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Parallel proof of concept phase 2 study of nivolumab and metformin combination treatment in advanced non-small cell lung cancer with and without prior treatment with PD-1/PD-L1 inhibitors

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Study Intervention(s): Nivolumab, Metformin

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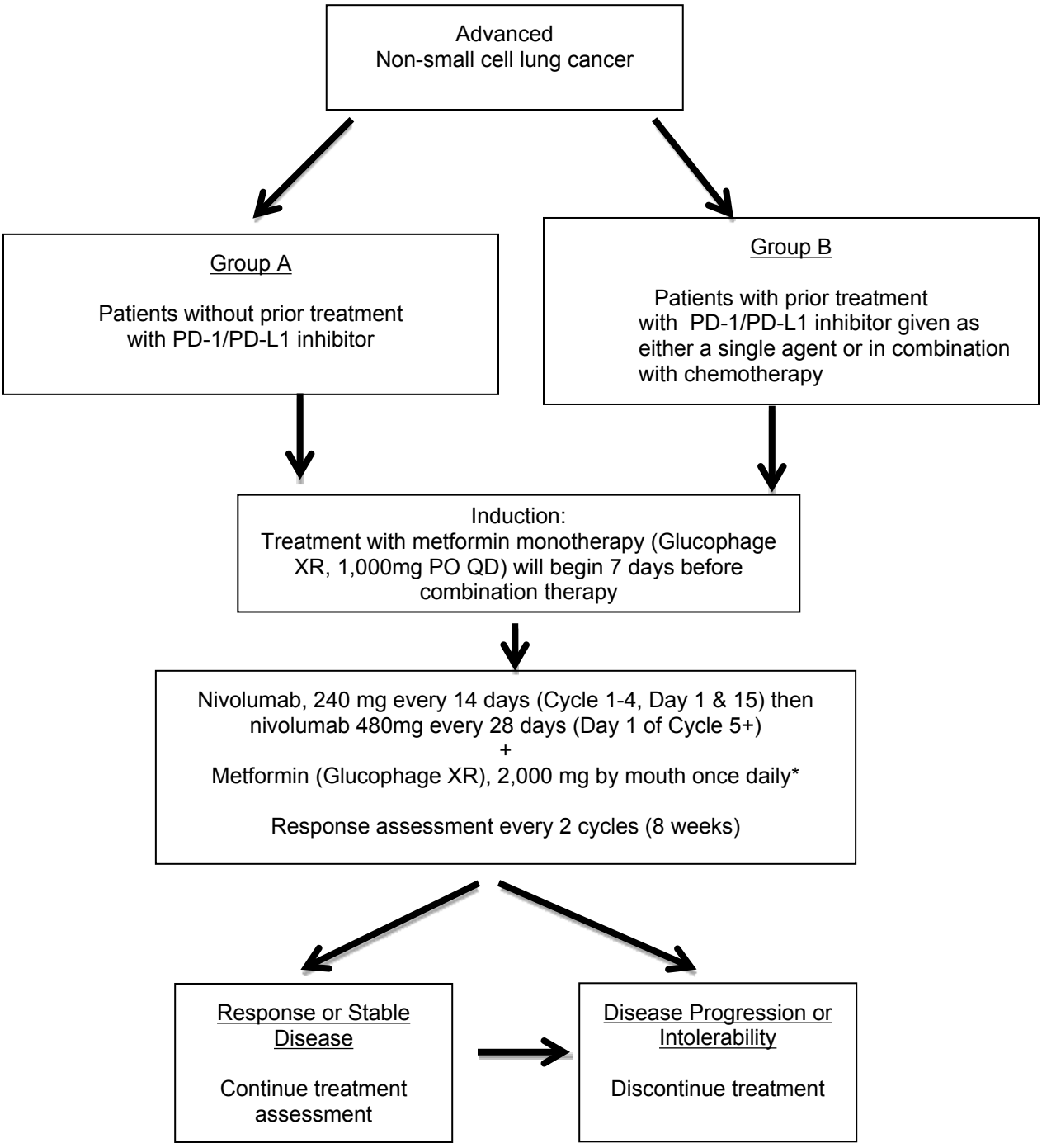
LIST OF ABBREVIATIONS

AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
GI	Gastrointestinal
H&PE	History & Physical Exam
HunMab	Human Monoclonal Antibody
IGF-1	Insulin like Growth Factor-1
IgG4	Immunoglobulin G4
IV (or iv)	Intravenously
MSI	Microsatellite Instability
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
NCI	National Cancer Institute
NSCLC	Non Small Cell Lung Cancer
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-(L)1	Programmed Death- (Ligand) 1
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
RCC	Renal Cell Carcinoma
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TCM	Central Memory T Cells
TEM	Effector Memory T Cells

TNBC	Triple Negative Breast Cancer
Tregs	Regulatory T Cells
TSC 1/2	Tuberous Sclerosis Complex 1/2
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cells

STUDY SCHEMA



* Metformin: start at 1,000 mg daily and escalate incrementally to 2,000 mg/day as tolerated (see section 4.0 for details)

STUDY SUMMARY

Title	Parallel proof of concept phase 2 study of nivolumab and metformin combination treatment in advanced non-small cell lung cancer with and without prior treatment with PD-1/PD-L1 inhibitors
Version	4.22.19 (Amendment 5)
Study Design	Phase II proof of concept study with two parallel groups
Study Center(s)	Northwestern University
Objectives	**Primary Objective:** To assess anti-tumor activity of the combination treatment of metformin with nivolumab in patients with non-small cell lung cancer with and without prior exposure to PD-1/PD-L1 inhibitors: Anti-tumor activity will be assessed by objective response rate (ORR, complete response and partial response) using RECIST criteria (version 1.1) **Secondary Objectives:** (1) To assess the efficacy of the combination treatment of metformin with nivolumab according to depth, duration, and persistence of response, disease control rate (DCR; CR, PR, and SD at 24 weeks), progression-free survival (PFS), and overall survival (OS) in patients with non-small cell lung cancer with and without prior exposure to PD-1/PD-L1 inhibitors using RECIST criteria (2) To assess the efficacy of the combination treatment of metformin with nivolumab according to depth, duration, and persistence of response, ORR, DCR, PFS, and OS in the above population using immune-related RECIST (irRECIST) criteria (3) To assess the safety and tolerability profile of the combination treatment of metformin with nivolumab in the above population using CTCAE version 4.03 Exploratory objective: (1) To assess the immune-related tumor and blood biomarkers including T cell markers and their association with treatment response in the above population (2) To assess the dynamic change in both immune and genomic biomarkers in blood that may correlate with response to treatment.
Sample Size	Up to 51 patients (minimum of 21 patients) Based on optimal Simon two stage design; - Arm A: If stopped earlier 9 patients will be enrolled to arm A, if continued, 24 patients will be enrolled. - Arm B: If stopped earlier 12 patients will be enrolled to arm B, if continued 25 patients will be enrolled. Total maximum number of evaluable patients=49 Given possible inevaluable patient and drop out from study, we will aim for 51 patients for total enrollment. This will be a single institution trial with duration of enrollment estimated to be 2 years. Estimated accrual rate will 25.5 per year, approximately 2 per month.

Diagnosis & Key Eligibility Criteria	Study population will consist of patients age 18 or older, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, with histologically confirmed, locally advanced or metastatic non-small cell lung cancer (arm A: naive to single agent PD-1/PD-L1 inhibitors that includes but not limited to durvalumab, pembrolizuamb, atezolizumab, nivolumab, avelumab; arm B: refractory to or progressed on one of the above agents; both cases are defined by initial PD or PD following CR, PR, or SD using RECIST criteria.). Patients need to have adequate kidney, bone marrow, and liver functions, and a measurable disease according to Response Evaluation Criteria of Solid Tumors (RECIST). Patient should not have received metformin within 6 months from the consent date. (Arm B: Patients who were on metformin while on PD-1/PD-L1 inhibitors will be excluded). Patients with exposure to prior immunotherapy, including combination treatment with PD-1/PD-L1 inhibitors are excluded from arm A. Immunotherapy agents include but are not limited to interleukin-2 and other immune checkpoint antagonist targeting CTLA-4, LAG-3, TIM-3, KIR etc. and/or agonists targeting OX40, ICOS, CD137, etc. Also, patients who are intolerant to PD-1/PD-L1 inhibitors or metformin are also excluded. Prior cancer vaccine treatments are permitted for both arms. Of note, patients with prior exposure to single agent PD-1/PD-L1 inhibitors or combination treatment with PD-1/PD-L1 inhibitor and chemothrapy (such as carboplatin, pemetrexed, and pembrolizumab) are eligible for enrollment in arm B. Patients cannot have a history of clinically significant autoimmune diseases or a syndrome that requires systemic steroids (>10mg prednisone or equivalent, premedication for contrast allergy is permitted) or immunosuppressive agents. Autoimmune diseases include but are not limited to autoimmune hepatitis, systemic lupus erythematous, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, vasculitis, or glomerulonephritis. Vitiligo, alopecia, hypothyroidism on stable doses of thyroid replacement therapy, psoriasis not requiring systemic therapy within the past 3 years is permitted. Short-term steroid premedication for contrast allergy is permitted. Metastatic brain parenchymal disease must have been treated and patient must be off steroids for at least two weeks. Patients with another primary malignancy within 2 years prior to starting study treatment with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine cervix, or any local cancers that are deemed to be cured from investigator's point of view.
Treatment Plan	Patients will start metformin (Glucophage XR) at 1,000mg by mouth once daily during a 7-day induction period prior to starting nivolumab Cycle 1 Day 1 (1 cycle = 28 days). The dose will be increased by 500mg every 7 days (C1D1 and C1D8) until reaching the target dose of 2000mg. Nivolumab will be administered at a fixed dose of 240 mg IV every14 days during Cycle 1-4 (Day 1 & 15) and 480mg IV every 28 days starting with Cycle 5 Day 1. Treatment will continue until disease progression confirmed by RECIST criteria v1.1, intolerable toxicity or withdrawal of consent. Imaging by CT or MRI will be scheduled every 2 cycles (8 weeks).

