survival advantage in CRCs, independent of tumor stage. [24] Individual molecular subtypes of CRCs have distinct immunological features. For example, CMS1 CRCs have upregulation of Th1 lymphocytes, cytotoxic T cells, NK cell infiltration and PD-1 expression. These features are correlated with better clinical outcomes in CRCs. [25] In contrast, tumors displaying an immune infiltration pattern with presence of Th17 cells, IL-17, Tregs, and MDSCs are associated with poorer outcomes in CRCs. [24, 26] Preclinical studies demonstrated that metformin could modulate the TME and improve CD8+ T cell infiltration and function, decrease tumor cell oxygen consumption and increase CD8+ T cell oxygen consumption. [22, 23] The current study aims to harness the immunomodulatory effects of metformin, and potential clinical benefit in combination with an anti-PD-1 agent, nivolumab, by modulating the cellular composition within the TME. Therefore, we aim to analyze the immunogenic profile of the tumors by paired biopsies and peripheral blood collection at the time points

specified in the protocol. In the paired pre and post-treatment biopsy specimens, we will aim to identify potential biomarkers for the combination therapy with Nivolumab and Metformin. Pre and post biopsy tissue will be evaluated using IHC or immunofluorescence for relevant lymphocyte, myeloid and stromal/vascular markers to provide a comprehensive view of the cellular composition within the TME. Tissue will also be dissociated and flow cytometry will be used to further define phenotypic properties of macrophages, lymphocytes or other cell populations. In addition, we plan to perform on a subset of these patients, genomic analysis of lymphocyte population.

Metformin is a mitochondrial electron transport chain Complex I inhibitor. The basis for co-administration of metformin with anti-PD-1 therapy relies on inhibiting Complex I activity in tumor cells, reducing oxygen consumption rates (OCR) in tumor cells while concomitantly increasing oxygen in the surrounding microenvironment and oxidative metabolism of the infiltrating T cell subsets. We will perform *ex vivo* studies to determine whether oxidative metabolism is indeed regulated in the tumor and T cell subsets. Pre and post therapy tumor sections will be evaluated for expression of the following: OCT-1 (metformin transporter), p-AMPK (that is known to be activated with metformin), mTOR pathway (should be suppressed as a consequence of AMPK activation), HIF1a, Caspase 3, and Ki67. Intracellular oxygen levels in tumor and stroma will be evaluated using Hypoxyprobe™ to confirm OXPHOS inhibition. Sorted T cells populations will be evaluated for baseline OCR and OCR/ECAR (extra-cellular acidification) with and without short-term exogenous metformin administration using a Seahorse Bioenergetics bioanalyzer. In addition, viability of T cells with metformin or specific complex I inhibitors (rotenone/piericidin) will be evaluated. Glycolytic gene expression and OCT-1 expression in tumor samples prior to therapy and their correlation to therapy response can prospectively help define biomarkers of sensitivity to the combinatorial administration of metformin with anti-PD1. Evaluation of the outlined endpoints in pre- and post-treatment samples will help assess the biology of an anti-tumor response.

5. PATIENT SELECTION

5.1 Eligibility Criteria

5.1.1 Patients must have histologically or cytologically confirmed stage IV colorectal adenocarcinoma with measurable disease.

5.1.2 Prior treatment with 5 Fluorouracil (or capecitabine), oxaliplatin and irinotecan containing chemotherapy (needs to be treated with anti-EGFR agent if extended RAS wild type)

5.1.3 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam.

5.1.4 Age ≥18 years.

5.1.5 ECOG performance status 0 or 1 (Karnofsky ≥70%, see Appendix A).

5.1.6 Life expectancy of greater than 3 months

5.1.7 Patients must have normal organ and marrow function as defined below

- Absolute neutrophil count ≥1,500/mcL
- Platelets ≥100,000/mcL
- Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L without transfusion or erythropoietin (EPO) dependency (within 7 days of assessment)
- Serum creatinine ≤1.5 x ULN

OR

creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels >1.5 x ULN. Creatinine clearance should be calculated per institutional standard

- Serum total bilirubin ≤1.5 x the upper limit of normal (ULN) OR direct bilirubin ≤ ULN for subjects with total bilirubin >1.5 ULN
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- Serum Albumin ≥2.5 mg/dl
- International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is
- within therapeutic range of intended use of anticoagulants
- Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

5.1.8 Patients with diabetes mellitus should be on a stable diabetic treatment regimen for at least 1 month prior to trial enrollment and keep a blood glucose level log at home for the first 4 weeks of the trial.

5.1.9 Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication; if the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5.1.10 Male subjects of childbearing potential must agree to use an adequate method of contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

- Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject

5.1.11 Female subjects of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication

- Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject

5.1.12 Ability to understand and the willingness to sign a written informed consent document.

5.2 Exclusion Criteria

5.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
Note: Subjects with ≤ grade 2 neuropathy are an exception to this criterion and may qualify for the study
Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy

5.2.2 Metformin use in the last 3 months

5.2.3 Patients who are receiving any other investigational agents.

5.2.4 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis; subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment; this exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

5.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to *Nivolumab and Metformin.*

5.2.6 Has a known history of active tuberculosis (TB) (Bacillus tuberculosis)

5.2.7 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment

5.2.8 Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs); replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

5.2.9 Has known history of, or any evidence of active, non-infectious pneumonitis.

5.2.10 Has an active infection requiring systemic therapy.

5.2.11 Has known substance abuse disorders that would interfere with cooperation with the requirements of the trial.

5.2.12 Has received prior therapy with an anti-programmed death (PD)-1, anti-PD-L1, or anti-PD-L2 agent.

5.2.13 Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

5.2.14 Has known active hepatitis B (e.g., hepatitis surface antigen [HBsAg] reactive) or hepatitis C (e.g., hepatitis C virus [HCV] ribonucleic acid [RNA] [qualitative] is detected).

5.2.15 Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and

are allowed; however intranasal influenza vaccines (e.g., Flu-Mist) are live attenuated vaccines, and are not allowed

5.2.16 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris or myocardial infraction within 6 months of study entry, serious cardiac arrhythmia requiring medications, baseline corrected QT (QTc) >450 mesc or previous history of QT prolongation while taking other medications.

5.2.17 Other medications, or severe acute/chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study

5.2.18 Has a known additional malignancy that is progressing or requires active treatment; exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. Subjects with prior malignancies are eligible if the subject has been disease free for >5 years.

5.2.19 Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

5.3 Screen Failures

Minimal data for subjects who fail screening will be collected such as demographic information and the reason for screen failure. Such subjects may be re-screened at the discretion of the investigator after approval by the Data and Safety Monitoring Committee (DSMC). The reason for the need to re-screen a subject will be documented in the subject's source documents.

6. TREATMENT PLAN

6.1.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Table 1: Cycle 1 only (Day -14 through 28) Lead-in period

Regimen Description					
Agent	**Premedications ; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
					42 days

Metformin	Take with food	500 mg tablet am, 500 mg pm	PO	Twice daily D-14 through -12	
Metformin	Take with food	500 mg tablet am, 1000 mg pm	PO	Twice daily D -11 through -8	
Metformin	Take with food	1000 mg tablet am, 1000 mg pm	PO	Twice daily D -7 through -1	
Metformin*	Take with food	1000 mg tablet and, 1000 mg pm	PO	Twice daily, D1-28	
*If subject cannot tolerate 1000 mg po twice daily, will resume the highest tolerated dose of Metformin.					

