NU Study Number: *NU 16B07*
Other Study Number: *CA 209-782*

A Phase II Window of opportunity trial of Ipilimumab and Nivolumab in metastatic recurrent HER2- inflammatory breast cancer (IBC)

THE WIN TRIAL

Principal Investigator: William Gradishar, M.D., FACP, FASCO
Betsy Bramsen Professor of Breast Oncology & Professor of Medicine
Northwestern University Feinberg School of Medicine
Division of Hematology / Oncology
676 N. St. Clair Street, Suite 850
Chicago, IL 60611
Phone: 312.695.4541
Fax: 312.695.6189
Email: w-gradishar@northwestern.edu

Sub-Investigator(s): Lisa Flaum, MD
Massimo Cristofanilli MD, F.A.C.P

Biostatistician: Alfred Rademaker Phd
rademaker@northwestern.edu

Collaborators: Kalliopi Siziopikou, MD (Pathologist)

Study Intervention(s): Nivolumab (Opdivo) and Ipilimumab (Yervoy)

IND Number/Holder: *N/A (Exempt)*

Funding Source: Bristol-Myers Squibb

Version Date: **March 1, 2018 (Amendment 5)**

Coordinating Center: **Clinical Research Office**
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
676 N. St. Clair, Suite 1200
Chicago, IL 60611
http://cancer.northwestern.edu/CRO/index.cfm

TABLE OF CONTENTS

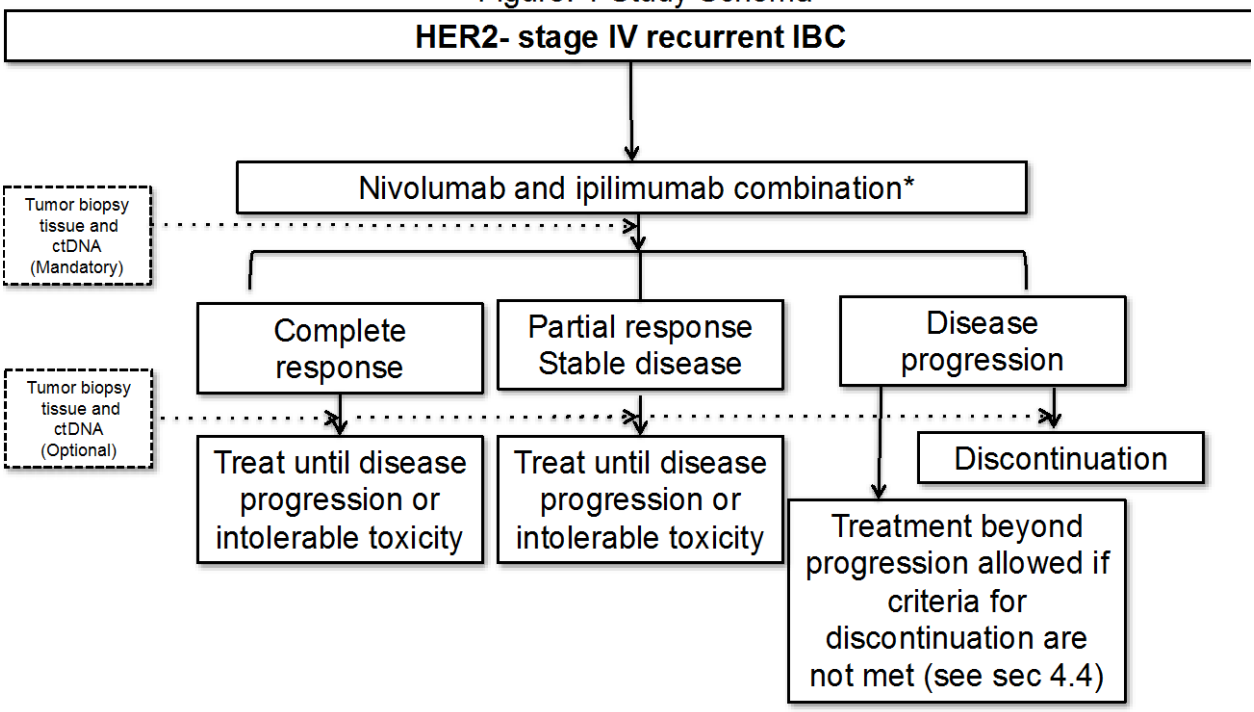
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BMS	Bristol-Myers Squibb
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CNS	Central Nervous System
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FOCBP	Females of Childbearing Potential
HER2	Human Epidermal growth factor Receptor 2
H&PE	History & Physical Exam
IBC	Inflammatory Breast Cancer
IHC	Immunohistochemistry
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Center
NCI	National Cancer Institute
NGS	Next-Genomic Sequencing
NSCLC	Non-small Cell Lung Cancer
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathological Complete Response
PD	Progressive Disease
PD-1	Programmed Death 1
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
QAM	Quality Assurance Monitor
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease

SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
ULN	Upper Limit of Normal
WBC	White Blood Cells

STUDY SCHEMA

Figure. 1 Study Schema



*Nivolumab will be administered at dose of 240mg every 2 weeks for the first 16 weeks; 480mg every 4 weeks thereafter. Ipilimumab will be administered at 1mg/Kg every 6 weeks as combination therapy until disease progression or intolerable toxicity. 1 cycle = 12 weeks