Statistical Methodology	Accounting for inevaluable patients and dropouts, up to 51 patients (Arm A=24, Arm B=25) will be entered into the trial based on optimal Simon two stage design as below. Arm A: In the first stage, 9 patients will be entered. If no patients show a response, then the trial will be terminated due to inactivity of the treatment. If 1 or more of 9 show a response, then an additional 15 patients will be added. If 2 or fewer of 24 show a response, then the trial will conclude that the response rate could be as low as 5%. If 3 or more respond, then the trial will conclude that the response rate is at least 20%. This design has a 20% chance of falsely concluding the rate is 5% (false negative Type II error rate = 20%, or power = 80%), and a 10% chance of falsely concluding that the rate is 20% (false positive Type I error rate = 10%). There is a 63% probability of early termination of the trial when the true response rate is 5%. Arm B: In the first stage, 12 patients will be entered. If 2 or fewer patients show a response, then the trial will be terminated due to inactivity of the treatment. If 3 or more of 12 show a response, then an additional 13 patients will be added. If 7 or fewer of 25 show a response, then the trial will conclude that the response rate could be as low as 20%. If 8 or more respond, then the trial will conclude that the response rate is at least 40%. This design has a 20% chance of falsely concluding the rate is 20% (false negative Type II error rate = 20%, or power = 80%), and a 10% chance of falsely concluding that the rate is 40% (false positive Type I error rate = 10%). There is a 56% probability of early termination of the trial when the true response rate is 5%.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Significant unmet need in treatments of advanced non-small cell lung cancers

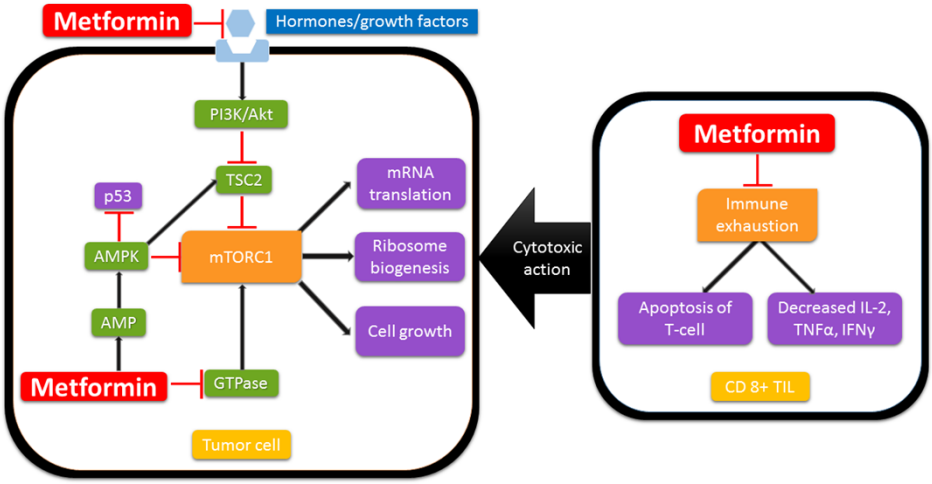
Despite the recent success of immune checkpoint inhibitors, only a small proportion of patients with non-small cell lung cancer gain clinical benefit from such therapies. Many patients are either refractory to or relapse after such therapies. Since the FDA approval of PD-1 (programmed death receptor-1) inhibitors (nivolumab, pembrolizumab) in advanced non-small cell lung cancer as single agents or in combination with chemotherapy first-line in metastatic nonsquamous NSCLC (carboplatin, pemetrexed, and pembrolizumab), many patients have been treated with these drugs as a standard of care treatment. However, many of them were found to be refractory to or progressed on such treatments. Moreover, many patients with various types of cancers who had PD-1/PD-L1 inhibitors administered as part of clinical trials are now refractory to such treatments.

Therefore there is high unmet need in non-small cell lung cancer to increase the efficacy of immune checkpoint inhibitors. Also, since most of novel immunotherapy trials, whether in single agent or in combination, exclude patients who have previously been exposed to other forms of immunotherapy including PD-1/PD-L1 inhibitors, these patients have significantly limited access to investigational therapeutics. Therefore, there is substantial unmet need for treatment options for patients with non-small cell lung cancer refractory to PD-1/PD-L1 inhibitors.

1.2 Immune stimulating properties of Metformin:

Metformin is one of the most commonly prescribed medications for the treatment of diabetes mellitus. Experiments in animal models of pancreatic cancer demonstrated anti-tumor properties of metformin via various mechanisms including inhibition of insulin like growth factor-1 (IGF-1) and mTOR, along with activation of AMPK and tuberous sclerosis complex (TSC1, TSC2)[1]. Furthermore, epidemiologic data have repeatedly demonstrated decreased cancer incidence and mortality in patients taking metformin [2-5]

Figure 1. Anti-cancer Mechanism of Metformin



Of note, recent experiments have also suggested that metformin has immune modulatory properties. Metformin inhibited immune exhaustion of CD8+ tumor induced lymphocytes (TIL), thereby enhancing T cell mediated immune response to tumor tissue. It decreased apoptosis of CD8+ tumor infiltrating lymphocytes (TILs), and also shifts the phenotype of CD8+ TILs expressing exhaustion markers (especially PD1 negative Tim3 positive) from central memory T cells (TCM, inactive against tumor cells) to effector memory T cells (TEM, active against tumor cells). The increase in TEM cell population has been found to correlate with regression of tumor cells [6]. In a study evaluating an experimental cancer vaccine, administration of metformin after vaccination in animal models showed an increase in CD8+ memory T cells which conferred protective immunity upon subsequent tumor challenge [7]. Figure 1 summarizes the effects of metformin on various cellular pathways.

We have further explored the immune modulatory function of metformin. We have confirmed the positive effect of metformin on cytotoxic CD8+ T cells. Moreover, we also demonstrated for the first time that metformin inhibits regulatory T cells (Tregs) (unpublished data).

1.3 Rationale for the Current Study

1.3.1 Generating synergy and overcoming resistance to PD-1/PD-L1 inhibitors with the combination of nivolumab and metformin:

Building upon the above scientific and clinical rationale supporting the use for metformin to maximize the benefit of immunotherapy and the high unmet need for more effective treatment options for patients with non-small cell lung cancer both with and without prior exposure to PD-1/PD-L1 inhibitors, we propose a proof-of-concept parallel phase 2 trial using the combination regimen of nivolumab and metformin.

We hypothesize that the combination of nivolumab and metformin will be synergistic in effect and also will overcome the resistance to single agent PD-1/PD-L1 inhibitors. The fact that metformin activates CD8+ TILs, aids in formulation of TEMs and suppress Tregs at the same suggests that the combination of metformin and anti-PD1 monoclonal antibody, nivolumab may exert more robust immune modulatory anti-cancer effect than single agent PD-1/PD-L1 inhibitors. In addition, non-immune anti-tumor property of metformin may have assist in providing additive anti-cancer effect.

In Group B, this trial will enroll both patients who initially responded to PD-1/PD-L1 inhibitors and progressed later on as well as patients had primary refractoriness to such agents. This trial will also serve as a proof of concept trial to later further explore the effectiveness of the metformin- immune check-point inhibition combination regimen in cancers that harbor primary or secondary resistance to PD-1/PD-L1 inhibitors.

Given that the indications for PD-1/PD-L1 inhibitors in solid cancers will only expand in the near future, time is right for this proof-of-concept trial that will answer the important clinical questions in both increasing efficacy and overcoming the resistance in PD-1/PD-L1 inhibitors. This trial may pave way for the next pivotal phase 3 trial in non-small cell lung cancer or for proof of concept phase 2 trial in other cancer types where the combination treatment may be of significant clinical value.

1.3.2 Rationale for the Study Design:

Group A and Group B will address two clinical questions. Group A is designed to assess possible synergistic effect of the combination treatment in immunotherapy naïve patients whereas group B is designed to determine whether the combination treatment of metformin with immunotherapy can overcome resistance to single agent PD-1/PD-L1 inhibitors.

Group A: In order to demonstrate synergy in anti-tumor effect, ORR of the combination treatment will be compared to that of historical control (20%) reported in phase 3 single agent nivolumab trials in lung cancer (CheckMate057 and CheckMate017). Optimal Simon's two stage design will be used with target ORR of 40% versus control ORR of 20% (type 1 error rate of 0.1 and power of 0.8)

Group B: In order to find signal in patients with prior exposure to single agent PD-1/PD-L1 inhibitors, ORR of the combination treatment will be described. Optimal Simon's two stage design will be used with target ORR of 20% versus control ORR of 5% (type 1 error rate of 0.1 and power of 0.8).

1.4 Nivolumab Clinical development

The U. S. Food and Drug Administration approved nivolumab (Opdivo Injection, Bristol-Myers Squibb Company) for patients with unresectable or metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, and Hodgkin's lymphoma.

1.4.2 Clinical efficacy

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed at all doses. Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Heavily pretreated patients with NSCLC treated with nivolumab (1, 3, or 10mg/kg) achieved median OS across all dose cohorts of 9.9 months with response rates of 17% and median duration of response 17 months [8]. In addition, responses were similar between both squamous and non-squamous carcinoma cohorts in this study. A subsequent phase 3 study compared nivolumab to docetaxel in second-line treatment setting of advanced squamous cell carcinoma among 272 patients. Nivolumab arm demonstrated superior median OS (9 vs. 6 months), 1 year survival rate (42 vs. 24%), response rates (20 vs. 9%), and significantly lower rates of grade 3-4 treatment related adverse events (7 vs. 55%) [9]. These results supported the FDA approval of nivolumab for second-line treatment of advanced squamous cell carcinoma following treatment with platinum-based chemotherapy.

Nivolumab also has clinically meaningful activity in RCC. A phase II study treated 168 patients with advanced clear cell RCC with progression after agents targeting VEGF pathway at three doses of nivolumab (0.3, 2 and 10mg/kg) [10]. Median overall survival was 18, 25, and 24 months for the three dose cohorts, respectively. More recently 821 patients previously treated with anti-angiogenic therapy were randomized to either nivolumab (3mg/Kg every 2 weeks) or everolimus (10mg daily).[11] The median overall survival was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The hazard ratio for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; P=0.002), which met the prespecified criterion for superiority (P≤0.0148). Response rates were in average 20% with only 11% incidence of grade 3-4 treatment-related adverse events.

1.4.3 Clinical Safety

For nivolumab monotherapy, the safety profile is similar across tumor types (investigator brochure v 2015). The only exception is pulmonary inflammation adverse events (AEs), which may be numerically greater in subjects with NSCLC, because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Safety data for subjects with previously treated advanced or metastatic NSCLC treated with nivolumab monotherapy in CA209017 (131 subjects), CA209057 (287 subjects), and CA209063 (117 subjects) were pooled and safety analyses were performed for these pooled subjects who receiving nivolumab monotherapy (a total of 535 subjects)(investigator brochure v 2015). Based on the pooled analyses, nivolumab monotherapy at a dose of 3 mg/kg administered IV Q2W has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation. The most common adverse events were fatigue (19.6%), decreased appetite (12.3%), nausea (12.0%), and asthenia (10.5%). The majority of drug-related AEs were of Grade 1-2 in severity.

1.4.4 Nivolumab dosing and rationale for the flat dosing

Anti-tumor activity was observed in study CA209003 at dose levels ranging from 1 to 10 mg/kg in RCC. The antitumor activity of nivolumab tended to increase with dose, as did the incidence of SAEs. The anti-tumor activity of nivolumab in RCC was investigated at dose levels 1 and 10 mg/kg, with the higher activity observed at 10 mg/kg. The observed anti-tumor activity in melanoma, and NSCLC was highest at 3 mg/kg, suggesting that anti-tumor activity approaches a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of the exposure-response analyses for these tumor types, show that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 and 10 mg/kg every 2 week dosing. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose (MTD) was identified. Although the spectrum, frequency, and severity of nivolumab-related AEs were generally similar across the dose levels tested, the 10 mg/kg doses level had numerically higher Grade 3/4 drug-related SAEs and AEs leading to discontinuation. Based on the totality of the safety, efficacy, and exposure-response data, a dose of 3 mg/kg every two weeks was selected as the dose anticipated achieving an appropriate balance of benefit and risk.