NOTE: The patient will be requested to maintain a medication diary of each dose of medication (Metformin). The medication diary (Appendix B) will be returned to clinic staff at the end of each course. Patients with diabetes mellitus will be requested to keep a blood glucose log for the first 4 weeks of the trial (Appendix C)

Table 2: Cycle 2 and subsequent cycles (28 days)

Regimen Description					
Agent	**Premedications ; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**

Nivolumab	Premedicate with Acetaminophen 650 mg po once prior to Nivolumab, optional	480 mg	IV over 30 minutes	Day 1	28 days (4 weeks)
Metformin*	Take with food	1000 mg tablet and, 1000 mg pm	PO	Twice daily, D1-28	
* If subject cannot tolerate 1000 mg po twice daily during Cycle 1, subject will continue the maximum tolerated dose of Metformin as in cycle 1 for the subsequent cycles.					

NOTE: The patient will be requested to maintain a medication diary of each dose of medication (Metformin). The medication diary (Appendix B) will be returned to clinic staff at the end of each course.

6.1.2 Investigational Agent(s)

Nivolumab: No premedication indicated, may give Acetaminophen 500 mg po once prior to Nivolumab administration, which is optional.
Metformin: No premedication indicated. AM dose should be taken with breakfast and PM dose should be taken with dinner.

6.2 DOSING DELAYS/DOSE MODIFICATIONS

6.2.1 Metformin

The following guidelines are provided for the modification of the dose of metformin in the event of toxicities attributed by the investigator to this study drug. Toxicities unrelated to metformin will not ordinarily result in the modification of dose. AEs will be defined based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.

In general, subjects experiencing **Grade 1 and 2** drug related toxicities should not have the dose of metformin modified. However, appropriate supportive care should be provided for the management of drug related toxicities. Grade 2 toxicities may require dose or schedule modifications (delaying or omitting individual doses) due to potentially greater clinical significance; however, this should occur after discussion with study PI.

Dosing of metformin must be delayed if a subject experiences a **Grade 3 non-hematologic** toxicity. If the toxicity resolves (returned to baseline or decreased to Grade ≤ 1) within 7 days, dosing of metformin may be resumed one lower dose level (See section 6 Table 3). Exceptions to this rule are as follows:

- Grade 3 fatigue: dose modification is left to the PI's discretion;

- Grade 3 nausea, vomiting and diarrhea: dose modification only after optimal prophylactic measures have failed to control the symptoms adequately;

In the case of Grade 4 **non-hematologic** toxicity, **or persistent Grade 3** toxicity despite one dose level reduction, metformin will be discontinued.

No dose adjustment of metformin will be performed for anemia.

No dose adjustment for Metformin will be performed for grade 1, 2, or 3 neutropenia or grade 1, 2, or 3(without bleeding) thrombocytopenia.

Dosing of metformin will be delayed if subjects develop grade 4 neutropenia or grade 3 thrombocytopenia complicated by bleeding or grade 4 thrombocytopenia. If the toxicity resolves (returned to baseline or decreased to Grade ≤ 1) within 14 days, dosing of metformin may be resumed one lower dose level (See section 6 Table 3).

Table 3: Dose reduction of Metformin

Dose Level	***Metformin***
1	*1000 mg AM/1000 mg PM*
-1	*500 mg AM/1000mg mg PM*
-2	*500 mg AM/500mg mg PM*

6.2.2 Nivolumab

Adverse events (both non-serious and serious) associated with nivolumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. nivolumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per 3 below. See Section 6.6.1 for supportive care guidelines, including use of corticosteroids.
Toxicities unrelated to nivolumab will not ordinarily result in the modification of nivolumab dose. AEs will be defined based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Dose Modification Guidelines for Drug-Related Adverse Events- Nivolumab

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where Nivolumab has been withheld, Nivolumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Nivolumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

4. Myocarditis: Withhold treatment for Grade 1 or 2. Permanently discontinue for Grade 3 or 4. Based on severity of AE administer corticosteroids.
5. Newly developed Type I diabetes mellitus: Follow endocrinopathy adverse event management algorithm. Permanently discontinue Nivolumab if associated hyperglycemia is grade 4.
6. Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor-investigator. The reason for interruption should be documented in the patient's study record.

GI Adverse Event Management Algorithm

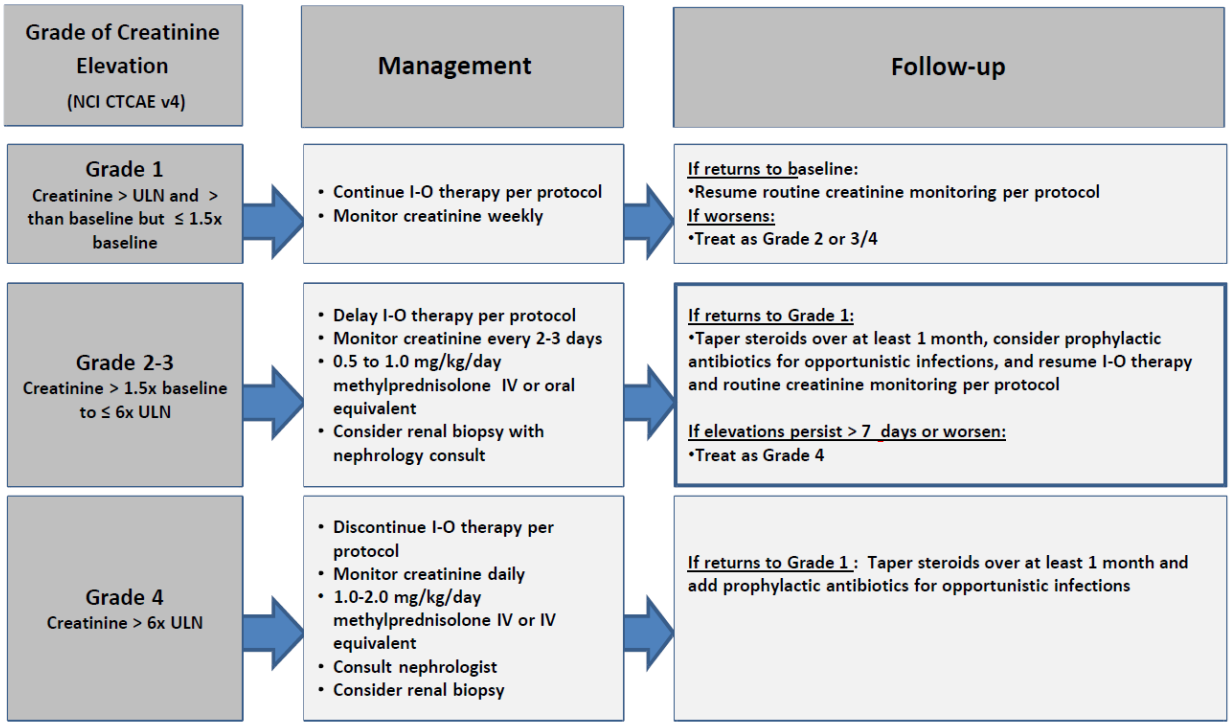
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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.