STUDY SUMMARY

Title	A Phase II Window of opportunity trial, of ipilimumab and nivolumab in metastatic recurrent HER2- inflammatory breast cancer (IBC)
Short Title	The WIN trial
Version	3/1/2018 (Amendment 5)
Study Design	This is a single arm phase II "window of opportunity" study of nivolumab in association with ipilimumab in patients with newly recurrent HER2 negative IBC.
Study Center(s)	Northwestern University
Objectives	Primary: To assess the progression free survival (PFS), overall response rate (ORR) and safety of nivolumab and ipilimumab treatment in patients with recurrent/metastatic HER-2 negative IBC Secondary: 1. To assess the overall response rate (ORR) and clinical benefit rate (CBR) according to RECIST criteria v1.1, 2. To assess overall survival (OS) in patients with recurrent HER2 negative IBC treated with nivolumab and ipilimumab 3. To assess the safety and tolerability of nivolumab and ipilimumab in patients with recurrent IBC according to CTCAE v 4.03)
Sample Size	29 patients
Diagnosis & Key Eligibility Criteria	Study population will consist of female patients age 18 or older, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, with histologically confirmed, recurrent HER2- IBC. Patients need to have adequate kidney, bone marrow, and liver functions, and with or without radiologically measurable disease according to Response Evaluation Criteria of Solid Tumors (RECIST). Patients cannot have a history of clinically significant autoimmune diseases or a syndrome that requires systemic steroids 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. Patients on treatment with prednisone > 10mg daily or equivalent corticosteroid will be excluded.
Treatment Plan	Treatment will consist of combination nivolumab and ipilimumab, given intravenously until disease progression or intolerable toxicity. Nivolumab will be administered at a dose of 240mg every 2 weeks for the first 16 weeks, and 480mg every 4 weeks starting with Cycle 2 Day 29 (1 cycle = 12 weeks). Ipilimumab will be given continuously at 1mg/Kg every 6 weeks until disease progression or intolerable toxicity. Patients will be evaluated for response every 12 weeks by CT, PET/CT or MRI.

Statistical Methodology	We will test the null hypothesis that median PFS is at most 3 months versus the alternative that it is at least 6 months. The null corresponds to 25% PFS at 6 months under the exponential distribution of PFS versus an alternative 6 month PFS rate of 50%. The null corresponds to 50% PFS at 3 months and the alternative corresponds to 70.71% PFS at 3 months under the same conditions. The chance of early study termination (3 months follow up with 15 patients) is 50% under the null and 4.4% under the alternative. Study power is 90% with overall type I error of 7%. The design follows: Early stopping designs based on progression-free survival at an early time point in the initial cohort

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

According to the Surveillance, Epidemiology End Results in the year of 2015 there will an estimated 231,840 new cases of breast cancer in the United States.[1] Inflammatory breast cancer (IBC) is a rare and aggressive form of disease accounting for 1-5 % of all breast cancers diagnosed.[2] Patients with this disease have much poorer prognosis when compared to locally advanced non-IBC (median survival time of 2.9 versus 6.4 years).[2] Lee and Tannenbaum first used the term “inflammatory breast cancer” in 1924 to describe this clinical presentation. Subsequently, Haagensen described diagnostic criteria for IBC including a rapidly enlarging breast, erythema involving at least one-third of the breast, generalized induration, and biopsy proven carcinoma.[3]

IBC is a clinico-pathological entity characterized by distinct skin changes including diffuse erythema and edema (peau-d’orange) often without a clinically evident underlying mass.[4] It is associated with an abrupt onset and rapid progression, with a high risk of axillary lymph node involvement and distant metastases at the time of initial diagnosis.[5] Despite multimodality therapy, survival rates are lower than those for other breast cancers. Its aggressive course, together with accumulating molecular and epidemiological data, also lends support to the fact that IBC may in fact be a distinct biological entity rather than a subtype on the spectrum of locally advanced breast cancer.

Once considered a uniformly fatal disease with fewer than 5% of patients alive at five years, management of IBC has evolved significantly over the last forty years. A multimodality approach, including primary systemic chemotherapy followed by mastectomy and radiation therapy has led to improved survival outcomes.[6] The National Comprehensive Cancer Center (NCCN) guidelines list the standard approach to IBC as neoadjuvant chemotherapy with an anthracycline based regimen and a taxane.[7] If HER2 is overexpressed, trastuzumab for a total of one year is indicated as part of the systemic chemotherapy regimen. Mastectomy with axillary lymph node dissection is standard in IBC patients who respond to pre-operative chemotherapy. Following surgery, postmastectomy radiation is recommended with adjuvant endocrine therapy if indicated.[8] Several studies demonstrated that pathological complete response (pCR) to neoadjuvant therapy is the strongest prognostic factor.[9,10] Patients with residual disease remain at high-risk of disease recurrence and in spite of optimal endocrine or HER-2 adjuvant therapies.[11,12] The prognosis of metastatic IBC is dismal compared to non-IBC irrespective of disease subtype suggesting the need to improve the understanding of disease biology for more effective treatments.[11]

In contrast with non-IBC breast cancer, most patients diagnosed with IBC do not express hormone receptor with estrogen receptor been overexpressed in only 30 to 44% of the cases.[13,14] Her2 hyper-expression on other hand is common in IBC with overexpression frequency estimated at about 32-60% on diagnosis.[11,15]

Matro colleagues recently reported the largest follow up study on the recurrence pattern of IBC in 478 patients with stage III at diagnosis.[11] Among the different tumor subtypes, 56% of patients with triple negative stage III disease subsequently developed metastases, compared with 43% of patients with HER2-positive disease and 35% with HR-positive disease. This indicates that triple negative tumors represent the most common type of recurrent IBC. Furthermore triple negative IBC is associated with poor prognosis when compared to Her2 and or HR + disease with dismal prognosis in the recurrent setting despite aggressive therapy.[16,17]

1.1.1 IBC molecular features

Regardless of hormone receptor and HER2 expression statuses the distinct biologic characteristics typical of IBC are associated with poor outcome, including high S-phase fraction, high grade, aneuploidy, lack of estrogen and progesterone receptor expression and overexpression of human epidermal growth factor receptor 2 (HER2).[13,18,19] Inflammatory breast tumors are more likely to have mutations in p53, associated with decreased response to chemotherapy and decreased survival outcomes.[20] Several genes have been identified which are thought to contribute to the aggressive nature of IBC. Nuclear factor kappa B (NF-kB) related genes which mediate cell migration, invasion and metastasis are reported higher in IBC.[21] Overexpression of Rhoc GTPase, a member of the *RAS* family of GTP binding proteins, upregulates angiogenic factors (VEGF, bFGF) promoting cell motility and invasion.[22] IBC is associated with loss of expression of Wisp 3, a tumor suppressor gene coding for insulin-like growth factor-binding protein related protein (IGFBP-rP9) regulates tumor cell growth and invasion.[11,23]