1.4.5 Nivolumab flat dose regimen

The safety and efficacy of 240 mg (monotherapy) Q2W flat dose of nivolumab has recently received FDA approval and is expected to be similar to 3 mg/kg Q2W dosing regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight in nivolumab clinical trials. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

In addition, nivolumab 480 mg administered once every 4 weeks (Q4W) is currently under investigation. The less frequent dosing regimen is designed to

afford more convenience to the target patient populations. The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) to provide an approximately equivalent dose of nivolumab 3 mg/kg Q2W. Exposures following nivolumab 480 mg Q4W regimen are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk. Hence, the flat dose of 480mg nivolumab is under investigation , and will be administered in this study after 4 months at the 240mg dose.

1.5 Metformin

1.5.1 Clinical safety, Development and Efficacy

Metformin is a well-studied drug, utilized by a large number of adults with diabetes. The following are considered contraindications to the use of metformin: hypersensitivity to metformin or any component of the formulation; kidney dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females) or abnormal creatinine clearance from any cause (including shock, acute myocardial infarction, or septicemia); acute or chronic metabolic acidosis. In addition, it is generally recommended to temporarily discontinue metformin in patients undergoing radiologic studies in which intravascular iodinated contrast media are utilized. It is also recommended that metformin be used cautiously in patients with congestive heart failure requiring pharmacologic management, because the risk of lactic acidosis may be increased secondary to hypoperfusion.

Metformin was developed as an anti-diabetes drug. However, recent research have found interesting anti-tumor properites of metformin. Of note, the immune modulating properties leading to significant anti-tumor effect has not yet been explored in a clinical trial setting.

1.6 Exploratory Studies

Exploratory biomarker studies will be pursued involving tissue samples and peripheral blood. These studies will focus on the use of biomarkers to predict response to immunotherapy. Current body of evidence suggests that PD-L1 expression and TIL (tumor infiltrating lymphocyte) at tissue and peripheral blood lymphocyte phenotype markers may correlate with response to immunotherapy although still controversial. Tissue and blood samples will be stored to explore further molecular biomarkers including but not limited to genomic, immunologic or proteomic alterations.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

To assess anti-tumor activity of the combination treatment of metformin with nivolumab in patients with non-small cell lung cancer with and without prior exposure to PD-1/PD-L1 inhibitors: Anti-tumor activity will be assessed by objective response rate (ORR, complete response and partial response) using RECIST criteria v1.1.

2.2 Secondary Objectives & Endpoints

2.2.1 To assess the efficacy of the combination treatment of metformin with nivolumab according to depth, duration, and persistence of response, disease control rate (DCR; CR, PR, and SD at 24 weeks), progression-free survival (PFS), and overall survival (OS) in patients with non-small cell lung cancer with and without prior exposure to PD-1/PD-L1 inhibitors using RECIST criteria v1.1. Depth of response (SD or PR) is defined as the change in the sum of the largest tumor diameters per RECIST.

2.2.2 To assess the efficacy of the combination treatment of metformin with nivolumab according to depth, duration, and persistence of response, ORR, DCR, PFS, and OS in the above population using immune-related RECIST (irRECIST) criteria. Depth of response (SD or PR) is defined as the change in the sum of the largest tumor diameters per irRECIST.

2.2.3 To assess the safety and tolerability profile of the combination treatment of metformin with nivolumab in the above population using CTCAE version 4.03.

2.3 Exploratory Objectives & Endpoints

2.3.1 To assess the immune-related tumor and blood biomarkers including T cell markers and their association with treatment response in the above population

2.3.2 To assess the dynamic change in both immune and genomic biomarkers in blood that may correlate with response to metformin.

3.0 PATIENT ELIGIBILITY

The target population for this study is all patients with advanced non-small cell lung cancer with and without prior exposure to PD-1 or PD-L1 inhibitors. This trial will be conducted at Northwestern University with the potential of opening the trial at other institutions.

A total of 51 subjects will be needed for this trial. Approximately 4 potentially eligible patients are seen per month, and it is anticipated that at least 2 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Young Chae, at 312-726-1234 or young.chae@northwestern.edu.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11.3 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically confirmed, locally advanced or metastatic stage IV or non-resectable stage III non-small cell lung cancer (NSCLC).

3.1.2 Patients may have received any number and type of prior treatment regimens for their NSCLC (aside from patients in Arm A, who cannot have had PD-1/PD-L1 inhibitors).

3.1.3 Arm A: patients must be treatment naive to PD-1/PD-L1 inhibitors including but not limited to durvalumab, pembrolizuamb, atezolizumab, nivolumab, and avelumab.

Arm B: patients' tumor must be either refractory to or progressed on one of the above agents.
NOTE: Prior treatment may include any number of PD-1/PD-L1 inhibitor therapies given as either a single-agent or in combination with chemotherapy..
NOTE: Patients must be eligible to receive the next line of therapy and not be suspected of having pseudoprogression. Both cases are defined by initial PD or PD after CR, PR, or SD using RECIST criteria, respectively.

3.1.4 Patients must have measurable disease according to the standard RECIST version 1.1.

NOTE: CT scans or MRIs used to assess the measurable disease must have been completed with 28 days prior to the study drug initiation.

3.1.5 Patients need to have adequate kidney, bone marrow, and liver functions ≤14 days of registration as specified below:

absolute neutrophil	≥ 1,000/mcL*
platelets	≥ 50,000/mcl*
hemoglobin	≥ 8 g/dL
total bilirubin	≤1.5 times the institutional upper limit of normal (ULN) (or ≤3 times ULN in case of liver metastasis or Gilbert Syndrome)
AST(SGOT)/ALT(SPGT)	≤ 2.5 X institutional ULN (or ≤5 times ULN in case of liver metastasis)
creatinine	≤ 1.4 ng/mL for females; ≤ 1.5 ng/mL for males** ng/ml

*Transfusion and/or growth factor are permitted within any timeframe.
**Patients with creatinine ≤ 2.0 ng/mL may still be eligible if in the opinion of the investigator, the benefits of treatment outweigh the risks.

3.1.6 Patients must be age ≥ 18 years; both male and female are eligible.

3.1.7 Patients must exhibit an ECOG performance status of ≤2.

3.1.8 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.1.9 Females of child-bearing potential (FOCBP) and men who are sexually active must agree to follow instructions for method(s) of contraception for the duration of treatment and the designated post-treatment period (see Appendix C for details on appropriate contraception methods)

NOTE: A FOCBP is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not undergone a hysterectomy or bilateral oophorectomy*
- *Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)*

3.1.10 FOCBP must have a negative pregnancy test ≤7 days prior to registration on study.

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

NOTE: CNS imaging is only required at baseline for patients with known history of CNS metastases.

3.1.12 Patients must have the ability to swallow oral medications.

3.1.13 Patients who are known to be EGFR- or ALK-positive must have received prior EGFR- or ALK-targeted therapy, respectively.

NOTE: In such cases, documentation of EGFR mutation or ALK translocation status should be provided if available.

3.2 Exclusion Criteria

3.2.1 Both arms: Patients should not have received metformin within 6 months prior to registration.
Arm B: Patients who were on metformin while on PD-1/PD-L1 inhibitors are not eligible.

3.2.2 Patients should not have received prior immunotherapies (exception: prior PD-1/PD-L1 inhibitors are allowed for arm B only).

NOTE: Prior cancer vaccine treatments are permitted. For arm B, exposure to PD-1/PD-L1 inhibitors given as either a single agentor in combination with chemotherapy are allowed ≥ 14 days from registration.

NOTE: Immunotherapies include but are not limited to interleukin-2 and other immune checkpoint antagonist targeting CTLA-4, LAG-3, TIM-3, KIR etc. and/or agonists targeting OX40, ICOS, CD137, etc.

3.2.3 Patients who are intolerant to PD-1/PD-L1 inhibitors and/or metformin are excluded.

3.2.4 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including chronic prolonged systemic corticosteroids (defined as corticosteroid use of duration one month or greater), should be excluded. These include but are not limited to patients with a history of:

- immune related neurologic disease
- multiple sclerosis
- autoimmune (demyelinating) neuropathy
- Guillain-Barre syndrome
- myasthenia gravis
- systemic autoimmune disease such as SLE
- connective tissue diseases
- scleroderma
- inflammatory bowel disease (IBD)
- Crohn’s
- ulcerative colitis
- patients with a history of toxic epidermal necrolysis (TEN)
- Stevens-Johnson syndrome
- anti-phospholipid syndrome

NOTE: Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.5 Patients are ineligible who have any condition requiring systemic treatment with corticosteroids (>10mg daily prednisone equivalents) or other immunosuppressive medications ≤14 days prior to registration.

NOTE: Inhaled steroids and adrenal replacement steroid doses >10mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

3.2.6 Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible:

- Uncontrolled hypertension – blood pressure ≥ 150/90 mmHg despite medical therapy
- Ongoing or active infection requiring systemic treatment
- Symptomatic congestive heart failure
- Unstable angina pectoris
- Cardiac arrhythmia
- Psychiatric illness/social situations that would limit compliance with study requirements
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

3.2.7 Patients must not have had another primary malignancy within 2 years prior to starting study treatment with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine cervix, or any local cancers that are deemed to be cured from investigator's point of view.

3.2.8 Patients may not be receiving any other investigational agents ≤ 14 days from registration.

3.2.9 Patients with known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) are excluded.

3.2.10 Patients who have any positive test for Hepatitis B or Hepatitis C virus indicating acute or chronic infection are excluded.

3.2.11 Patients with known diabetes whose glucose control or general health condition may be adversely affected by the use of metformin as per the study protocol as deemed by either the study investigator or endocrinologist are excluded.

3.2.12 Patients must not have any of the following contraindications to metformin:

- Hypersensitivity to metformin or any component of the formulation
- Kidney dysfunction or abnormal creatinine (Cr < 2ng/mL) from any cause
- Acute or metabolic acidosis

4.0 TREATMENT PLAN

4.1 Overview

Nivolumab and metformin combination will be administered intravenously and orally, respectively, until disease progression or intolerable toxicity. Metformin will be initiated during a 7-day Induction period at 1,000mg orally once daily. Metformin will then be escalated by 500mg every 7 days as tolerated (C1D1 and C1D8) until the full 2,000mg dose is reached. Extended release formulation - Glucophage XR will be used for the study and commercial supply will be used which will be purchased and dispensed by NU investigational pharmacy. During Cycle 1-4 (1 cycle = 28 days), nivolumab will be given at 240mg every 14 days (Day 1 & 15) over approximately 30 minutes (-5 / +15 minutes). Starting with Cycle 5 Day 1, nivolumab will be given at 480mg IV every 28 days over approximately 60 minutes (-10 / +15 minutes). Patients will be assessed for response every 8 weeks (2 cycles).