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.

Pulmonary Adverse Event Management Algorithm

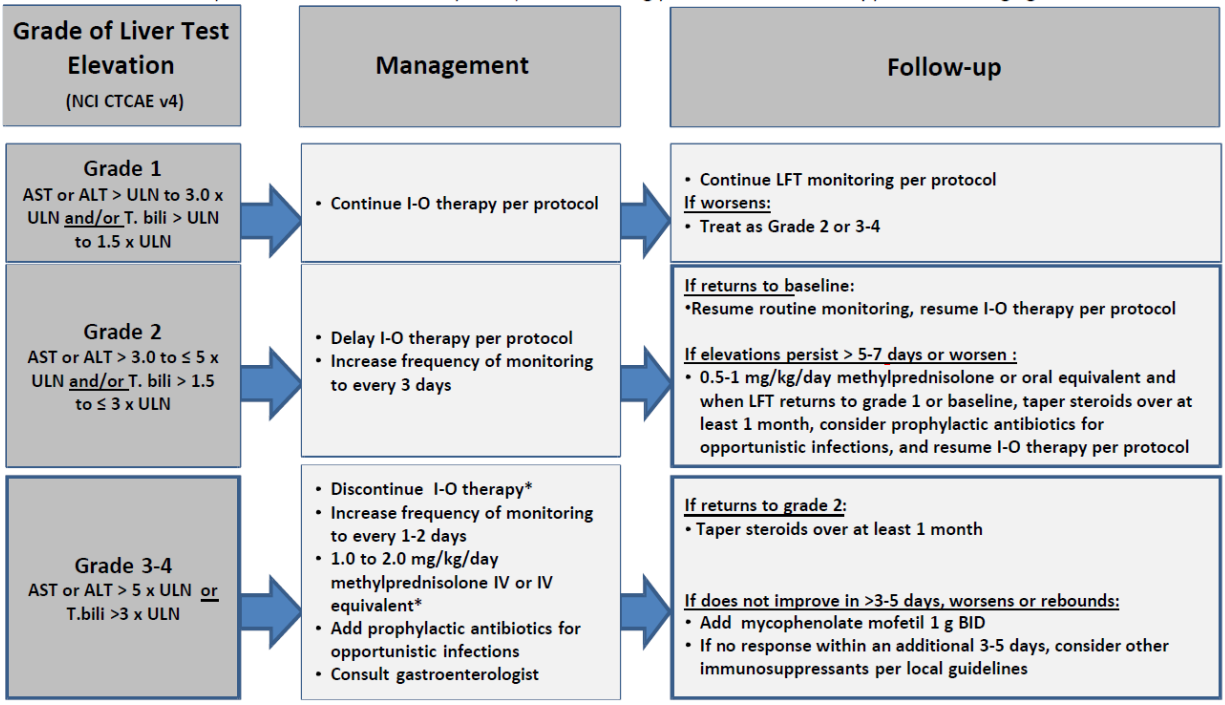
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

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

Hepatic Adverse Event Management Algorithm

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

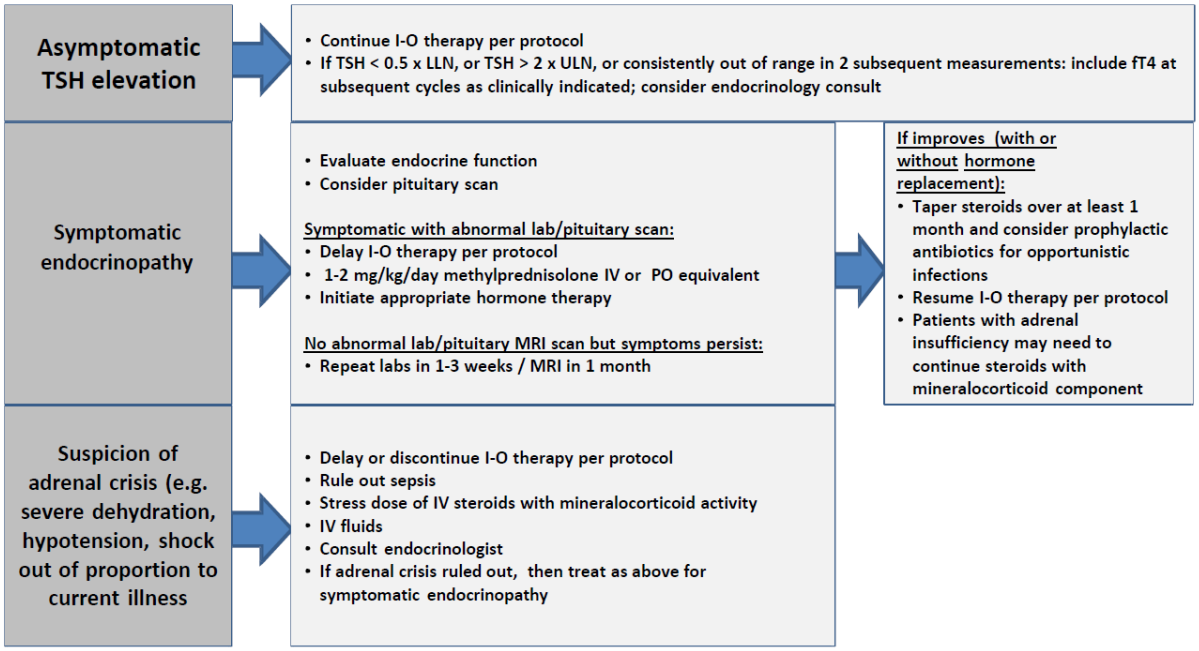


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Endocrinopathy Adverse Event Management Algorithm

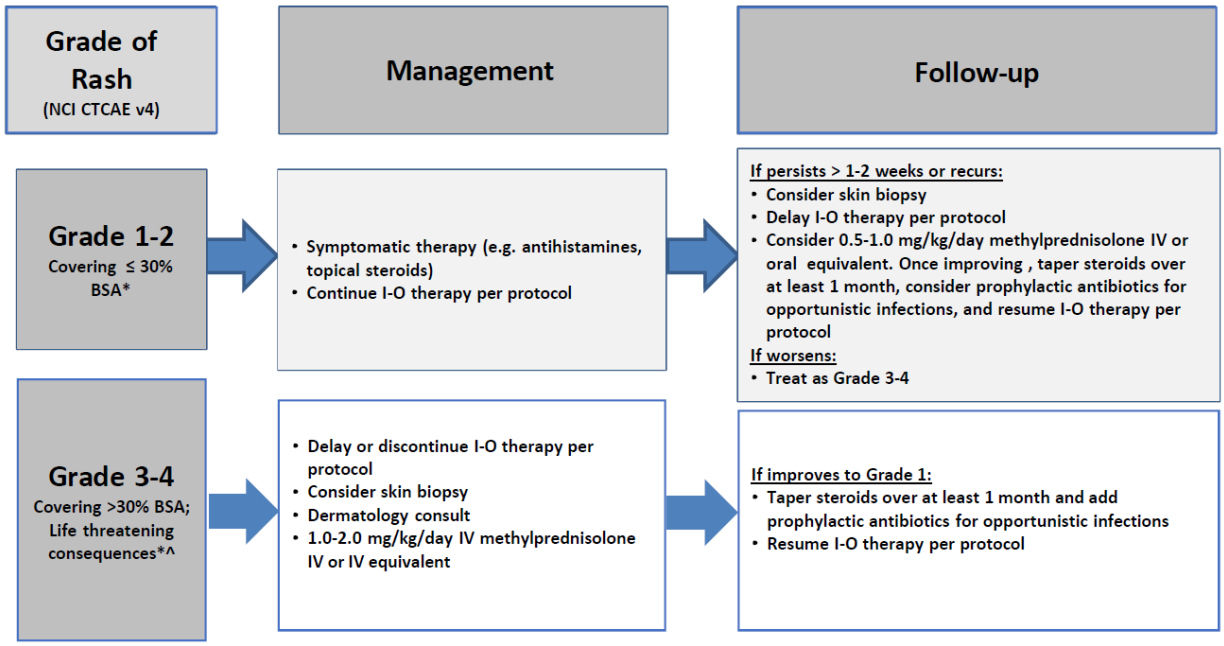
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