1.1.2 Advanced Diagnostics in IBC

In the last few years the clinical application of next-genomic sequencing (NGS) allowed for molecular analysis of metastatic breast cancer, including IBC and showed the ability to identify mechanisms of resistance and actionable mutations. Palma, Cristofanilli and colleagues recently reported the result of a retrospective study involving patients with metastatic IBC that had a diagnostic biopsy of metastatic lesion and subsequent NGS by Foundation One™ panels.[24] The analysis revealed a total of 84 unique mutations with a total of 156 mutational events. The five most commonly mutated genes in order of frequency were *TP53* (53.33% of patients), *PIK3CA* mutations or amplification (36.7%), *MYC* amplification (30%), *ERBB2* amplification (26.7%) and *ZNF217* amp and *PTEN* loss or mutation (16.7%). In total, 21 of 30 patients (70%) had at least one actionable mutation. Of these 21 patients, 28.5% were ER+/HER- (Luminal A), 28.5% ER+/HER+ (Luminal B) and 28.5% ER-/HER- (TNBC) while the remaining were ER-/HER+ (HER2+). 9.5% of these 21 patients expressed HER positivity by IHC although *ERBB2* amplification was not detected. Fourteen 14 of 84 mutations (16.7%) were actionable and comprised of *PIK3CA* mutations/amplifications, *ERBB2* amplifications, *AKT* mutations and *PTEN* loss/mutations *(unpublished data, manuscript submitted for publication).*

In a separate study, Hamm, Cristofanilli and colleagues used a custom hybridization capture based probe library was designed using Agilent SureDesign portal (Agilent Technologies) to analyze 20 IBC specimens.[25] This panel captures full coding regions of 208 cancer relevant genes and introns of 13 genes to detect the substitution, deletions, copy number changes in the 208 targeted genes and structural rearrangements in 17 genes.

Analysis of the types of genetic variants revealed that missense mutations were the most common variant (73%), followed by frameshifts (8%), splice site alterations (6%), nonsense mutations (5.5%), amplifications (5.5%), and In-frame insertions-deletions (3%). In total, NGS identified 391 genetic variants in 19 IBC

tissues. In the IBC cohort, the 5 most commonly altered genes are: TP53 (altered in 58% [n=11] of IBC tumors), HER2 (amplified in 53% [n=10] of IBC tumors), ATM (altered in 53% [n=10] of IBC tumors, APC (altered in 37% [n=7] of IBC tumors), and HER3 (altered in 26% [n=5] of IBC tumors). In total, 47 genes have alterations in at least three independent IBC tumor samples. Pathway analysis of the NGS data reveals prominent genomic variation of core biologic pathways in multiple IBC tumors. Genes with reoccurring variants across IBC tumors grouped into distinct biologic pathways, and the most frequent gene alterations occur in pathways that influence genomic stability/DNA repair, PI3K signaling, chromatin modification, and HER signaling.

1.1.3 Immune checkpoints in IBC

The study from Hamm Cristofanilli and colleagues investigated also the role of immune infiltrate and immune checkpoints in relation with genomic abnormalities.[25]

The pathological examination of IBC tissues identified a subset of IBC tumors associated with infiltration of immune or inflammatory cells. To further investigate the nature of these infiltrates, CD8 (cytotoxic T cell marker) and FOXP3 (T regulatory cell marker) IHC staining was performed on tissues to characterize T cells populations present in each tumor. Twelve IBC tumors had sufficient tissue for IHC analysis. Infiltrates stained minimally for FoxP3+ Tregs. IHC staining identified the majority of infiltrating cell populations as CD8+ cytotoxic T cells. CD8+ T cells typically localized in associated intra-tumoral and contiguous peri-tumoral desmoplastic stroma. Each tumor was scored by a pathologist as high CD8+ (infiltrating cells occupying ≥5% of tumor area occupied by tumor cells) or low CD8+ (infiltrating cells occupying <5% of tumor area occupied by tumor cells). High levels of CD8+ infiltration were observed in 5/12 tumors, and frequently presented as cell aggregates. Remaining tumors generally displayed low levels of single cell spreads of CD8+ cells across tissues, which was further confirmed by image analysis of average size of cellular aggregates in each tissue.

In order to explore the possible role of PD-L1 in IBC, the investigators performed IHC stained of IBC tissues. Evaluation of PD-L1 staining demonstrated low-intensity tumor cell staining in 3/12 tumors studied and high-intensity tumor cell staining in 1/12 tumors. Notably all immune cell infiltrates stained positively for PD-L1. Intensity of PD-L1 staining on immune infiltrates was generally high with IHC scores typically ranging from 2+ to 3+. To further understand the differences in levels of immune cell infiltration between IBC tumors, NGS data was analyzed in tumors with high and low levels of immune infiltrate (Due to limited tissue availability 12 of 19 IBC samples were available for IHC analysis). Notably, somatic mutation rates were significantly higher in high infiltration vs low infiltration tumors ($p<0.05$). The authors speculated that this correlation between somatic mutation rate and immune cell infiltration might be related to the exposure of tumor neo-antigens to the immune system. They next proposed that a score (iScore) that combines the somatic mutation rate and average mutant allele frequency might better represent the level and variability of neo-antigens throughout the bulk of the tumor. The iScore is calculated by multiplying the average mutant allele frequency by the total number of somatic mutations in the tumor. Comparison of iScores between high infiltration and low infiltration tumors demonstrated high significance in the association between levels of CD8+ infiltration and iScore in IBC tumors, suggesting that the iScore may be a reliable NGS-based estimate of immune infiltrate in IBC tumors.