Note: Please refer to section 4.4 for patients who may continue treatment after initial progression.

Dosing schedule is summarized in the table below.

Table 4-1: Dosing of Nivolumab and Metformin

Drug	Dose	Route	Schedule
Nivolumab (Opdivo)	**C1-4**: 240mg **C5+**: 480mg	IV	**Cycle 1-4**: every 14 days **Cycle 5+**: every 28 days until progression of disease, intolerable toxicity, or withdrawal of consent
Metformin hydrochloride (Glucophage XR)	2,000mg*	PO	daily with evening meal until progression of disease, intolerable toxicity, or withdrawal of consent • starting dose: 1,000mg • dose escalation plan: weekly by 500mg

*Metformin will be initiated at 1,000mg during the Induction period and escalate by 500mg (1 tablet) every 7 days until the final dose of 2,000mg.

4.2 Treatment Administration

4.2.1 Nivolumab

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

During Cycle 1-4, nivolumab will be administered at a fixed dose of 240 mg intravenously over approximately 30 minutes (-5 / +15 minutes) every 14 days. Starting with Cycle 5, nivolumab will be administered at 480mg IV over 60 minutes (-10 / +15 minutes) every 28 days until disease progression, intolerable toxicity, or withdrawal of consent.

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days or 24 days from the previous dose (for 240 mg and 480 mg doses, respectively). There are no pre-medications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.3.3.

Nivolumab is to be administered as a 30-minute (-5 / +15 minutes) or 60-minute (-10 / +15±± minutes) IV infusion (for 240mg and 480mg respectively), using a volumetric pump with a 0.2- 1.2 micron low-protein binding in-line filter at the

protocol-specified dose. The drug can be infused undiluted or diluted so as not to exceed a total infusion volume of 120mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Subjects will be monitored continuously for AEs while on study. Treatment delay or discontinuation will be based on specific laboratory and adverse event criteria.

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

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

4.2.2 Metformin

Metformin will be administered orally once daily until disease progression, intolerable toxicity or withdrawal of consent. Extended release formulation - Glucophage XR, 500 mg will be used for the study. Two tablets (1,000 mg) PO once daily will be given for the first 7 days, then 3 tablets (1,500 mg) for the next 7 days, then 4 tablets (2,000 mg) for the rest of the treatment period. Metformin should be taken with meals. This dose escalation plan is to minimize possible gastrointestinal toxicity of metformin. 2550mg of metformin is the FDA approved maximum dose of metformin. Tablets should not be cut, crushed, or chewed. Metformin will be held per institutional guidelines with IV contrast dye injection required for each imaging studies. Metformin dosing can occur independently of nivolumab dosing. No premedications are needed.

Patients will maintain a drug diary throughout the study to monitor compliance of metformin dosing. Patients will return completed drug diaries, drug bottles, and any unused metformin tablets at each study visit.

4.3 Toxicity Management & Dose Delays/Modifications

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table. Toxicity will be assessed according to the NCI CTCAE v. 4.03.

4.3.1 Dose delays: nivolumab

There will be no dose modifications allowed for management of toxicities. Should the treating physician decide to delay treatment given suspicion for a drug-related side effect, the side effect should be attributed to one study drug to the best of the physician's ability. Nivolumab should be delayed based on this attribution, or both drugs if a definite attribution is not possible. Nivolumab can be held for a maximum of 56 days.

Nivolumab administration should be delayed for the following until resolution to ≤ Grade 1 or baseline:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay

- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia or leukopenia does not require dose delay
  - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

4.3.2 Treatment discontinuation: nivolumab

Should the treating physician decide to discontinue treatment given suspicion for a drug-related side effect, the side effect should be attributed to one study drug to the best of the physician's ability. Nivolumab should be discontinued based on this attribution, and the patient must come off study treatment. The patient may not receive metformin monotherapy on-study.

Nivolumab should be discontinued permanently for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding (aside from minor bleeds ≤ Grade 1) requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 5-10 x ULN for > 2 weeks
      - AST or ALT > 10 xUL
      - Total bilirubin > 5 x ULN
      - Concurrent AST or ALT > 3 xULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia < 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. PI and Data and Safety Monitoring Committee (DSMC) should be consulted for Grade 4 amylase or lipase abnormalities.

- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

- Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation.

- Any event that leads to interruption in dosing lasting > 4 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruptions lasting > 4 weeks from the previous dose, the PI and DSMC must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 4 weeks or more frequently if clinically indicated during such dosing interruptions.
  - Dosing interruptions lasting > 4 weeks from the previous dose that occur for non-drug- related reasons may be allowed if approved by the PI and DSMC. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 4 weeks, the PI and DSMC must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 4 weeks or more frequently if clinically indicated during such dosing interrupted.
  - Any adverse event, laboratory abnormality, or intercurrent illness, which in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.
  - If the patient is still receiving clinical benefit, he or she can hold drug for a maximum of 8 weeks (56 days) and subsequently continue therapy following the original treatment schedule.

4.3.3 Treatment of Nivolumab-related infusion reactions

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

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

Table 4-2: Nivolumab Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Remain at bedside and monitor subject until recovery from symptoms.	The following prophylactic pre-medications are recommended for future infusions: • Diphenhydramine 50 mg (or equivalent) and/or • Acetaminophen 325 to 1000 mg at least 30

Table 4-2: Nivolumab Infusion Reactions		
NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
		minutes before additional nivolumab administrations
Grade 2 Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for < 24 hours	Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; Remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.	For future infusions, the following prophylactic pre-medications are recommended: • Diphenhydramine 50 mg (or equivalent) and/or • Acetaminophen 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
Grades 3 or 4 Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life-threatening; pressor or ventilatory support indicated	Immediately discontinue infusion of nivolumab infusion. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor	No subsequent dosing

Table 4-2: Nivolumab Infusion Reactions		
NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
	subject until recovery of the symptoms In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids	

Immunotherapy agents such as nivolumab are associated with AEs that can differ in severity and duration compared to other therapeutic classes of medications. Early recognition and management of AEs associated with nivolumab can mitigate severe toxicity. Corticosteroids are the primary therapy for drug-related AEs. Management algorithms have been developed to assist investigators in assessing and managing nivolumab associated AEs, which can be found in Appendix D of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment.

4.3.4 Metformin

The most common adverse reactions to metformin are diarrhea, nausea/vomiting, flatulence, indigestion, and headaches. These side effects occur most commonly upon initiation of therapy and are short lived. These effects are mitigated by dose escalation regimens that are used in this trial. Dose reduction or discontinuation will be applied in patients with persistent gastrointestinal symptoms related to metformin. A rare but serious side effect of metformin is lactic acidosis, which is most common in patients with renal insufficiency and congestive heart failure. Lactic acidosis can be evaluated by checking a patient's renal function in addition to their serum lactic levels. Any clinical or laboratory indication of metabolic acidosis will lead to immediate discontinuation of metformin.

For commonly observed gastrointestinal AEs of metformin such as nausea, vomiting and diarrhea the dose should be withheld. Metformin should be held until the AE resolves to ≤ Grade 1 or baseline and restarted at a lower dose level as per Table 4-3. Metformin can be held for a maximum of 28 days. Patients who permanently discontinue metformin for toxicity must come off study treatment – they may not receive nivolumab monotherapy on-study.

Metformin-induced side effects as determined by the study investigator should be managed as listed below in tables 4-3 and 4-4.

Table 4-3: Metformin-related toxicity dose reductions	
CTCAE Grade	**Metformin Dosing**
0-2	No change from original starting dose
3 (1st occurrence)	Hold until resolved to ≤ grade 1 or baseline, then reduce to lower dose
3 (2nd occurrence)	Hold until resolved to ≤ grade 1 or baseline, then reduce to lower dose
3 (3rd occurrence) or 4	Discontinue treatment

Table 4-4: Dose reduction of Metformin for toxicity	
Current dose	**Reduced dose**
2000 mg	1500 mg
1500 mg	1000 mg
1000 mg	500 mg
500 mg	Discontinue*

Note: For the purpose of imaging with CT scan with IV contrast, metformin can be held according to the institution's CT scan protocol.
*Patients will discontinue all study treatment

4.4 Continuation of Investigational Therapy after Progression

In the event of an initial assessment of progressive disease (PD, based on RECIST Version 1.1), a subject may continue to receive the assigned study treatment as long as the criteria listed below are met and eligibility to continue is documented in the medical record at the time the decision is made to continue treatment.

1. No confirmed PD: a subsequent scan obtained at least 4 weeks from prior scan is not suggestive of PD by RECIST 1.1 (see section 6.4.2), and the patient does not have clinical decline.
   NOTE: If PD is confirmed but the patient continues to have clinical benefit (e.g. improvement of symptoms and is tolerating treatment), the patient can continue treatment beyond PD per clinician's discretion.
2. Does not meet any of the other investigational product discontinuation criteria (Section 4.4.2)
3. Clinical symptoms or signs indicating significant PD such as the benefit-risk ratio of continuing therapy is no longer justified.
4. No decline in ECOG performance status.
5. No threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention, and continuation of study therapy would prevent institution of such intervention.

If the lesions included in the tumor burden subsequently regress to the extent that the criteria for PD are no longer met, then treatment may continue according to the treatment schedule.

4.5 Concomitant Medications/Treatments

4.5.1 Permitted Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Inhaled or topical steroids, and adrenal replacement steroids are permitted at any dose in the absence of active autoimmune disease.

Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed if initiated prior to first dose of study therapy.

All concomitant medications received from informed consent until 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered past 30 days of treatment should be recorded if associated with an SAE.

4.5.2 Prohibited Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy (≤14 days prior to registration)
- Immunotherapy not specified in this protocol (≤14 days prior to registration)
- Investigational agents (≤14 days prior to registration)
- Corticosteroids are not permitted ≤ 14 days prior to registration unless they fall under the criteria listed in 4.5.1
- For the purpose of imaging with CT scan with IV contrast, metformin can be held according to the institution's CT scan protocol.

4.6 Duration of Therapy

Patients may continue with treatment until any of the following occur:

- Disease progression, unless the patient meets criteria for continuing treatment beyond progression. See section 4.4 for details.
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s) requiring discontinuation of at least one study drug
- Patient decides to withdraw from either study treatment or the as a whole study
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)

4.7 Duration of Follow Up

All patients will be followed for adverse events for 30 days after last dose of study treatment (100 days for SAEs), or until the patient starts a new treatment, whichever occurs first. Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event (i.e. the grade is not changing). If a patient stops treatment due to unacceptable adverse event(s) but has not demonstrated disease progression, then the patient will be followed with imaging studies every 8 weeks until the time of progression radiographically according to RECIST 1.1 criteria. In the event that a radiographic response is detected, then this event will be included as a response in the final analysis, and the time of progression used in calculation of the survival analysis. Patients will be followed for survival status every 3 months for 1 year and every 6 months for a total of 3 years after treatment discontinuation for survival or progression of disease.