Skin Adverse Event Management Algorithm

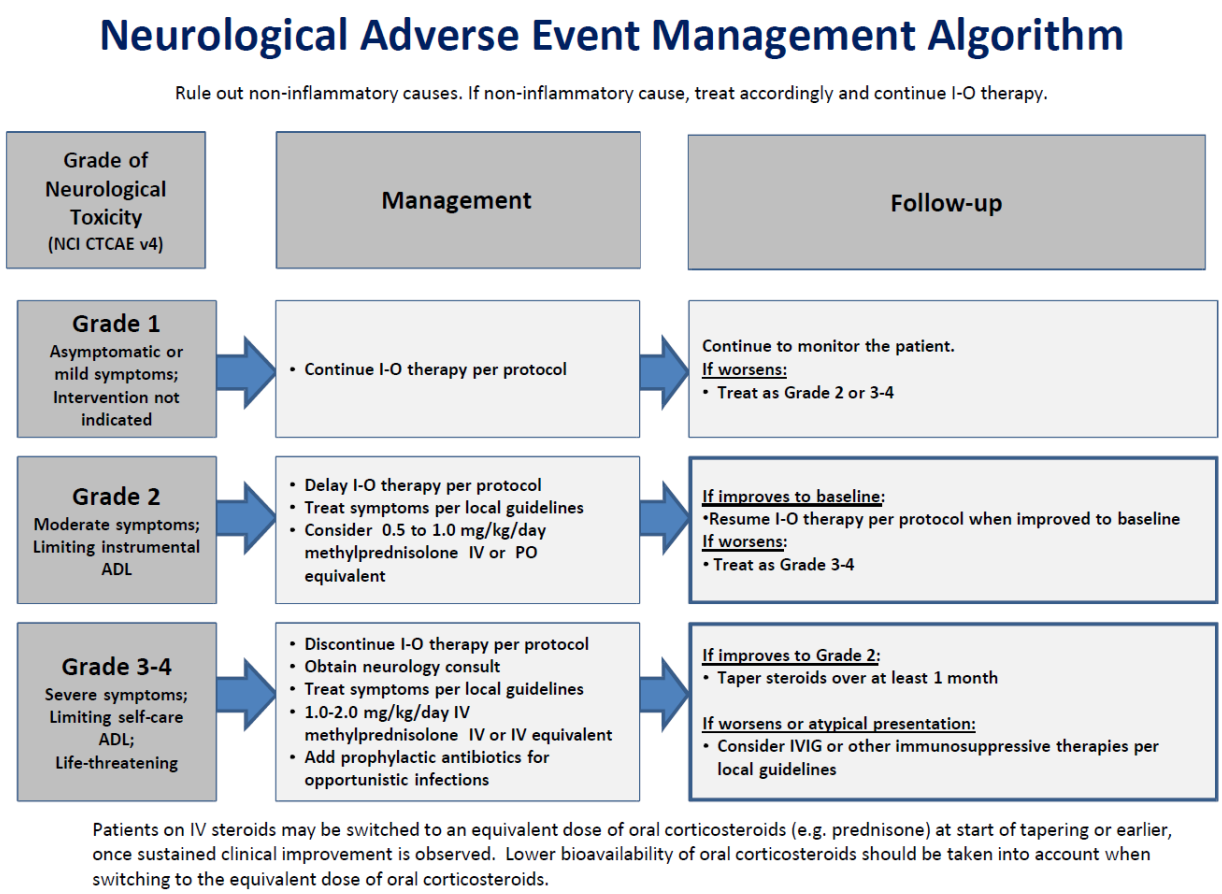
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.



6.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of *nivolumab and metformin* with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.
Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the PI. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician

6.4 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF)

including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs (event of clinical interests) as defined in Section 8.2.

6.5 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy, monoclonal antibody or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than Nivolumab and Metformin
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. Nivolumab will be held during radiation and can be resumed after radiation is finished and patient is stable per the treating physician. Metformin can be resumed during radiation.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor - investigator.
- Inhibitors of CYP3A4 and/or PgP

  Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) is prohibited.
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be avoided.. Co-administration with moderate CYP3A4 can be done with caution and only if other alternatives are not available.
- Lists of CYP3A4 inducers and inhibitors can be found on: http://medicine.iupui.edu/clinpharm/ddis/table.aspx and http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).
- Inducers of CYP3A4 and/or PgP

Strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort) should only be used if alternatives are not available. Moderate inducers of CYP3A4 are allowed if alternatives are not available.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.6 Rescue Medications & Supportive Care

6.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in Section 6.2. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to nivolumab.
Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 6.2 for dose modification.
It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.6.2 Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics	Subject may be premedicated at least 30 minutes prior to infusion of nivolumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr), if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor the subject closely. If symptoms recur, then no further study medication will be administered at that visit. Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6.7 Diet/Activity/Other Considerations

6.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity and concomitant use with nivolumab and metformin combination should be avoided.

6.7.2 Contraception

Nivolumab and Metformin may have adverse effects on a fetus in utero. Furthermore, it is not known if nivolumab and metformin have transient adverse effects on the composition of sperm. For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle

stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in

women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in

the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with Nivolumab and Metformin, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to BMS without delay and within 24 hours to BMS and within 2 working days to Sponsor if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).
The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Sponsor as described above and in Section 8.2.4.

6.7.4 Use in Nursing Women

It is unknown whether Nivolumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment. Patients should be advised not breastfeed while on Nivolumab and Metformin or for at least 3 months after discontinuation.

6.8 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for *2 years* or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.9 Duration of Follow Up

Patients will be followed as outlined in study calendar in section 7 after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6.10 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6.11 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with nivolumab and metformin and had at least two treatments with nivolumab and metformin beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for additional treatment with nivolumab and metformin via the Second Course Phase at the discretion of the investigator as detailed in Section 8.1.7.2.

6.12 Subject Replacement Strategy

Patients who do not complete the intended course of therapy due to reasons other than toxicity, clinical or radiographic disease progression will be considered as in-evaluable for the primary endpoint and will be replaced. Subject are not able to tolerate metformin despite 2 dose reductions in the first 2 weeks of the trial (Metformin only phase) will be considered inevaluable and replaced.