It is important to review that proposed correlation between high mutational burden of tumors and clinical benefit from immunotherapy strategies (i.e. checkpoint inhibitors anti-CTLA-4 and anti-PD-1 antibodies) is seen in other tumors, with remarkable effects seen with tumors displaying the highest rates of mutations such as melanoma[26,27].This is also illustrated by the anti-tumoral immunologic response to anti-PD-1 antibody in patients with colorectal cancer and increased mutational burden secondary to mismatch repair deficiency.[28]

The potential importance of immune checkpoint guided therapy in breast cancer is also underscored by recent reports of PD-1 inhibitor activity in non-IBC triple negative breast. Pembrolizumab, which is a monoclonal anti-PD-1 antibody was tested in a phase Ib trial on 32 female patients with PD-L1 IHC + and heavily pretreated metastatic recurrent non-IBC triple negative breast cancer. The clinical benefit rate (partial response + disease stabilization rates) was 25.8%.[29]

1.2 Intervention Background & Overview

1.2.1 Nivolumab, ipilimumab and nivolumab/ipilimumab combination

Nivolumab (BMS-936558, MDX-1106) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HunMab) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [cd279]) cell surface membrane receptor (Investigator brochure version 2014). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an “exhausted” phenotype. Nivolumab anti-tumor activity has been investigated in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC).[30-32] The combination of nivolumab and ipilimumab (anticytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in phase 1/2 trial showed markedly enhanced clinical activity with acceptable safety profile in melanoma patients.[33] Nivolumab is currently FDA approved for BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent., unresectable or metastatic melanoma, in combination with ipilimumab., metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy andAdvanced renal cell carcinoma who have received prior anti-angiogenic therapy, the treatment of patients with advanced stage non-small cell lung cancer after progression on platinum based chemotherapy and patients with metastatic renal cell carcinoma. Nivolumab is well tolerated when compared to chemotherapy with rare grade 3 or 4 toxicities. Nonetheless is has been associated with immune related adverse events such as pneumonitis, colitis, which have frequency of less than 5%.[30]

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody. Several preclinical studies demonstrated that CTLA-4 blockade could augment T cell-mediated immune responses against tumors.[34,35] This let to the development of ipilimumab, a fully humanized IgG1 monoclonal antibody to CTLA-4. Two phase 3 trials demonstrated a durable clinical benefit for approximately 20-25% of metastatic melanoma patients with ipilimumab resulting in FDA approval of this compound as a first and second-line agent in metastatic melanoma.[36,37] Ipilimumab has been associated with immune mediated toxicities such as diarrhea, colitis, rash, pruritus, hypothyroidism. The risk of grade 3 and 4 immune-related adverse is estimated at approximately 14%.[36]

Preclinical data show that the combination blockade of the PD-1/PD-L1- and CTLA-4-negative costimulatory pathways allows tumor-specific T cells that would otherwise be inactivated to continue to expand and carry out effector functions, thereby shifting the tumor microenvironment from suppressive to inflammatory.[38] A recently published phase III on patients with untreated metastatic melanoma

showed significant PFS in patients treated with the combination of nivolumab and ipilimumab when compared to either agent along.[39] The combination of ipilimumab and nivolumab is now a standard first line option in the treatment of metastatic melanoma patients. Grade 3 and 5 treatment-related toxicities were described in 55% of patients treated with diarrhea, fatigue, elevations of liver enzymes happening in less than 10% of the patients.[39]

1.2.2 Clinical development

Nivolumab in combination with ipilimumab is being evaluated in completed and ongoing BMS-sponsored clinical trials in melanoma, renal cell carcinomas, glioblastomas, lung cancer and gastrointestinal (GI) malignancies including colorectal cancer with microsatellite instability (MSI), and triple-negative breast cancer (TNBC) with an expanding group of indications (Investigator Brochure version 2015). On September 30, 2015, the U. S. Food and Drug Administration granted accelerated approval to nivolumab (Opdivo Injection, Bristol-Myers Squibb Company) in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma.

1.2.3 Clinical efficacy

Nivolumab and ipilimumab have demonstrated clinical activity as monotherapy and as combination therapy in several tumor types. The majority of responses was durable and exceeded 6 months (Investigator Brochure version 2015).

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 [40]. 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%) [30]. These results supported the FDA approval of nivolumab for second-line treatment of advanced squamous cell carcinoma following treatment with platinum-based chemotherapy.

Nivolumab has also 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) [41]. Median overall survival was 18, 25, and 24 months for the three dose cohorts, respectively. More recently 821 patients previously treated with antiangiogenic therapy were randomized to either nivolumab (3mg/Kg every 2 weeks) or everolims (10mg daily).[42] 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.

The clinical efficacy of ipilimumab monotherapy was assessed in phase 3 trial among 676 patients with metastatic progressive melanoma.[36] total of 676 HLA-

A*0201-positive patients with unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease, were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus gp100 (403 patients), ipilimumab alone (137), or gp100 alone (136). Ipilimumab, at a dose of 3 mg per kilogram of body weight, was administered with or without gp100 every 3 weeks for up to four treatments (induction). Eligible patients could receive reinduction therapy. The primary end point was overall survival. The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio for death, 0.68; P<0.001). The median overall survival with ipilimumab alone was 10.1 months (hazard ratio for death in the comparison with gp100 alone, 0.66; P=0.003). No difference in overall survival was detected between the ipilimumab groups (hazard ratio with ipilimumab plus gp100, 1.04; P=0.76). Ipilimumab is now FDA approved for the treatment of patients with metastatic unresectable melanoma.

In an advanced melanoma phase 1 study, nivolumab and ipilimumab combination was administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) [33]. The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%. These results demonstrate significant clinical activity of nivolumab across multiple histologies with favorable toxicity profile.