4.8 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)

- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

Patients who are permanently discontinued from receiving investigational product will be followed for disease progression and safety, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or administered subsequent therapy. All subjects will be followed for survival and disease progression. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

4.9 Patient Replacement

If a patient is enrolled in the study but comes off study before cycle 1 day 1 of treatment, the patient may be replaced

5.0 STUDY PROCEDURES TABLE

Table 5-1: Study Procedures

STUDY PROCEDURES	Screening[2,10]	Induction[15] (7 days)	Cycle 1-4 (Cycle=28 days)		Cycle 5+ (Cycle = 28 days)	End of Treatment[13]	Follow Up[16]
Study window		D1	D1 (±3 day)	D15 (±3 day)	D1 (± 3 days)	± 7 days	
Informed Consent[1]	X						
Medical history	X				X		
Physical Exam	X	X	X	X	X	X	
Vital signs[3]	X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	
AE reporting		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	
Chemistry panel[4]	X	X	X	X	X	X	
CBC with differential[5]	X	X	X	X	X	X	
Pregnancy test [6]	X		X			X	
Thyroid function test[7]	X						
ECHO/ECG	X[17]						
Imaging (CT or MRI)[8]	X		X[8]		X[7]		
Biopsy tissue[9,14]	X						
Blood biomarker[14]		X	X[14]			X	
Nivolumab infusion[11]			X[11]	X[11]	X[11]		
Metformin dispensing[12]		X	X		X		
Survival							X

1. Informed consent must be signed within 30 days of registration. If signature is outside that window a new consent should be signed.
2. Pre-study H&P and all labs must be ≤ 14 days before registration. Tumor measurements and radiologic evaluations must be ≤28 days before registration.
3. Vital signs include pulse, blood pressure, and weight. Height will be recorded at baseline only.
4. Serum Chemistry will include calcium, chloride, magnesium, phosphorus, creatinine, sodium, potassium, blood urea nitrogen, bicarbonate, glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, and total protein.
5. CBC: Performed at each study visit, prior to nivolumab. For patients experiencing significant drop in WBCs or platelets felt related to treatment, CBCs should be obtained more frequently (weekly or more frequently) to assess timing for retreatment or need for transfusion support.

6. Serum or urine test only for women of childbearing potential; must be tested within 7 days prior to registration and on Cycle 1 Day 1 (prior to nivolumab).
7. Thyroid function tests will include thyroid stimulating hormone and free T4. This will be done at baseline then only as clinically indicated thereafter.
8. The same modality used at baseline should be used throughout for imaging. CT imaging with contrast will occur every 2 cycles starting with Cycle 3 Day 1 (± 7 days) and should include chest, abdomen, and pelvis. Neck will be included only if measurable lesions are present. Metformin should be held prior to scans per each institutional protocol. Tumor measurements will be performed using RECIST 1.1. Progressive Disease (PD) must be confirmed by repeat scan within 8 weeks at least after 4 weeks. Patients with a known history of CNS disease must have CNS imaging at screening to rule out activity.
9. Patients will undergo a fresh tissue biopsy prior to study enrollment, unless deemed to be clinically inappropriate per PI. If not feasible, archived tissue will be used (if available).
10. The maximum time interval between registration and the first dose of study drug will be 14 days
11. Nivolumab will be given as follows:
    Cycle 1-4: 240mg IV over 30 minutes (-5 / +15 minutes) every 14 days (Day 1 & 15, ±3 days)
    Cycle 5+: 480mg IV over 60 minutes (-10 / +15 minutes) every 28 days (Day 1, ±3 days) until disease progression, intolerability, or withdrawal of consent.
12. Metformin will be dispensed Day 1 of each cycle. Dosing will begin at 1,000mg po once daily and escalate by 500mg every 7 days until the final dose of 2,000mg is reached. Patients will return unused drug and drug bottles at each study visit and will maintain a drug diary to track compliance.
13. The end of treatment visit should occur 30 days after the last dose of study treatment (+/- 7 days) or before starting another line of treatment, whichever comes first.
14. Correlatives from peripheral blood will be collected for all patients at Induction Day 1, C1D1, C3D1, and at the EOT. Biopsy samples (fresh or archived) will be collected for all patients if possible. See separate lab manual for specifications. See section 9.0 for details.
15. Metformin monotherapy will be given at 1,000mg PO QD during the 7-day Induction period, prior to starting nivolumab on Cycle 1 Day 1.
16. After patients come off treatment they will be followed up at 3, 6, 9, and 12 months (±7 days) and then every 6 months (±14 days) for 3 years for survival and progression of disease via either clinic visits or phone calls.
17. Echocardiogram and/or ECG should be performed at screening as clinically indicated for patients with a history of congestive heart failure or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs. Cardiac toxicities should be closely monitored throughout treatment.

6.0 ENDPOINT ASSESSMENT

6.1 Solid Tumors

6.1.1 Response will be evaluated using the modified Response Evaluation Criteria in Solid Tumors, based on RECIST v1.1.[12]

6.1.2 Clinical evaluation and tumor assessments will be performed as indicated in Table 7, based on physical examination and radiologic evaluation.

6.1.3 Any lesion that has been previously treated with radiotherapy should be considered as a non-target lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a target lesion.

6.1.4 Definitions for measurable and non-measurable lesions, and criteria for response, should be based on RECIST v1.1.

6.1.5 Measurable Lesions
Must be accurately measured in at least one dimension (greatest diameter) with a minimum size of 10mm by CT scan (cuts of 5mm or less), MRI, or physical exam (ideally using calipers). Bone only disease is allowed, however, must have an osteoblastic component that can be easily measured.

6.1.6 Non-measurable Lesions
Defined as all other lesions less than 10mm. Examples of non-measurable lesions include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung.

6.1.7 RECIST Response criteria (used for patient evaluation and treatment decisions)

- **Complete Response** - Disappearance of all lesions.
- **Partial Response** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Objective Response Rate** – the sum of complete responses and partial responses
- **Progressive Disease** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- **Stable Disease** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.2 Immune-related RECIST (irRECIST)

6.2.1 In addition to above, tumor response will be assessed by the irRECIST for investigational purposes, not assessment of primary objective or treatment decisions.[13] In RECIST v1.1, the appearance of new lesions indicates PD. However, in irRECIST, new measurable lesions are incorporated in the tumor burden, which is used to determine irPD, immune-related partial response (irPR), and immune-related complete response (irCR). New nonmeasurable lesions preclude irCR. Under RECST v1.1, there is no confirmation for PD. Under irRECIST, responses and irPDs must be confirmed by consecutive scans at least 4 weeks apart, assuming no clinical deterioration. We will define immune-related clinical benefit rate as immune-related stable disease (irSD), irPR, or irCR.

Table 6-1: Immune-related Response Evaluation Criteria: Overall Response

Tumor Burden (Baseline and New)	Non-Target Lesions (Baseline and New)	Response
Disappearance of non-nodal lesions. All pathologic lymph nodes <10 mm (short axis)	Disappearance of non-nodal lesions. All pathologic lymph nodes < 10 mm (short axis)	irCR
≥30% decrease from baseline	Any	irPR
≥20% increase from nadir and at least 5 mm	Any	irPD
Neither sufficient decrease to qualify for PR, nor sufficient increase to qualify for PD	Any	irSD
Disappearance of all non-nodal lesions. All pathologic lymph nodes <10 mm	Any other than disappearance of all non-nodal lesions and reduction of pathologic lymph nodes <10 mm	irPR
Not all evaluated	Any	irNE

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irNE = immune-related not evaluable; irSD = immune-related stable disease;

-Tumor burden is the sum of single diameters (short axis for nodal lesions, longest diameter for other lesions) for the target lesions. In subsequent scans, the diameters of new measurable lesions are added to the tumor burden.

-Best overall response based on 2 consecutive measurements at least 4 weeks apart.

6.3 Primary Endpoint

To assess anti-tumor activity of the combination treatment of nivolumab and metformin in patients with advanced non-small cell lung cancer: Anti-tumor activity will be assessed by objective response rate (ORR, complete response and partial response) using RECIST criteria. All patients who receive treatment will be considered evaluable except those removed from the study for adverse drug reactions.

6.4 Secondary Endpoints

6.4.1 To assess the efficacy of the combination treatment of metformin with nivolumab according to depth, duration, and persistence of response, disease control rate (DCR; CR, PR, and SD at 24 weeks), progression-free survival (PFS), and overall survival (OS) in patients with non-small cell lung cancer with and without prior exposure to PD-1/PD-L1 inhibitors using RECIST criteria. Depth of response (SD or PR) is defined as the change in the sum of the largest tumor diameters per RECIST criteria.

6.4.2 To assess the efficacy of the combination treatment of metformin with nivolumab according to depth, duration, and persistence of response, ORR, DCR, PFS, and OS in the above population using immune-related response criteria (irRC) criteria. Depth of response (SD or PR) is defined as the change in the sum of the largest tumor diameters per irRECIST.

6.4.3 To assess the safety and tolerability profile of the combination treatment of nivolumab and metformin in the above population using CTCAE version 4.03

6.5 Exploratory end points

6.5.1 To assess the immune-related tumor and blood biomarkers including T cell markers and their association with treatment response in the above population

6.5.2 To assess the dynamic change in both immune and genomic biomarkers in blood that may correlate with response to metformin. Blood will be collected prior to starting metformin and after 7 days of metformin treatment (C1D1, pre-dose).

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires high level monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the

abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.
An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is *life-threatening*.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- **Results in *persistent or significant disability or incapacity*.**
- **Is a *congenital anomaly/birth defect.***
- **Is an *important medical event*.**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.2.5 Hepatic Function Abnormality

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE. Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event. The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

7.2.6 Pneumonitis

Adverse events of pneumonitis are also of interest, as pneumonitis has been observed with anti-PD-1 and anti-PD-L1 mAbs. Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

7.2.7 Other events requiring immediate reporting

Overdose

An overdose is defined as a patient receiving a dose of investigational product in excess of dose detailed in this protocol.

Any overdose of a study patient with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event. If the overdose results in an AE, the AE must also be recorded on the AE eCRF. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE. The investigator will use clinical judgment to treat any overdose.

7.3 Reporting of pregnancy and lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the

pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

7.4 Adverse events Reporting

7.4.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

7.4.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.4.3 Expedited Reporting of SAEs/Other Events

7.4.3.1 Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DSMC at their next meeting. **See section 7.4.3.3 for instructions on reporting to BMS Global Safety.**

7.4.3.2 Reporting to the Northwestern University IRB

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment) will be promptly reported to the NU IRB within 24 hours of notification, per Lurie Cancer Center policy.
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.4.3.3 Reporting to BMS

SAE reports (including death by any cause), regardless of attribution will be reported within 24 hours to BMS Global Safety (using the NU CRO SAE Form and referencing the BMS study number, CA 209-801). The assigned study coordinator will facilitate all reporting to BMS Global Safety and email QA a copy of the report upon completion. BMS Global Safety can be notified at:

Email Address: Worldwide.Safety@BMS.com

8.0 DRUG INFORMATION

8.1 Nivolumab

8.1.1 Other names

ONO-4538, BMS-936558, or MDX1106, Opdivo

8.1.2 Classification - type of agent

Human IgG4 anti-PD-1 monoclonal antibody

8.1.3 Mode of action

Nivolumab acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells anti-PD1.