7. STUDY CALENDAR

Study Flow Chart

Trial Period:		**Treatment Cycles [a]**											**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1 [a]				2	3	4	5	To be repeated beyond 8 cycles 6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Day		D-14	D-7	D1	D15											
Scheduling Window (Days):	-28 to -1			± 3	± 3*	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Informed Consent	X															
Inclusion/Exclusion Criteria	X															
Demographics and Medical History	X															
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Metformin Administration [c]		X	X	X	X	X	X	X	X	X	X	X				
Drug Diary and Pill Count (Metformin) section 13.5 [c]		X		X	X	X	X	X	X	X	X	X	X			
Blood glucose log for diabetic patients		X	X	X	X											
Nivolumab administration [c]				X		X	X	X	X	X	X	X				
Post-study anticancer therapy status														X	X	
Survival Status														X	X	X
Review Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X	X		X		X	X	X	X	X	X	X				
Directed Physical Examination					X								X	X	X	
Vital Signs and Weight	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status [d]	X[d]	X		X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test – Urine or Serum β-HCG	X[j]															
PT/INR and aPTT	X															
CBC with Differential	X	X[e]		X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X[e]		X	X	X	X	X	X	X	X	X	X	X	X	
Fasting triglyceride, cholesterol and glucose	X						X			X						
CEA		X			X	X		X		X		X				
Urinalysis	X						X			X			X			
T3, FT4 and TSH	X					X			X			X	X	X		
ECG	X															

Trial Period:		**Treatment Cycles** [a]											**End of Treatment**	**Post-Treatment**		
										To be repeated beyond 8 cycles						
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1 [a]				2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Day		D-14	D-7	D1	D15											
Scheduling Window (Days):	-28 to -1			± 3	± 3*	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Tumor Imaging	X					X[g]		X[g]		X[g]		X[g]				
Newly Obtained Tissue Collection [h]	X			X [h]	X [h]											
Correlative Studies Blood Collection [i]	X			X[i]	X[i]		X[i]						X[i]			

a. Each cycle is 4 weeks, and there is 14 days lead in period in cycle 1
b. Only for patients with ongoing treatment related toxicities
c. Metformin will be taken 500 mg po BID for D-14 to-12, 500 mg am and 1000 mg pm for D-11 to 8, 1000 mg am and 1000 mg pm for D- 7 to -1, and continued 1000 mg BID for the rest of the study (if not able to tolerate 1000 mg BID during D1-14 period subject will be on maximum tolerated dose). Study coordinator will call the patient on Day -13 to confirm the subject is taking the right dose of medication. Nivolumab will be given after biopsy#2 (same day or up to 5 days later), and then repeated every 4 weeks.
d. ECOG performance status should be done within 14 days or less from day 1 of cycle 1
e. Lab results from screening may be used if completed within 1 week of day -1
f. Baseline imaging within 4 weeks of day 1 is acceptable
g. Scans will be done at the end of cycle 2 (± 3 days), then repeated every 2 cycles (q 8 weeks)
h. Paired biopsies (biopsy#1) will be obtained at baseline from all 28 patients within 28 days before Cycle 1 day 1 after consent is signed, subject #1-9, 19-23 (14 patients in total) will get post treatment biopsy (biopsy#2) cycle 1 Day 1 (same day or up to 5 days later) nivolumab will be given after biopsy#2 (same day or up to 5 days later) and subject# 10-18, 24-28 (14 patients in total) will get post treatment biopsy (biopsy#2) C1 Day 15 (same day or up to 5 days later). Most accessible metastatic disease tumor site will be biopsied by Emory Interventional Radiology. Same site will be biopsied at biopsy#1 and biopsy#2. 3 core biopsies will be obtained each time. If a patient undergoes biopsy#1 and refuse biopsy#2 this subject will be replaced. Subjects continue metformin on days of biopsy#2, and take metformin preferably 2 hours prior to the biopsy.

i. Correlative samples will be collected at baseline, cycle 1 day 1, cycle 1 day 15, Cycle 3 Day 1 and at progression. Analysis will include phenotypic and functional analysis of T and myeloid cell subsets.
j. Must be within 72 hours of the study drug

*Unless otherwise specified

8. TRIAL PROCEDURES

8.1 Trial procedures

The Trial Flow Chart - Section 7.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

8.1.1 Administrative Procedures

8.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.
A copy of the signed and dated consent form should be given to the subject before participation in the trial.
The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent

form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.
The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

8.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

8.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are

considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

8.1.1.4 Prior and Concomitant Medications Review

Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.2.

8.1.1.5 Disease Details and Treatments

Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

8.1.1.6 Trial Compliance (Medication/Diet/Activity/Other)

Compliance with Metformin will be determined using drug diary and pill counts performed on day 1 of each cycle. Patients who take less than 80% of their prescribed dose of nivolumab and/or metformin in the first 2 cycles due to reasons other than toxicity, clinical or radiographic disease progression will be considered inevaluable for the primary endpoint and will be replaced.

8.1.2 Clinical Procedures/Assessments

8.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (**see Section 11.2**). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with nivolumab all AEs of unknown etiology associated with nivolumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs, see section 6.2.2).
Please refer to section 8.2 for detailed information regarding the assessment and recording of AEs.

Winship Cancer Institute's Clinical Trials Office will perform the quality assurance and quality control checks on this clinical trial. Before enrollment of any subject in this study, CTO personnel and the Investigator will review the protocol; the Investigator's Brochure; the CRFs/electronic CRFs and instructions for completion; the informed consent process; and the procedure for reporting AEs and SAEs.

8.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

8.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

8.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

8.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening (within 14 days of day 1 cycle 1), prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

8.1.3 Tumor Imaging and Assessment of Disease

Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors
RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

8.1.3.1 Tumor Tissue Collection and Correlative Studies Blood Sampling

Paired biopsies (biopsy#1) will be obtained at baseline from all 28 patients within 28 days before Cycle 1 day 1 after consent is signed, subject #1-9, 19-23 (14 patients in total) will get post treatment biopsy (biopsy#2) cycle 1 Day 1 (same day or up to 5 days later) and subject# 10-18, 24-28 (14 patients in total) will get post treatment biopsy (biopsy#2) C1 Day 15 (same day or up to 5 days later). Most accessible metastatic disease tumor site will be biopsied by Emory Interventional Radiology. Same site will be biopsied at biopsy#1 and biopsy#2. We don't believe biopsy site bias the study as any metastatic site which is deemed safe and accessible can be biopsied. 3 core biopsies will be obtained each time. If a patient undergoes biopsy#1 and refuse biopsy#2 this subject will be replaced. The obtained tissues will be handled in the following way:

1) RNAlater for RNA stabilization and tissue storage
2) Formalin-fixed paraffin block with one cut H&E stained slide
3) Liquid nitrogen frozen tissue in cryo-preservation vials

All collected tissues are stabilized and stored in -80°C freezers (RNAlater stabilized, OCT embedded, short term storage) or the vapor phase of a liquid nitrogen freezer (long term storage) in single use aliquots. All FFPE tissue blocks are stored in a climate-controlled storage room that is temperature (less than 27ºC) and humidity controlled.
Tissue will be evaluated using IHC or immunofluorescence to measure relevant immune markers (i.e. CD3, CD4, CD8, CD163, PD-1, PD-2, PDL-1, MIF, TAM and stromal/ vascular markers). When sufficient quantities of fresh tissue is available, it will also be dissociated and flow cytometry will be used to determine the phenotypic characteristics of cell populations in the tumor microenvironment. Tissue will be preserved for future exploratory studies including genomic profiling.