In a phase 2 study of nivolumab in combination with ipilimumab vs. ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma, the combination of nivolumab with ipilimumab demonstrated clear evidence of clinical activity over ipilimumab monotherapy, as measured by statistically significant improvements in ORR and PFS, and a higher proportion of subjects with complete responses.[32] A phase 3 study of nivolumab monotherapy or nivolumab in combination with ipilimumab vs. ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma, the combination of nivolumab with ipilimumab demonstrated clear evidence of clinical activity over ipilimumab monotherapy, as measured by statistically significant improvements in median PFS in the combination arm (11.5 vs 6.87 vs 2.89 months) [39] Based on descriptive analyses, the combination of nivolumab with ipilimumab demonstrated improved PFS nivolumab and ipilimumab monotherapies.

Most recently, nivolumab at 3mg/Kg every 2 weeks combined with ipilimumab at 1mg/KG every 6 weeks was evaluated in patients with advanced NSCLC in the first line setting(CheckMate 012 trial).[43] In this trial 4 different combinations of nivolumab were compared (nivolumab 1mg/Kg every 3 weeks x 4+ ipilimumab 1mg/Kg every 3 weeks x 4 followed nivolumab 3mg/Kg every 2 weeks (N=31), nivolumab 1mg/Kg every 2 weeks + ipilimumab 1mg/kg every 6 weeks (N=40), nivolumab 3mg/Kg every 2 weeks + ipilimumab 1mg/Kg every 12 weeks (n=38) and finally nivolumab 3mg/Kg every 2 weeks combined with ipilimumab 1mg/Kg every 6 weeks until disease progression (n=46). The efficacy data showed response rates of 13, 25, 39 and 31% respectively. These results suggest that continuation of dual CTLA4 and PD-1 inhibition can improve clinical outcomes when compared to currently used regimen.

1.2.4 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.

The toxicity profile of ipilimumab at the dose of 3mg/Kg for 4 doses in previously treated patients with metastatic melanoma was assessed in phase 3 trial. One hundred and thirty one patients with received ipilimumab as monotherapy, 380 received it with gp100 peptide, and 132 received gp100 peptide vaccine alone. Patients in the study received a median of 4 doses. Ipilimumab was discontinued for adverse events in 10% of patients. The most common adverse events in patients who received ipilimumab at 3mg/Kg were fatigue (31%), pruritus (23%) and rash (22%)(package insert v 2013). The majority of drug-related AEs were of Grade 1-2 in severity.

In several ongoing clinical trials, the safety of nivolumab in combination with ipilimumab is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab + ipilimumab in subjects with melanoma. Thus far, the combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases with a greater frequency [33].

Safety data for subjects with previously untreated unresectable or metastatic melanoma treated with nivolumab in combination with ipilimumab in phase III (313 subjects) and phase II (94subjects) trials were pooled and safety analyses were performed for these pooled subjects receiving nivolumab in combination with ipilimumab (a total of 407 subjects) as described in the investigator brochure BMS-936558/MDX1106 Version No14, 30-Jun-2015.[32,39] Based on the pooled analyses, nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg administered IV Q3W for 4 doses followed by nivolumab 3 mg/kg 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 frequently reported drug-related AEs of any grade were diarrhea (43.0%), fatigue (35.4%), pruritus (33.4%), rash (31.0%), nausea (24.8%), pyrexia (18.7%), ALT increased (18.2%), AST increased (16.7%) and decreased appetite (16.2%). The most frequently reported drug-related Grade 3-4 AEs (≥ 5% of subjects) were colitis (9.6%), diarrhea (8.80%), ALT increased (8.4%), lipase increased (8.4%), and AST increased (5.9%). Study drug toxicity was considered responsible for 2 deaths; 1 subject died of ventricular arrhythmia within 30 days of the last dose and the other died of pneumonitis between 31 and 100 days of the last dose.

Most recently, nivolumab at 3mg/Kg every 2 weeks combined with ipilimumab at 1mg/KG every 6 weeks was administered in patients with advanced NSCLC in the first line setting.(CheckMate 012 trial)[43] In this trial 4 different combinations of nivolumab were compared (nivolumab 1mg/Kg every 3 weeks x 4+ ipilimumab 1mg/Kg every 3 weeks x 4 followed nivolumab 3mg/Kg every 2 weeks (N=31), nivolumab 1mg/Kg every 2 weeks + ipilimumab 1mg/kg every 6 weeks (N=40), nivolumab 3mg/Kg every 2 weeks + ipilimumab 1mg/Kg every 12 weeks (n=38) and finally nivolumab 3mg/Kg every 2 weeks combined with ipilimumab 1mg/Kg every 6 weeks until disease progression (n=46). Toxicity data favored the latter group with estimates of grade 3 and 4 treatment related adverse events 29, 35, 29 and 28%, respectively. These results indicate that the nivolumab dose of 3mg/Kg administered every 2 weeks combined with ipilimumab 1mg/Kg every 6 weeks until disease progression has favorable disease profile and should be further explored in future clinical trials.

1.2.5 Biomarkers

Significant efforts continue to explore potential tumor cells and microenvironment-related biomarkers that could predict response to nivolumab and other checkpoint inhibitors. For instance, tumor cell expression of PD-L1 was characterized with the use of IHC staining and pharmacodynamics changes in the peripheral blood absolute lymphocyte count in the study investigating the combination of nivolumab and ipilimumab in melanoma [33]. PD-L1 positivity was defined as expression in at least 5% of tumor cells. Among patients treated with the concurrent regimen of nivolumab and ipilimumab, ORs were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22). In the sequenced regimen cohorts, a higher number of overall responses were seen among patients with PD-L1–positive tumor samples (4 of 8 patients) than among patients with PD-L1–negative tumor samples (1 of 13) suggesting the possibility that these tumors have higher response rates to the combination. Other biomarkers such as tissue expression of PDL-2, interferon-γ (IFN- γ), IDO (indoleamine-pyrrole 2,3-dioxygenase), and T cell CD8+ infiltration are also being investigated. However, there is no definitive date to support the use of any of these biomarkers to select patients for treatment at this time.