8.1.4 Storage and stability

Nivolumab solution for infusion is a sterile, non-pyrogenic single-use, isotonic aqueous solution. Vials must be stored in a secure, limited-access location at 2 to 8 degrees C (36 to 46 degrees F) and protected from light, freezing, and shaking. The product is a clear to opalescent solution, which may contain proteinaceous and extraneous particulates. The product is intended for IV administration. The drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Opened or accessed vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered.

After preparation, store the Nivolumab infusion either:

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

- Do not freeze.

8.1.5 Protocol dose specifics

A fixed dose of 240 mg IV every 2 weeks (Cycle 1-4) and 480mg IV every 4 weeks (starting with Cycle 5 Day 1)

8.1.6 Preparation

- Nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.
- Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white amorphous particles.
- Mix by gently inverting several times. Do not shake.
- Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag.
- If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall.
- Do not enter into each vial more than once. Do not administer as an IV push or bolus injection.
- Nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL.

8.1.7 Route of administration for this study

Intravenous infusion. Do not administer as an IV push or bolus injection. Administer nivolumab 240 mg as an intravenous infusion over 30 (-5/+15) minutes and 480mg as an intravenous infusion over 60 (-10/+15) through a 0.2 micron to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter.

8.1.8 Incompatibilities:

No incompatibilities between nivolumab injection and polyvinyl chloride (PVC), DEHP (di[2-ethylhexyl]phthalate), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed. Nivolumab should not be infused concomitantly in the same intravenous line with other medicinal products.

8.1.9 Availability & Supply

Nivolumab will be supplied by the study as 100 mg/Vial (10 mg/mL) clear to opalescent, colorless to pale yellow liquid in 10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals. May contain particles.

A supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS. The first request may take place upon screening of the first patient. The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is imperative that only drug product designated for this protocol number be used for this study.

Drug re-supply request form should be submitted electronically 10 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.
When assessing need for resupply, keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific.

8.1.10 Side effects

Nivolumab has been studied in over 8,600 subjects and is widely approved in multiple indications. Extensive details on the safety profile of nivolumab are available in the Investigator Brochure, and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix D. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies).

Below are safety data from 268 subjects with unresectable or metastatic melanoma and 117 patients with metastatic squamous NSCLC who received nivolumab alone. Related side effects reported in subjects receiving nivolumab alone were:

Very Frequent – Expected to occur in more than 20% of people (more than 20 out of 100 people): Fatigue (50%), Dyspnea (38%), Musculoskeletal pain (36%), Rash (21%), Increased AST (28%), Increase alkaline phosphatase (22%), Hyponatremia (25-38%)

Frequent - Expected to occur in 10% to 20% of people (10 to 20 out of 100 people): Pruritus (19%), Cough (17%), URI (11%), Peripheral edema (10%), Increased ALT (16%), Hyperkalemia (15%)

Not Frequent – Expected to occur in less than 10% of people (less than 10 out of 100 people): ventricular arrhythmia, iridocyclitis, infusion-related reactions, increased amylase, increased lipase, dizziness, peripheral and sensory neuropathy, exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis

Deaths thought to be related to nivolumab when given alone were reported in approximately 0.5% of subjects treated (approximately 1 out 200 people).

8.1.11 Nursing implications

The first day of dosing is considered Day 1. Infusion duration for nivolumab will be approximately 30 minutes or 60 minutes for each individual infusion, for 240mg and 480mg doses, respectively.
Each dose of investigational product should be administered using the following guidelines:

1. Investigational product must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein or central line. Prior to the start of the infusion, ensure that the bag contents are at room

temperature to avoid an infusion-related reaction due to the administration of the solution at low temperatures.

2. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available. Investigational product must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.
3. The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with 0.22- or 0.2-µm in-line filters.
4. The duration of the investigational product administration will be recorded.

Nivolumab will be administered as an IV infusion over approximately 30 minutes. When an IV bag is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice).

8.1.12 Return and Retention of Study Drug

The clinical study team will be responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and returned not used 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.

Table 8-1 – Nivolumab Product Description:(Other names = MDX-1106, ONO-4538, anti-PD-1

Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab (BMS-936558-01)* for Injection	100 mg (10 mg/Vial	10 mL vial	Clear to opalescent, colorless to pale yellow liquid. May contain particles	**BMS-936558-01 Injection** must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

8.2 Metformin

8.2.1 Other names

Glucophage, N,N-dimethylimidodicarbonimidic diamide hydrochloride

8.2.2 Classification - type of agent

Oral antihyperglycemic drugs

8.2.3 Mode of action

Metformin is classified as an antidiabetic agent, a biguanide derivative. It decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. More recent data has revealed an immunomodulatory effect on cancer cells as described in section 1.2.

8.2.4 Storage and stability

Store at 20°–25° C (68°–77° F); excursions permitted to 15°–30° C (59°–86° F). [See USP Controlled Room Temperature.] Product will be dispensed in light-resistant containers.

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8.2.5 Protocol dose specifics

Extended formulation of 500 mg tablets will be used. Metformin will be initiated during a 7-day Induction period at 1,000mg orally once daily. Metformin will then be escalated by 500mg every 7 days as tolerated (C1D1 and C1D8) until the full 2,000mg dose is reached**.**

8.2.6 Preparation

None

8.2.7 Route of administration for this study

Oral

8.2.8 Incompatibilities

No formal drug-drug interactions have been reported with metformin and PD-1 or PD-L1 inhibitors.

- Cephalexin: May increase the serum concentration of metformin.
- Cimetidine: May decrease the excretion of metformin.
- Corticosteroids (systemic): May diminish the hypoglycemic effect of antidiabetic agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use.
- Iodinated Contrast Agents: May enhance the adverse/toxic effect of metformin. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis.Use of these agents should be avoided while patients are receiving metformin and for 48 hours after discontinuation; if it is necessary to conduct imaging while taking metformin, it should be performed with adequate hydration, and the use of mucomyst may be considered.

8.2.9 Availability & Supply

As of January 2019, BMS will not provide Extended release Metformin tablets for the study. We will be switching from metformin supplied by BMS, to commercial supply of metformin which will be purchased and distributed through Northwestern University's investigational pharmacy.

It will be handled as an investigational agent and dispensed by the Investigational Pharmacy.

8.2.10 Side effects

Frequent (>10%)

Diarrhea, nausea, and flatulence. These side effects typically subside after continued use of the medicine.

Less Frequent (≤ 10%)

Asthenia, Indigestion, abdominal discomfort and Headache

Rare and serious

A rare severe side effect is lactic acidosis (1 in 33,000 patients). The symptoms of lactic acidosis included feeling very weak, tired, or uncomfortable, unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, and suddenly developing a slow or irregular heartbeat.

8.2.11 Nursing implications

Administer with food (to decrease GI upset) and with a full glass of water when feasible. Monitor bicarbonate levels on chemistry panels to ensure they stay within the normal range per institution.

8.2.12 Return and Retention of Study Drug

Unused metformin, dispensed during previous visits, must be returned and drug accountability records updated. Returned capsules must be discarded and cannot be re-used in this study or outside the study.

8.3 Combination of metformin and nivolumab

8.3.1 Side Effects when nivolumab and metformin are given together

To our knowledge, no clinical trials combining metformin and nivolumab have been reported. Therefore, the side effects will be carefully monitored during the study.

9.0 CORRELATIVES/SPECIAL STUDIES

A fresh tissue biopsy of the primary tumor or a metastatic site at baseline will be collected if possible. If not feasible archived tissue will be used (if available). Fresh tissue biopsies will be performed using an image-guided core needle according to institutional practice. Tumor samples will be stored and may be used for additional correlative studies at a later date such as, but not limited to, immunohistochemistry, tumor mutation analysis, and proteomic analysis.

9.1 Sample Collection Guidelines

Blood samples are mandatory and will be collected for Flow and Biomarker analysis at Induction Day 1, C1D1, C3D1, and EOT.

9.2 Sample Processing, Storage, and Shipment

Refer to the lab manual for sample processing, storage, and shipment information.

9.3 Assay Methodology

9.3.1 PD-L1 immunohistochemistry

Formalin-fixed, paraffin-embedded tumor specimens will be stained with anti-PD-L1 monoclonal antibodies. PD-L1 will be scored as a percentage by two independent pathologists who are unaware of clinical data. PD-L1 staining as a predictive measure will be explored at various thresholds of positivity.

9.3.2 Tumor infiltrating lymphocytes

TILs (CD8+, CD4+, nuclear FOXP3+) will be quantified by immunohistochemistry and assessed on hematoxylin and eosin stained tumor sections. TIL subsets will be classified as intraepithelial (iTILs) or stromal (sTILs), where iTILs are defined as the percentage of lymphocytes in direct contact with tumor cells, and sTILs are defined as the percentage of lymphocytes relative to the tumor stroma. Scoring, as a continuous percentage, will be performed by two independent pathologists who are unaware of clinical data.

9.3.3 T cell subpopulations

Population of CD4+, CD8+, and regulatory T cells (CD4+/CD25+) will be counted by cell sorting of PBMCs. Expression of CD4, CD8, and FOXP3 will be also examined in the tumor tissues to estimate relative ratio between T helper cells, killer T cells, and regulatory T cells.

9.3.4 Immune and Genomic Biomarkers

To assess the dynamic change in both immune and genomic biomarkers in blood that may correlate with response to metformin. Blood will be collected prior to starting metformin, pre-dose on C1D1, C3D1, and EOT.

9.4 Specimen Banking

Patient samples collected for this study will be retained at Robert H Lurie Cancer Center of Northwestern University Pathology Core Facility. Specimens will be stored indefinitely or until they are used up, and such samples may be shared with researchers at other institutions. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Dr. Young Chae will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of Northwestern University. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of Northwestern University for publication and any licensing agreement will be strictly adhered to.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This will be a phase II study of nivolumab and metformin in patients with advanced non-small cell lung cancer.
The **primary endpoint** is **objective response rate** (ORR, complete response and partial response) using RECIST criteria v1.1 measured at 24 weeks from the start of treatment.

Secondary endpoints include assessing the efficacy of the combination treatment of nivolumab and metformin according to ORR, DCR, PFS, and OS in the above population using immune-related RECIST criteria (irRECIST) criteria in addition to RECIST criteria, and to assess assess the safety and tolerability profile of the combination treatment of nivolumab and metformin using CTCAE version 4.

Exploratory endpoints include biomarkers predictive of response from tissue and/or blood. They include but are not limited to assessment of tissue-based immunohistochemical expression of PD-L1; TILs; peripheral T cell subpopulations.