<u>Peripheral blood samples</u>
Approximately 20 mL of peripheral blood will be collected prior to initiation of study therapy (at baseline), cycle 1 day 1, cycle 1 day 15, Cycle 3 Day 1 and at progression. The peripheral blood mononuclear cells will be isolated from these samples and stored in -80°C freezers until analysis. Samples will be evaluated for:
i. Determine whether there are phenotypic changes in of T-cell or myeloid cell surface markers (including co-stimulatory/immune checkpoint molecules) in PBMCs after treatment. Samples will be collected at baseline, cycle 1 day 1, cycle 1 day 15, Cycle 3 Day 1 and at progression.
ii. Determine whether functional changes are evident in PBMCs in response to treatment and whether these data correlate with clinical outcome measures. Samples will be collected at baseline and week 10th. Pending quantity of cells a variety of assays may be performed, including but not limited to intracellular cytokine production and expression of CD107.

Shipping and handling instructions

After appropriate processing, the blood samples, tissue blocks, slides or frozen tissue samples will be sent to:

Lesinski Laboratory
Suite C3038, Bay 34
1365-C Clifton Rd. NE
Winship Cancer Institute of Emory University
Atlanta, GA 30322

On the day that the specimens are to be shipped, notify Dr. Matthew Farren at matthew.r.farren@emory.edu, and Dr. Gregory Lesinski at gregory.b.lesinski@emory.edu of the pending specimen shipments. Include the Fed-Ex tracking number in the email.

Research blood contact Information:
Matthew Farren, Ph.D. 404-778-8230
Gregory B. Lesinski, Ph.D., MPH 404-778-3072

Methods and materials per Lab Manual

Table 5 Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		

Hematology	Chemistry	Urinalysis	Other
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			
‡ If considered standard of care in your region.			

8.1.4 Other Procedures

Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with nivolumab and metformin combination may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 8.1.7.2 After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 8.1.6) and then proceed to the Follow-Up Period of the study (described in Section 8.1.7).

8.1.5 Visit Requirements

Visit requirements are outlined in Section 7.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 8.0 - Trial Procedures.

8.1.5.1 Screening

Screening Period

All subjects must sign an informed consent document prior to the initiation of any study related procedures. The informed consent document must be signed within 28 days of Cycle 1 Day 1. Screening procedures are to be conducted within 28 days of Cycle 1 Day 1.

- Review of study eligibility criteria
- Medical History
- Record concomitant medications taken up to 28 days prior to day 1 cycle 1
- Vitals [temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR)]
- Physical Examination, including height and weight
- ECOG Performance Status evaluation (within 14 days or less of cycle 1 day 1)
- Laboratory Assessments

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
- Serum chemistry: sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin. Fasting triglycerides, cholesterol and glucose.
- Serum or urine pregnancy test for women of childbearing potential. Must be within 72 hours of study drug
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
- Urinalysis
- Tumor markers: CEA
- T3, FT4, TSH

- 12-lead ECG
- Radiologic imaging studies to evaluate tumor status. contrast computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen and pelvis. Additional imaging may be obtained as clinically indicated. Baseline scans may be done within 4 weeks prior to cycle 1 day 1.
- Baseline fresh biopsy (in all patients, 28 total) will be obtained within 28 days of day 1 cycle 1 and after consent is signed.
- Blood sample 20 cc for correlative work

8.1.5.2 Treatment Period

8.1.5.3 Lead in Cycle 1 Day -14

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count, blood glucose log for diabetic patients
- ECOG performance status
- Toxicity assessment
- Laboratory Assessments
  - Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
  - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
  - For the cycle1 day -1 labs, lab results from the screening tests maybe used if completed within 1 week of day -1

- Tumor marker – CEA

- Metformin

8.1.5.4 Cycle 1 Day -7 phone call

- Metformin
- Review of adverse events, dosing compliance and concomitant medication (by clinical trial coordinator via phone call

8.1.5.5 Cycle 1 Day 1

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count, blood glucose log for diabetic patients
- ECOG performance status
- Toxicity assessment
- Laboratory Assessments
  - Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
  - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
- Blood sample 20 cc for correlative work
- **Subject# 1-9, 19-23** (14 patients in total) will get biopsy#2 of paired biopsy (same day or up to 5 days later)
- Continue metformin
- Nivolumab will be started after biopsy#2 (same day or up to 5 days later).
- Nivolumab 480 mg will be administered as a 30-minute IV infusion in the infusion center. Given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

8.1.5.6 Cycle 1 Day 15

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count, blood glucose log for diabetic patients
- ECOG performance status

- Toxicity assessment
- Laboratory Assessments
    - Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
    - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
    - Tumor marker – CEA
- Blood sample 20 cc for correlative work
- The second half of the patients **Subject #10-18, 24-28** (14 patients in total) will get biopsy#2 of paired biopsy (same day or up to 5 days later)
- Continue metformin

8.1.5.7 Cycle 2 Day 1

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count
- ECOG performance status
- Toxicity assessment
- Laboratory Assessments
    - Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
    - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
    - Tumor marker – CEA (every 2 cycles after cycle 2)
    - T3, FT4, TSH at cycle 2 and then after every 3 cycles
- Metformin and Nivolumab combination
- Cross sectional imaging (CT or MRI) for restaging at the end of C#2 (± 3 days), then repeat every 2 cycles (every 8 weeks)

8.1.5.8 Cycle 3 Day 1 and Day 1 of each subsequent cycle

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, pill diary and pill count
- ECOG performance status

- Toxicity assessment
- Laboratory Assessments
    - Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
    - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
    - Fasting triglycerides, cholesterol and glucose (Cyle#3 and every 3 cycles)
    - Urinalysis (Cyle#3 and every 3 cycles)
- Metformin and Nivolumab combination
- Blood sample 20 cc for correlative work

8.1.5.9 End of treatment visit

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Toxicity assessment

- Laboratory Assessments
    - Hematology hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
    - Chemistry sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, and albumin
    - Tumor markers - when applicable.
    - Urinalysis
    - T3, FT4, TSH
- Blood sample 20 cc for correlative work

8.1.6 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with nivolumab/metformin (as described in

Section 8.1.7.2) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

8.1.7 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with nivolumab and metformin as detailed in Section 7.1.6.2. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated. Details are provided in Section 7.0 – Trial Flow Chart.