1.3 Rationale for the Current Study

IBC is associated with significant level of genomic instability. Moreover, the level of genomic mutation rate, indicated as iScore is associated with infiltrate of CD8 cytotoxic T cells together with PDL-1 staining. Immune checkpoint targeted therapies showed significant activity and is currently approved in other solid tumors. The data provide a strong rationale for testing of immune checkpoint modulators in metastatic IBC.

1.3.1 Study design

The rationale for use of a “window of opportunity” study is based on the fact that it allows to assess the efficacy of immunotherapy in IBC when the tumor is still unperturbed by other systemic treatments routinely used the metastatic setting.

1.3.2 Nivolumab flat dose regimen

The safety and efficacy of 240 mg (combined with 1mg/kg of ipilimumab) Q2W flat dose of nivolumab is expected to be similar to the 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. Hence, the flat dose of 240 mg nivolumab is under investigation.

1.3.3 Ipilimumab dose regimen

Ipilimumab will be administered at 1mg/Kg every 6 weeks until disease progression in combination with nivolumab 240mg every 2 weeks. As discussed above, this drug combination regimen has been compared with the current FDA approved combination regimen of nivolumab 1mg/Kg every 3 weeks x 4 and ipilimumab 3mg/Kg every 3 weeks x 4 followed by nivolumab 3mg/Kg every 2 weeks until disease progression and showed favorable toxicity profile with maintained efficacy among patient with lung cancer.[43]

1.4 Exploratory Studies

In the era of personalized therapy appropriate patient selection to immune-check point inhibitors remain an elusive goal. There are conflicting data on the predictive value of PD-L1 expression on PD-1 directed therapy in solid tumors [30,44]. Herbst et al showed that patients with solid tumors including non-small cell lung cancer and melanoma treated with humanized PD-L1 antibody had higher ORR when immunohistochemistry showed intense staining for PD-L1 in the tumor [45]. The same correlation was not observed on stratified analysis according to tumor cell membrane PD-L1 expression of non-small cell lung cancer patients treated with nivolumab therapy in the second line setting.[30]

The most recent archival diagnostic tissue biopsy performed as part of the standard of care approach to recurring breast cancer will be obtained for all patients and sent for NGS and evaluation of iScore (baseline assessment). The same specimen will be assessed for PDL-1 expression. A fresh tissue biopsy will be obtained for all patients where archival tissue is not available.

Should repeat tumor tissue biopsy be performed after initiation of treatment on protocol as part of standard of care approach, specimens will be sent for NGS, iScore and PDL-1 staining. Correlations between efficacy endpoints (PFS and ORR) and biomarker statuses will be conducted.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

To determine progression free survival (PFS) in patients with newly recurrent HER2 negative IBC treated with nivolumab and ipilimumab according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1.[46]
The time in months from start of treatment to progression or death will be measured for all patients who receive at least one dose of study drug. Patients will be followed up to 2 years after completion of treatment.

2.2 Secondary Objectives & Endpoints

2.2.1 To assess the overall response rate (ORR) and clinical benefit rate (CBR) according to RECIST criteria v1.1, in patients with recurrent IBC treated with nivolumab and ipilimumab

Overall response rate (ORR) is defined as Complete Response (CR) + Partial Response (PR). Clinical benefit rate (CBR) is defined as CR + PR + Stable Disease (SD). Patients will have scans every 12 weeks.

2.2.2 To assess overall survival in patients with recurrent HER2 negative IBC treated with nivolumab and ipilimumab.

Patients will be followed from the start of treatment until 2 years post-treatment or death, whichever occurs first, and average survival time will be measured.

2.2.3 To assess the safety and tolerability of nivolumab and ipilimumab in patients with recurrent IBC according to the National Cancer Institute Common Terminology Criteria Adverse events v 4.03).

The number, frequency, and severity of adverse events will be collected from time of consent until 12 weeks after study treatment.

2.3 Exploratory Objectives & Endpoints

2.3.1 To assess the predictive value of baseline iSCORE and PDL-1 expression using archival tissue samples as well as any standard of care tissue obtained during study treatment.

All patients will provide archival or fresh tumor tissue at study registration, and will have the option to provide tissue from any biopsies performed during study treatment.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with stage IV early recurrence HER2 negative IBC. This will be a single center trial conducted at Northwestern University.

A total of 29 subjects will be needed for this trial. Approximately 8 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. William Gradishar at (312) 695-4541.

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 or cytologically confirmed stage IV breast carcinoma with a previous clinical diagnosis of IBC based on the presence of inflammatory changes in the involved breast, such as diffuse erythema and edema (peau d'orange), with or without an underlying palpable mass involving the majority of the skin of the breast. Pathological evidence of dermal lymphatic invasion should be noted but is not required for diagnosis.

3.1.2 Patients must have local or metastatic recurrence of IBC after prior surgery.

3.1.3 Patients must have a metastatic tumor negative for HER2. The lack of HER2 overexpression by immunohistochemistry (IHC), is defined as 0 or 1+ where as hyperexpression is defined as 3+. If equivocal IHC, 2+, the tumor must be non-gene amplified by FISH performed upon the primary tumor or metastatic lesion (ratio <2 and HER2 copy number <4).[47]

3.1.4 Patients may have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension in accordance with RECIST criteria v. 1.1 OR non-measurable tumors (see section 6.5).

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

3.1.5 Patients must be in consideration for 1st line systemic therapy for recurrent IBC.

NOTE: Patients must not have received chemotherapy in the metastatic setting, but adjuvant treatment after surgery is acceptable.

3.1.6 Patients must have confirmed availability of archival or freshly biopsied tumor tissue meeting protocol-defined specifications prior to study enrollment.