Clinical outcome will be analyzed according to three levels of PD-L1 expression: <1%, 1-50%, and >50%.
Patients in Arm B (those who received prior PD-L1) will be categorized into two groups:

1. Those who progressed while taking prior PD-L1 therapy ("checkpoint failures")
2. Those who responded to and failed or recurred after coming off PD-L1 therapy

10.2 Sample Size and Accrual

Up to 49 patients (Arm A=24, Arm B=25) will be entered into the trial based on optimal Simon two stage design as below.

Arm A: In the first stage, 9 patients will be entered. If no patients show a response, then the trial will be terminated due to inactivity of the treatment. If 1 or more of 9 show a response, then an additional 15 patients will be added. If 2 or fewer of 24 show a response, then the trial will conclude that the response rate could be as low as 5%. If 3 or more respond, then the trial will conclude that the response rate is at least 20%. This design has a 20% chance of falsely concluding the rate is 5% (false negative Type II error rate = 20%, or power = 80%), and a 10% chance of falsely concluding that the rate is 20% (false positive Type I error rate = 10%). There is a 63% probability of early termination of the trial when the true response rate is 5%.

Arm B: In the first stage, 12 patients will be entered. If 2 or less patients show a response, then the trial will be terminated due to inactivity of the treatment. If 3 or more of 12 show a response, then an additional 13 patients will be added. If 7 or fewer of 25 show a response, then the trial will conclude that the response rate could be as low as 20%. If 8 or more respond, then the trial will conclude that the response rate is at least 40%. This design has a 20% chance of falsely concluding the rate is 20% (false negative Type II error rate = 20%, or power = 80%), and a 10% chance of falsely concluding that the rate is 40% (false positive Type I error rate = 10%). There is a 56% probability of early termination of the trial when the true response rate is 5%.

Due to inevaluable patients and dropout, target accrual will be 51 patients. It is anticipated that 2 patients will be accrued per month so that accrual to this study will take 2 years.

Thus, this study will be a single institution trial with duration of enrollment being 2 years. The study will be done via both internal and external referral system. Being one of the busiest lung cancer programs in the area with good advertisement plan towards partnering institutions on this clinical trial, the above accrual plan is deemed to be a feasible one.

10.3 Data Analyses Plans

Summary of Analytic plan for primary objective	Summary of Analytic plan for secondary objectives
Please refer to the below sample size justification for the parallel Simon's two stage design which defines how the endpoints are met. For Group A. Estimated ORR for historical control is 20% versus target ORR of 40% for niovulomab and metformin combination treatment.	Depth of response: waterfall plot Duration and persistence of response: swimmer's plot PFS: PFS at 1 and 2 years (Kaplan-Meier analysis) OS: OS at 1 and 2 years (Kaplan-Meier analysis) ORR, DCR by irRC (descriptive statistics,

For Group B. Estimated ORR for refractory patients is 5% versus target ORR of 40% for niovulomab and metformin combination treatment.	exact binomial confidence intervals) We will use descriptive statistics and graphical displays to evaluate change in serum biomarkers between pre- and post-treatment. A Wilcoxon signed rank test will be used to determine if there is a statistically significant change in serum biomarkers. Toxicities will be tabulated by type and grade.

The primary analysis will be on the evaluable analysis set, including all evaluable patients regardless of drug exposure. Clinical benefit rate will be defined as stable disease (for ≥12 weeks), complete or partial response by both the Response Evaluation Criteria in Solid Tumors (RECIST) and irRECIST. Maximum response prior to disease progression will be used. The overall response rate will be estimated by the proportion of overall response, and its 80% confidence interval (CI) and 95% CI will be estimated using the exact binomial distribution.
Additionally, we will evaluate overall response rate, defined as complete or partial response using RECIST guidelines in a similar manner. We will also perform similar analyses using Immune Related RECIST (irRECIST). Duration of response, defined as the duration from the first documentation of clinical benefit to the first documented progressive disease or death of any cause, whichever occurs first, will also be analyzed. For patients alive and progression-free at the time of data cut off, duration of response will be censored as of the last tumor assessment date. Duration of response will only be evaluated for the subgroup of patients with a clinical benefit using the Kaplan-Meier method.
PFS is defined as the time from treatment initiation to documented disease progression. OS is defined as the time from the start of treatment until death due to any cause. For patients alive at the time of data cut-off, PFS and OS will be censored as of the last tumor assessment date or known to be alive, respectively. The PFS and OS will be estimated using the Kaplan-Meier method. The number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03) will be recorded.

Baseline percent PDL1 expression, TILs (sTILs, iTILs, and their ratio), and changes in T cell subpopulations will be used as a continuous variable to predict clinical benefit or overall response rates using appropriate statistical summaries. Cox proportional hazards regression will be used to compare how these biomarkers are associated with PFS and OS as well.
Changes in these biomarkers will also be analyzed to assess for pharmacodynamic effects of treatment. Continuous variables will be analyzed using either paired t-tests (normally distributed data), signed rank tests (non-normally distributed data) or repeated measures analysis of variance (correlated normally distributed data).

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by BMS Scientific Affairs. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

Training on eCRF completion will be provided at the time of site activation. Please refer to the eCRF demonstration videos on the CRO website for additional instructions on registering a patient.

The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document in NOTIS).

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires high Intensity monitoring as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the Appendices for additional data submission instructions.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and

the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study's primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study's biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician and QAM gives final approval, the publication may be submitted to external publisher.

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APPENDICES

Appendix A.
Common Terminology Criteria for Adverse Events V4.0.3 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix B – ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) performance status scale	
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self- care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Appendix C – Contraception Requirements

Investigators shall counsel FOCBP and male subjects who are sexually active with FOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise FOCBP and male subjects who are sexually active with FOCBP on the use of highly effective methods of contraception from the time of treatment initiation to 5 months (for FOCBP) or 7 months (for males with FOCBP partners) after the last dose of nivolumab. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

a) Male condoms with spermicide
b) Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by FOCBP subject or male subject's FOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.
c) Nonhormonal IUDs, such as ParaGard®
d) Tubal ligation
e) Vasectomy.
f) Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

a) Diaphragm with spermicide
b) Cervical cap with spermicide
c) Vaginal sponge
d) Male Condom without spermicide*
e) Progestin only pills by FOCBP subject or male subject's FOCBP partner
f) Female Condom*

*A male and female condom must not be used together

Appendix D– Adverse Event Algorithms

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

Endocrinopathy Management Algorithm

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

Asymptomatic TSH elevation

- Continue I-O therapy per protocol
- If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as clinically indicated; consider endocrinology consult

Symptomatic endocrinopathy

- Evaluate endocrine function
- Consider pituitary scan

Symptomatic with abnormal lab/pituitary scan:
- Delay I-O therapy per protocol
- 1-2 mg/kg/day methylprednisolone IV or PO equivalent
- Initiate appropriate hormone therapy

No abnormal lab/pituitary MRI scan but symptoms persist:
- Repeat labs in 1-3 weeks / MRI in 1 month

If improves (with or without hormone replacement):
- Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
- Resume I-O therapy per protocol
- Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness

- Delay or discontinue I-O therapy per protocol
- Rule out sepsis
- Stress dose of IV steroids with mineralocorticoid activity
- IV fluids
- Consult endocrinologist
- If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy

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

GI Adverse Event Management Algorithm

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

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.

Hepatic Adverse Event Management Algorithm

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

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

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

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

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

Neurological Adverse Event Management Algorithm

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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. **If worsens:** • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	**If improves to baseline:** •Resume I-O therapy per protocol when improved to baseline **If worsens:** • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	**If improves to Grade 2:** • Taper steroids over at least 1 month **If worsens or atypical presentation:** • Consider IVIG or other immunosuppressive therapies per local guidelines

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

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.

Renal Adverse Event Management Algorithm

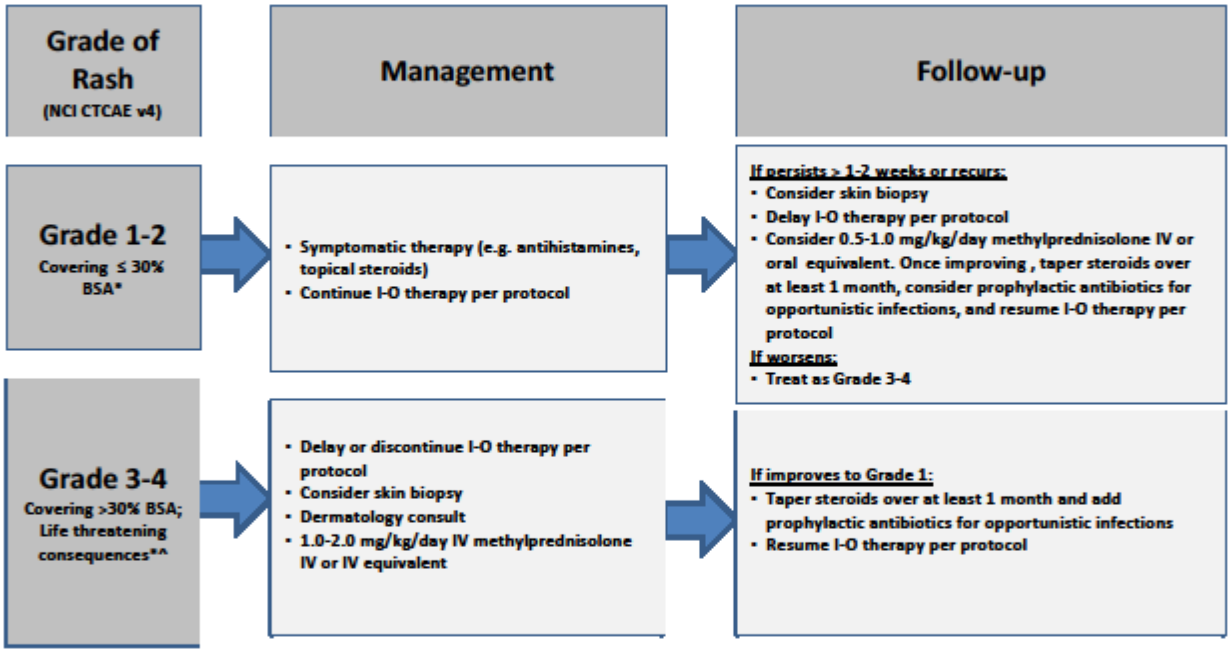
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

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

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

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-Otherapy.