8.1.7.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.1.7.2 Second Course Phase (Retreatment Period)

Subjects who stop nivolumab/metformin with SD or better may be eligible for up to one year of additional nivolumab/metformin therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with nivolumab/metformin after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 24 weeks with nivolumab/metformin before discontinuing therapy
        - Received at least two treatments with nivolumab/metformin beyond the date when the initial CR was declared

    OR

    - Had SD, PR or CR and stopped nivolumab/metformin treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with nivolumab/metformin

- Did not receive any anti-cancer treatment since the last dose of nivolumab/metformin
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.7
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.1.10). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last nivolumab/metformin. Treatment will be administered for up to one additional year.
Visit requirements are outlined in Section 7.0 – Trial Flow Chart

8.2 Assessing and Recording Adverse Events

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

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

8.2.1 Serious Adverse Events

A **S*erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Unusual Failure in Efficacy (for Phase IV Canadian studies)

Although pregnancy and potential drug-induced liver injury (DILI), are not always serious by regulatory definition, however, these events must be reported within the SAEs timeline.

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

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, 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 (eg, 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)

8.2.1.1 Reporting of Serious Adverse Events Associated with Nivolumab

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days for nivolumab 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 to BMS.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own Institutional form, it must be reviewed by the BMS Protocol Manager prior to study initiation to ensure that at a minimum all of the data elements on the CIOMS form are present. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

- ✓ The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
- ✓ The MedWatch form is available at: MedWatch 3500 Form

-
- The Sponsor-investigator will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
    - The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
    - GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
    - 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 (Worldwide.Safety@bms.com).
- In addition to the Sponsor Investigator's responsibility to report events to the FDA , suspected serious adverse reactions (whether expected or unexpected) shall be reported by

BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.
  - ✓ Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.
  - ✓ Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

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

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

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.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

8.2.2 Nonserious Adverse Event

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

8.2.2.1 Non-serious Adverse Event Collection and Reporting

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

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

8.2.3 Laboratory Test Abnormalities

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

The following laboratory abnormalities should be documented and reported appropriately:

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

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

8.2.4 Reporting of Pregnancy and Lactation to the BMS

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

The investigator must immediately notify Worldwide.Safety@bms.com of this event and complete one of the following forms within 24 hours of awareness of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

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

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

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

8.2.5 Other Safety Considerations

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

8.3 Expedited Adverse Event Reporting

8.3.1 Expedited AE reporting for this study must be reported to the FDA/IRB per FDA and IRB guidelines.These requirements are briefly outlined in the tables below (Section 8.3.2). Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

8.3.2 Table 6 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of investigational product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of investigational products and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to BMS within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to BMS within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause investigational products to be discontinued?	
Relationship to investigational **Product(s)**	Did investigational product(s) cause the adverse event? The determination of the likelihood that investigational product(s) caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between** investigational **product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely BMS product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to investigational product(s) such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of investigational product(s)? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to investigational (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was investigational product(s) discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the BMS product; or (3) the trial is a single-dose drug trial); or (4) BMS product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to investigational product(s) in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) BMS's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY investigational PRODUCT, OR IF REEXPOSURE TO BMS PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding investigational product(s) or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of** investigational **product(s) relationship).**	
Yes, there is a reasonable possibility of investigational **product(s) relationship.**	There is evidence of exposure to investigational product (s) . The temporal sequence of the AE onset relative to the administration of investigational product(s) is reasonable. The AE is more likely explained by investigational product(s) than by another cause.	
No, there is not a reasonable possibility of investigational **product(s) relationship**	Subject did not receive the investigational product OR temporal sequence of the AE onset relative to administration of investigational product(s) is not reasonable OR the AE is more likely explained by another cause than the BMS product. (Also entered for a subject with overdose without an associated AE.)	

8.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. ALL **AEs are to be reported through ONCORE.**

8.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported through **ONCORE.** Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

8.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).
A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in investigator`s brochure.

9. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

9.1.1 Nivolumab

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.
Clinical Supplies will be provided by BMS as summarized in Table X.

Clinical Supplies will be provided by BMS.

9.1.2 Metformin ER

Metformin will be bought by the investigational pharmacy services at Winship Cancer Institute and the funding will be provided by BMS.
The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

9.1.3 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.1.4 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor-investigator and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.1.5 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.
Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.
Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.1.6 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints/ Determination of Sample Size

This is a phase II trial. Primary objective is to determine the overall response rate. Historically ORR with single agent Nivolumab in CRC is <5% and Metformin and Nivolumab combination will have ORR of 15%. Simon's MinMax two stage design is employed for the study with power of 80% and alpha of 0.1. If there is 1 response in first 18 patients in the first stage of the study, then it will proceed with second stage to enroll total of 28 patients. If there are 3 or more responders out of the 28 patients then it would be positive study. This will enable us to evaluate clinical endpoints (ORR, CEA, RFS, OS) as well as evaluate the impact on immune biomarkers.

10.2 Statistical and Analytical Plans

Summary statistics will be presented for all safety, efficacy and biomarker parameter analyses. The purpose of these analyses is hypothesis generating. Various exploratory statistical tests may be applied to data generated from this trial to generate hypotheses to be tested in subsequent trials. In general, data for continuous parameters will be presented using descriptive statistics including sample size, mean, and median; standard deviation; and minimum and maximum. Categorical parameters be displayed using counts and percentages. Toxicities will be presented as worst toxicity per patient and will be reported as percent toxicity.

Objective response rate will be calculated as proportion (Responders/Total patients) along with 95% confidence intervals using the Clopper-Pearson method. Chi-square test or Fisher's exact test will be used to compare the efficacy in term of response rate, biochemical response (CEA) between the different groups stratified by biomarkers or other factors, respectively. Logistics regression

model will be further employed to test the adjusted effect of biomarkers on the response rate after adjusting for other clinical factors and demographic factors.

For progression free survival, progression or death from any cause will be defined as the event. Patients will be censored at time of last follow-up. For overall survival, death from any cause will be defined as the event. Patients will be censored at time of last follow-up. Overall survival (OS) and progression free survival (PFS) rates of two patient groups stratified by response or other factors will be estimated with the Kaplan-Meier method and compared between different groups using the log-rank test, respectively. The PFS and OS of each patient group at specific time points, such as 6 moths, 1 year, 3 year, and 5 year, etc. will be also estimated alone with 95% CI. Cox proportional hazards models will be further used in the multivariable analyses to assess adjusted effect of response on the patients' OS and PFS after adjusting for other factors. Interaction terms between these factors will also be tested for statistical significance. The proportional hazards assumption will be evaluated graphically and analytically with regression diagnostics. Violations of the proportional hazards assumptions will be addressed by use of time-dependent covariates or extended Cox regression models.

For the biomarker study, descriptive statistics will be first used to summarize biomarker endpoints, including analyses of tumor biopsies. Biomarker data will also be displayed graphically, where appropriate. Depending on whether data is normally distributed, t-test or Wilcoxon rank sum test will be used to compare each biomarker between any two groups stratified by response or other factors, respectively. General linear model (GLM) will be used to compare each biomarker between responders and nonresponders with and without adjusting for other factors. Logistics regression model will be further employed to test the adjusted effect of biomarker on the response rate after adjusting for other factors.

10.3 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in

exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

10.4 Analysis Sets

All subjects who receive any amount of study drug will be included in the evaluation of safety and efficacy.

10.5 Subject Disposition and Baseline Characteristics

The number and percentage of subjects who enrolled, were treated, and who discontinued will be tabulated. The reasons for treatment and study discontinuation will be presented. Demographic and other baseline characteristics will be summarized using descriptive statistics or counts and percentages, as appropriate.