3.1.7 Patients must be female and age ≥ 18 years.

3.1.8 Patients must exhibit an ECOG status of 0-1. ECOG performance status 2 and 3 will be allowed only if decline in performance status is thought to be directly secondary to breast cancer disease burden by treating physician.

3.1.9 Patients must have adequate organ and bone marrow function ≤14 days prior to registration, as defined below:

• leukocytes	≥ 2,000/mcL
• absolute neutrophil count	≥ 1,500/mcL, regardless of transfusion or growth factor support
• platelets	≥ 100,000/mcl, regardless of transfusion or growth factor support
• total bilirubin	total bilirubin ≤1.5× institutional upper limit of normal (ULN) (except patients with Gilbert Syndrome or liver metastasis, who can have total bilirubin <3.0 x ULN)
• AST(SGOT)/ALT(SPGT)	≤ 2.5 X institutional upper limit of normal (ULN) (or ≤5 times ULN in case of liver metastasis)
• creatinine	Serum creatinine of < 3.0 X ULN (upper limit of normal)

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

NOTE: Patients are not required to have CNS imaging prior to study entry.

3.1.11 Females of childbearing potential (FOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours of registration.

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)

3.1.12 FOCBP and men who are sexually active with FOCBP 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)

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

3.2 Exclusion Criteria

3.2.1 Patients must not have had chemotherapy or radiotherapy ≤ 28 days prior to study registration.

3.2.2 Patients who already received chemotherapy for recurrent metastatic IBC are not eligible.

3.2.3 Patients who have not recovered to ≤ Grade 1 from adverse events due to agents administered ≥28 days prior to registration are not eligible.

3.2.4 Patients may not be receiving any other investigational agents.

3.2.5 Patients who have had prior exposure to immune checkpoint inhibitors are not eligible. Please contact principal investigator, William Gradishar at 312-695-4541 for specific questions on potential interactions.

Mechanism of action	Agent
PD-1 monoclonal antibody	Pembrolizumab, Pidilizumab, MEDI-0680, AMP-224, PF-06801591, AMP224, BGB-A317, PDR001,REGN2810, SHR-1210
PD-L1 monoclonal antibody	Durvalumab, avelumab, MDX-1105, atezolizumab, MPDL3280A
CTLA4 monoclonal antibody	Tremulimumab, abatacept
OX40	MEDI6383,MEDI6469, MEDI0562, oxelumab, PF-04518600

3.2.6 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
- leptomeningeal disease

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.

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

- Ongoing or active infection (including minor localized infections) requiring oral or IV treatment
- Symptomatic congestive heart failure, defined as a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
- 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

3.2.8 Patients should not have any condition requiring systemic treatment with corticosteroids (<10mg daily prednisone equivalents) or other immunosuppressive medications ≤14 days prior to registration.

NOTE: Inhaled or topical 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.

3.2.9 Female patients who are pregnant or nursing are not eligible.

3.2.10. Patients with a history of another malignancy within 3 years prior to registration are not eligible for participation, with the following exceptions:
- adequately treated basal cell or squamous cell skin cancer,
- in situ cervical cancer

3.2.11 Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) is not permitted.

3.2.12 Any known positive test for Hepatitis B or Hepatitis C virus indicating acute or chronic infection is not permitted.

3.2.13 Patients who have received a live attenuated vaccine ≤ 30 days prior to registration are not eligible.

4.0 TREATMENT PLAN

4.1 Overview

Nivolumab and ipilimumab combination will be administered intravenously until disease progression or intolerable toxicity. Nivolumab will be given at 240mg every 2 weeks for the first 16 weeks, and at 480mg every 4 weeks thereafter (starting with C2D29, 1 cycle = 12 weeks). Ipilimumab will be given at 1mg/Kg every 6 weeks over approximately 90 minutes. On days when both nivolumab and ipilimumab are administered, nivolumab should be given first, followed by ipilimumab about 30 minutes later. Scans will take place every 12 weeks for disease assessment. Note: Please refer to section 4.4 for patients who may continue treatment after initial progression.

4.2 Treatment Administration

Treatment Administration Summary

Agent	Premedications	Dose	Route	Schedule	Cycle Length	Supportive Therapies
Nivolumab	None	240mg	IV infusion over ~30 minutes*	Q2Ws	12 weeks	As needed
		480mg	IV infusion over ~60 minutes	Q4W's		
Ipilimumab*	None	1mg/Kg	IV infusion over ~90 minutes*	Q6Ws		As needed

*On days when both drugs are administered, nivolumab should be given first, followed by ipilimumab ~30 minutes later.

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.

Nivolumab will be administered at a dose of 240mg (combined with ipilimumab) as an intravenous infusion over approximately 30 minutes (-5 / +15 minutes)

every 2 weeks for the first 16 weeks (1 cycle = 12 weeks). Starting with Cycle 2 Day 29, nivolumab will be given at 480mg IV over approximately 60 minutes (-10 / +15 minutes) every 4 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.
NOTE: The first two nivolumab doses of Cycle 2 will be given at 240mg q2weeks.

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 240mg and 480mg 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 diluted with 0.9% Sodium Chloride or 5% Dextrose for delivery but the total drug concentration of the solution cannot be below 0.35 mg/mL. 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 Ipilimumab

Ipilimumab will be administered at a dose of 1mg/Kg as an intravenous infusion over approximately 90 minutes (-5 / +15 minutes) every 6 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. Dosing will be based on actual body weight in kg on the day of the infusion. On days when both ipilimumab and nivolumab are administered, nivolumab should be given first, followed by ipilimumab ~30 minutes later.

There will be no dose escalations or reductions of ipilimumab allowed. There are no pre-medications recommended for ipilimumab on the first cycle. If an acute infusion reaction is noted subjects should be managed according to Section 4.3.3.