Appendix E – Protocol Summary of Changes

IRB Response – January 11, 2017			
Section(s) Affected	***Prior Version***	***Response Changes***	***Rationale***
3.1.3 (Inclusion Criteria)	n/a	Adds "NOTE: Patients must be eligible to receive the next line of therapy and not be suspected of having pseudoprogression."	Clarification requested by IRB
3.1.5 (Inclusion Criteria)	n/a	Adds hemoglobin requirement ≥8g/dL	Safety measure requested by IRB
Amendment 1 – February 16, 2017 *Approved by Scientific Review Committee: March 15, 2017*			
Section(s) Affected	***Prior Version***	***Response Changes***	***Rationale***
Cover Page	IND Number: "TBD"	IND Number: 133341	Administrative; IND number now available
Study Schema	Metformin will "escalate to 2,000 mg/day"	Metformin will "escalate **incrementally** to 2,000 mg/day"	Clarification to account for 1,500 mg dose level
1.4.5 (Nivolumab flat dose regimen)	Referred to 240mg nivolumab being "under investigation	Updates 240mg nivolumab as being FDA approved	Clarification for updated information
4.1 (Overview); 4.2.1 (Nivolumab); 5.0 (Study Procedures #11)	Nivolumab infusion windows were as follows: Over 30 mins (±5 mins) Over 60 mins (±10 mins)	Updates nivolumab infusion windows: Over 30 mins (-5 / +15 mins) Over 60 mins (-5 / +15 mins)	Allows for flexibility of infusion duration without compromising safe administration
5.0 (Study Procedures #9); 9.0 (Correlatives)	n/a	#9: Archived tissue will be used (if available)	Clarification; patients will still be eligible if tissue is not available
5.0 (Study Procedures)	#7: Thyroid function test was to include TSH, free T3, and free T4	#7: Removes free T3 as requirement	Free T3 is not typically drawn and is not clinically relevant
	#14: Blood biomarker was listed at Cycle 5+ with a footnote "13"	#14: Removes Cycle 5+ time point; adds footnote "14" to Cycle 1-4 time point; Adds tube types to footnote 14	Correction of error; Clarification for easy referencing
	n/a	#17: Adds ECHO/ECG as clinically indicated at baseline for patients with underlying cardiovascular disease or history of CHF	CTEP recommendation for newly reported myocarditis toxicities associated with nivolumab
7.0 (Adverse Events); 7.4.1	n/a	Adds relevant hyperlink to DSMP reference	Administrative; to align with current protocol template

(Routine Reporting)			
7.2.2 (Severity of AE's)	"All non-hematologic adverse events" will use CTCAE 4.03	Removes "non-hematologic"	Correction of error; all AE's will follow CTCAE 4.03
9.1 (Sample Collection Guidelines)	Referenced section 5.0 for timing of correlatives	Lists tube types and timing of correlatives, removing references to 5.0.	Clarification for easy referencing.
9.3.4 (Immune and Genomic Biomarkers)	Blood was to be collected prior to metformin and C1D1.	Adds time points at C3D1 and EOT. Adds tube type (6mL EDTA tube)	Clarifications
11.6.2 (Other Protocol Deviations)	"Promptly Reportable Non-Compliance (PRNC)"	"Reportable New Information (RNI)"	Administrative; to align with current internal policies
Amendment 2 – June 21, 2017 *Approved by Scientific Review Committee: June 26, 2017*			
Section(s) Affected	***Prior Version***	***Response Changes***	***Rationale***
Cover Page	Included Sachin Pai and Ricardo Costa as sub-investigators	Removes Sachin Pai and Ricardo Costa as sub-investigators	Administrative; faculty no longer at Northwestern
5.0 (Study Procedures, #5)	CBC to be performed "every 2 weeks"	CBC to be performed "at each study visit, prior to nivolumab"	To fix discrepancy; table does not indicate study visits every 2 weeks past Cycle 4
5.0 (Study Procedures, #14); 9.1 (Sample Collection Guidelines)	Specified that correlative samples were to be collected in a 6mL EDTA and 6mL NaHep tube	Removes tube types from correlative instructions	Specific tube types will be delineated only in the lab manual to avoid the need for protocol amendments
8.2.5 (Protocol Dose Specifics)	Metformin was to be provided as 500mg and 750mg tablets	Removes 750mg tablet	Correction; only the 500mg tablet will be supplied by BMS
Amendment 3 – December 6, 2017 *Approved by Scientific Review Committee:*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Study Schema; Study Summary; 3.1.3 (Inclusion Criteria); 3.2.2 (Exclusion Criteria)	Patients in Arm B may have been treated with prior single-agent PD-1/PD-L1 inhibitors. Patients in Arm A must have been naïve to single-agent PD-1/PD-L1 inhibitors. Eligibility was ambiguous for patients treated with	Clarifies eligibility and stratification of patients: Patients in Arm B may be treated with prior PD-1/PD-L1 inhibitors, **only as a single agent**. Patients in Arm A must be naïve to any PD-1/PD-L1 inhibitor.	Clarification of ambiguous language.

	PD-1/PD-L1 inhibitor in combination with chemotherapy, however it was interpretable that such patients were eligible for Arm A.		
1.1 (Significant unmet needs in advanced NSCLC); 1.3 (Rationale for the Current Study);	References FDA approvals of PD-1 inhibitors, which previously only included single agents	References FDA approval of PD-1 inhibitors as single agents or in combination with chemotherapy	Updated to reflect recent FDA approvals
3.1.3 (Inclusion Criteria)	"Arm A: patients must be treatment naive to single-agent PD-1/PD-L1 inhibitors"	Removes "single agent"; Patients in Arm A must be treatment naïve to any PD-1/PD-L1 inhibitors.	Clarification of intended eligibility and stratification.
4.2.1 (Nivolumab)	"Subjects may be dosed no less than **25 days** from the previous dose [of nivolumab]."	"Subjects may be dosed no less than **12 days or 24 days** from the previous dose (**for 240 mg and 480 mg doses, respectively**)."	Correction to account for 240 mg doses of nivolumab, which are scheduled every 14 days. This is consistent with other NU protocols involving nivolumab.
4.2.1 (Nivolumab); 8.1.6 (Preparation)	"The drug can be diluted with 0.9% Sodium Chloride of 5% Dextrose for delivery but the total drug concentration of the solution cannot be below 0.35 mg/mL."	"The drug can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL."	Updated to align with new IB and flat dosing regimen. Prior language reflected instructions for weight-based dosing.
4.3.2 (Treatment discontinuation: nivolumab); 7.4.1 (Routine Reporting); 7.4.3 (Expedited Reporting of SAE's); 11.8 (Publication Policy)	Referred to internal Data Monitoring Committee (DMC)	Changes to Data **and Safet**y Monitoring Committee (D**S**MC)	To align with updated internal policies.
5.0 (Study Procedures Table)	Visit window was set at ±1 day, with a treatment window of ±7 days (footnote 11)	Updates all windows to ±3 days	Updated for consistency within the table and with treatment window provided in section 4.2.1
	#8: Imaging was marked at "Cycle 1-4, Day 1" with no footnote	Adds footnote 8 to Imaging at "Cycle 1-4, Day 1"	To clarify that imagining is only needed every 2 cycles starting with Cycle 3
8.1.4 (Storage and Stability); 8.1.6 (Preparation); 8.1.8 (Incompatibilities)	n/a	Replaces language with internal nivolumab template language (same content)	For consistency with other protocols involving nivolumab
8.1.7 (Route of administration for this study)	n/a	Adds infusion times and windows for nivolumab doses	To be thorough and consistent throughout the protocol

8.1.9 (Availability & Supply)	Did not specify timing for drug re-supply requests	Replaces language with internal nivolumab template language. Drug re-supply should be submitted 10 business days before the delivery date	Updated for accuracy per BMS
8.1.12 (Return & Retention of Study Drug)	n/a	Updates table to reflect accurate packaging of nivolumab product	Clarification
9.4 (Specimen Banking)	n/a	Adds section on specimen banking with instructions for retention of samples at Northwestern. Specifies that samples may be shared with researchers at other institutions.	Updated to reflect the plan for samples to be collected for banking and possible future analysis.
Appendix C	n/a	Adds timeframe of contraception requirements for both females (5 months) and males (7 months) after the last dose of nivolumab	To align with BMS template and requirements
Appendix D	Contained outdated AE Management Algorithms. Specific outdated parameters include: Hepatic: • Discontinue for AST/ALT >5xULN **and/or** Tbili >3xULN Pulmonary (G3-4): • Includes example immunosuppression Renal (G2-3): • "Consider renal biopsy" Skin (G3-4): • n/a	Updates AE Management Algorithms to align with nivolumab IB v16. Specific changes to AE management include: Hepatic: • Discontinue for AST/ALT > 5xULN **or** Tbili > 3xULN Pulmonary (G3-4): • Removes examples of immunosuppression Renal (G2-3): • "Consider renal biopsy with nephrology consult" Skin (G3-4): • Adds footnote: "If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy."	Updated per BMS for consistency with new nivolumab IB v16 and additional or clarified safety measures.

Amendment 4 – January 17, 2019			
Section(s) Affected	***Prior Version***	***Response Changes***	***Rationale***
Section 8.2.9 (Metformin drug availability and supply); Section 8.2.5 (Metformin dose specifics) and Section 4.1 (treatment)	Language stating that Metformin extended release tablets will be used and will be supplied by BMS.	Language updated to state that as of January 2019 BMS will NOT provide metformin. We will be switching from metformin supplied by BMS, to commercial supply of metformin which will be purchased and distributed through Northwestern University's investigational pharmacy	***As of December 31st 2018, BMS will no longer provide Metformin.***
Section 8.2.5 (Metformin protocol dose specifics)	The starting dose of Metformin was listed as 500mg PO BID.	Language updated to state "Metformin will be initiated during a 7-day Induction period at 1,000mg orally once daily. Metformin will then be escalated by 500mg every 7 days as tolerated (C1D1 and C1D8) until the full 2,000mg dose is reached."	***To align with the rest of the protocol (Correction of discrepancy within the protocol)***
Section 11.8 Publication policy	Previous template language	Updated with most current template language for publication policy	***Template update (administrative)***
Amendment 5 dated 4.22.19			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Section 3.1.3 Inclusion criteria and Study Schema	Arm B: patients' tumor must be either refractory to or progressed on one of the above agents. *NOTE: Prior treatment may include any number of PD-1/PD-L1 inhibitor therapies given as a single-agent*	The language in the note has been modified to state that PD-1/PD-L1 inhibitor therapies can be given either as single agent or in combination with chemotherapy	***Correction of discrepancy*** ***To be in alignment with language that already existed in the eligibility description in the Summary section of the protocol. This criteria has been approved by BMS.***

Section 3.2.2 Exclusion criteria	Patients receiving prior immunotherapies are excluded and the note stated the exception of allowing patients receiving PD-1/PD-L1 inhibitors as single agent.	Modified the note to state that PD-1/PD-L1 inhibitor therapies can be given either as single agent or in combination with chemotherapy	***To align with modifications made to Section 3.1.3***
Section 3.2.3 Exclusion criteria	The exclusion criteria stated that for arm B, patients must not have had prior exposure to combination treatment with PD-1/PD-L1 inhibitors and another systemic treatment.	This exclusion criterion has been removed, since it is in contradiction to the current modification to the inclusion criteria, which now allows PD-1/PD-L1 inhibitor therapies to be given either as single agent or in combination with chemotherapy The rest of the exclusion criteria have been re-numbered accordingly.	***To align with modifications made to Section 3.1.3***

Section 8.1.12 Table 8-1	Secondary packaging information present in the table	Secondary packaging information removed from the table	***For flexibility***