10.6 Safety Analysis

10.6.1 Adverse Events

Adverse events will be classified using MedDRA System Organ Classes and Preferred Terms. Furthermore, SAEs, AEs with a severity grade of 3 or above using NCI CTCAE version 4.0, AEs deemed related to study drug, AEs leading to discontinuation of study drug, and AEs leading to death will also be summarized in preferred term by system organ class and listed on an individual subject basis.

10.6.2 Laboratory Data

Descriptive statistics for worst grade of each laboratory parameter by the NCI CTCAE scale version 4.0 at baseline and follow-up will be presented along with change from Baseline. Additionally, laboratory values ≥ Grade 3 severity will be tabulated and listed on an individual subject basis.

10.6.3 Dose Modifications and Reasons

The number of subjects with skipped doses, dose delays and dose reductions as well as major reasons for dose modifications will be summarized.

11. ADMINISTRATIVE AND REGULATORY DETAILS

11.1 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2 Pre-study Documentation

The Sponsor-Investigator must provide BMS with the following documents prior to the enrollment of any subjects:

- Copy of the IRB/IEC approval letter for protocol, informed consent, Investigator and site
- Signed and dated current curricula vitae of the investigator
- Copy of approved informed consent document
- Copy of the FDA letter and IND receipt and number assignment
- Signed Clinical Trial Agreement

11.3 Protocol Adherence

By signing the Form FDA 1572, the Investigator agrees to conduct the study according to the protocol and the FDA regulations set forth in 21 CFR Parts 50, 54, 56, and 312.

11.4 Retention of Study Documents

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained as required by FDA and Emory policy.

11.5 Data Management

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within

Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Dr. Gbolahan and the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet to review and discuss study data to ensure subject safety weekly. During the meetings the PI or co-I will review the eligibility criteria for each new patient. In addition, during these meeting the group will review all the toxicity (AE/SAE) logs, random checks of case report form completion and roadmap for each patient on the trial. All study personnel will be trained on the protocol by the PI or co-I. Study personnel will sign training log prior to being included on delegation of authority log. All AE and SAE will be handled according to Section 8.2 which provides detailed instructions on reporting requirements.

12. REFERENCES

Please provide the citations for all publications referenced in the text.

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13. APPENDICES

13.1 APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

13.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan,

D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

13.4 APPENDIX B-E

Appendix B

Pill Diary for Cycle 1 Lead in phase (Day -14 to -1)

Protocol	Subject Number	Subject Initials	Visit
WCI			Cycle 1

Patient Diary

Please use this diary to record your daily protocol medication.
Metformin Dose
Please take _1_ capsule of __500___ mg twice daily for 3 days

	Date:	Time:	Time:
Record date and time taken for each day			
Day -14			
Day -13			
Day -12			

Please use this diary to record your daily protocol medication.
Metformin Dose
Please take _1_ capsule of __500___ mg AM and 2 capsules of 500 mg PM for 4 days

	Date:	Time:	Time:
Record date and time taken for each day			
Day -11			

Day -10			
Day -9			
Day -8			

Please use this diary to record your daily protocol medication.
Metformin Dose
Please take _2_ capsules of __500___ mg AM and 2 capsules of 500 mg PM for 7 days

	Date:	**Time:**	**Time:**
Record date and time taken for each day			
Day -7			
Day -6			
Day -5			
Day -4			
Day -3			
Day -2			
Day -1			

Please sign at the completion of this cycle and **<u>return with pill bottle</u>** to the study team.
Patient's
Signature _____ Date_____

Please use this diary to record your daily protocol medication.

Pill Diary for Cycle 1 (Day 1 to 28) and further cycles

Protocol	Subject Number	Subject Initials	Visit
WCI			Cycle 1

Metformin Dose

Please take _____ mg AM and _____ mg PM

	Date:	Time:	Time:
Record date and time taken for each day			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			

Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			
Day 22			
Day 23			
Day 24			
Day 25			

Day 26			
Day 27			
Day 28			

Please sign at the completion of this cycle and **return with pill bottle** to the study team.
Patient's
Signature _____ Date_____

Appendix C

Blood glucose log
Please check your blood glucose level and record the date and time

	Date:	**Time and glucose level**	**Time and glucose level**
Record date and time taken for each day			
Day -14			
Day -13			
Day -12			
Day -11			
Day -10			
Day -9			
Day -8			

Day -7			
Day -6			
Day -5			
Day -4			
Day -3			
Day -2			
Day -1			
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			

Day 10			
Day 11			
Day 12			
Day 13			
Day 14			

Please sign at the completion and **return with pill bottle** to the study team.
Patient's
Signature _____ Date_____

Appendix D

Health/Medical Complaints

Please record all health/medical complaints you may have experienced below.

Please describe what you experienced	Date Started	Date Stopped

Appendix E

Other Medications

Record all medications taken during this cycle for example prescriptions and over the counter including vitamins.

Name of Medication	Why did you take the medication?	Date Medication Started	Date Medication Stopped

If you have any questions, please call: _____

Protocol Review Checklist

(Please delete after review)

□ Phase of Study Clear in Title and throughout protocol
□ Correct Contact Information
□ IND/IDE # (if Applicable) or IND/IDE Exempt Clearly stated on cover page clearly stated
□ Version # & Version Date correct throughout (cover page & header)
□ Study Schema / Synopsis
□ Table of Contents
  □ Designated pg # match section
□ Objectives
□ Background
□ Science
  □ Reasoning for this study treatment/device (combination)
□ Eligibility
□ Inclusion Criteria
□ Exclusion Criteria
□ Do parameters match remainder of protocol?
□ Procedures Match throughout Protocol?
□ Have visit windows been designated?
□ Font Type & Size Consistent
□ Have procedures been spelled out? (i.e. vitals, chemistry)
□ Registration Process clearly designated
□ Treatment Clearly Specified
  □ DLT clearly specified
  □ Dose Modifications
□ Stopping Rules
□ Accrual goal # and timeline clearly stated
  □ Accrual population?
□ Is this a Multi-Site study?
  □ Multi-Site Monitoring Plan inserted
  □ Registration procedures detailed
  □ Eligibility confirmation process
  □ Randomization/dose assignment
  □ SAE/DLT reporting requirements for sub-sites
  □ Data reporting for sub-sites
  □ Does anything have to be sent to Emory?
□ Clear Follow-up
□ References
□ Appendicies (QOL, Response Criteria, Staging Criteria, etc)
□ Conmed
  □ Supportive meds
  □ Prohibited meds
□ Calendar of Events
□ Statistician Review / Consultation
□ DSMP plan identified
□ Investigator Signature Page
□ Data Capture
  □ eCRF system
  □ Data Collection timeline
□ Correlatives/correlative science
  □ Correlative specimens?
  □ Lab utilized for correlatives?
  □ QOL
  □ Collection procedures
  □ Shipping/storage procedures
  □ Processing procedures
□ Definition of SAE
□ SAE reporting
□ Deviations / reporting requirements
□ Does Budget match Protocol expectations
□ IRB/Regulatory expectations
□ Treatment
  □ Drug shipment
  □ Commercial or through IDS
  □ Storage/destruction
  □ Side effects
□ Study Termination