Ipilimumab is to be administered as a 90-minute IV infusion (a window of -5 / +15 minutes is allowed), using a volumetric pump with a 0.2/1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 1 mg/mL. 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 delays 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

4.3 Toxicity Management & Dose Delays

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: Ipilimumab and/or 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. Either ipilimumab or nivolumab should be delayed based on this attribution, or both if a definite attribution is not possible. Both drugs can be held for a maximum of 56 days.

Ipilimumab and/or nivolumab administration should be delayed for the following until resolution to ≤ Grade 1:

- 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.

Immunotherapy agents such as nivolumab and ipilimumab 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.

4.3.2 Treatment discontinuation: Ipilimumab and/or nivolumab

Should the treating physician decide to discontinue treatment given suspicion for a drug related side effect, the side effect (adverse event) should be attributed to one study drug to the best of the physician's ability. Either ipilimumab or nivolumab should be discontinued based on this attribution, or both if definite attribution is not possible.

Ipilimumab and/or 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 Monitoring Committee (DMC) 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 > 56 days (8 weeks) from the previous dose requires discontinuation.

4.3.3 Treatment of Nivolumab or Ipilimumab-related infusion reactions

Since both nivolumab and ipilimumab contain 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. All grade 3 or 4 infusion reactions should be reported within 24 hours to the study QAM and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

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

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 minutes before additional nivolumab or ipilimumab 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/ipilimumab 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 or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
Grades 3 or 4	Immediately discontinue infusion of nivolumab/ipilimumab infusion.	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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	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 or ipilimimuab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor 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	

4.4 Treatment with ipilimumab and or nivolumab beyond progression

In the event of an initial assessment of PD (based on RECIST Version 1.1), a subject may continue to receive the assigned study treatment as long as none of the criteria listed below are met. Criteria for discontinuation of investigational product include:

1. Confirmed PD: An initial assessment of PD by RECIST Version 1.1 will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later (see Section 4.3.1 for disease evaluation).
2. Meets any of the other investigational product discontinuation criteria (Section 4.1.6)
3. Clinical symptoms or signs indicating significant PD such as the benefit-risk ratio of continuing therapy is no longer justified.
4. Decline in ECOG performance status.
5. 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 steroid doses < 10 mg daily prednisone equivalent, are permitted 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.

Antihormonal therapy is permitted for patients with hormonal receptor positive IBC.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs.

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
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than nivolumab or ipilimumab
- Radiation therapy
- Corticosteroids are not permitted unless they fall under the criteria listed in 4.5.1

4.6 Duration of Therapy

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

- Disease progression (please refer to 4.4 for guidance regarding treatment beyond progression),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) as already described in session.

4.7 Duration of Follow Up

All patients will be followed for adverse events for 12 weeks after last dose of nivolumab and or ipilimumab, 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 2 years after treatment discontinuation or until death, whichever occurs first.

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 (follow-up permitted)
- Patient demonstrates disease progression (per parameters above, follow-up permitted)
- 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)

4.9 Patient Replacement

Any patient who signs consent but does not receive study treatment may be replaced.

5.0 STUDY PROCEDURES

		On Treatment (1 cycle = 12 weeks)[12,13]																		Off Treatment	
		Cycle 1 (±3 days)						Cycle 2 (±3 days)						Cycle 3+ (±3 days)						End of Treatment[14]	Follow-Up[15]
Day of each cycle	Screening[1]	1	15	29	43	57	71	1	15	29	43	57	71	1	15	29	43	57	71		
Weeks on study		1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	31	33	35 +		
Assessment or Activity																					
Informed Consent	X																				
Medical history	X																				
Physical exam [2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X
ECOG status	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
ConMeds	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X[15]
Scans[3]	X	X[3]						X[3]						X[3]						X	
Lesion Photos[16]	X	X						X						X						X	
CBC with diff [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	
Chemistry panel [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	
Amylase/Lipase	X	X[6]						X[6]						X[6]						X	
TSH (free T4) [7]	X	X[7]						X[7]						X[7]							
Pregnancy test[8]	X	X						X						X						X	
Nivolumab [9]		T	T	T	T	T	T	T	T	F		F		F		F		F			
Ipilimumab [10]		X			X			X			X			X			X				
Tissue collection[11]	X	X[11]																			
Survival status																					X

T = 240mg nivolumab
F = 480mg nivolumab

[1] CBC with diff and Chemistry panel should be within 14 days of registration; all other screening procedures should take place within 28 days of registration unless specified otherwise.
[2] Includes vital signs (pulse, blood pressure), height and smoking history (baseline only) and weight.
[3] Imaging must include Chest, Abdomen, and Pelvis as well as a bone scan. Scans may be by CT, PET/CT or MRI (per treating investigator's discretion) with contrast unless strictly contraindicated as well as a bone scan; the same modality used at baseline should be used

throughout. Tumor assessment should be done at screening, cycle 2 day 1 (± 1 week) and Day 1 of each cycle (every 12 weeks) thereafter, regardless of dosing schedule until progression or treatment discontinuation whichever occurs later. Tumor assessments will incorporate both RECIST and clinical criteria. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is only required during screening for eligible subjects with symptomatic CNS involvement.
If PD is confirmed at any time, see section 4.4 on how to determine whether patient can be considered for further treatment. If patient continues, scans should be obtained every 12 weeks until PD is confirmed by 2 consecutive scans.

[4] CBC with differential will included WBC, ANC, ALC, Platelets, and Hemoglobin. It will be collected within 14 days of registration, every 14 days during cycles 1 & 2, and prior to each treatment thereafter (day 1, 29, 43, and 57 of each cycle).

[5] Chemistry panel will include glucose, calcium, albumin, ALT, AST, sodium, potassium, total bilirubin, alk phos, and creatinine. It will be collected within 14 days of registration, every 14 days during cycles 1 & 2, and prior to each treatment thereafter (day 1, 29, 43, and 57 of each cycle).

[6] Amylase and lipase will be assessed at screening and Day 1 of each cycle.

[7] TSH will be tested at screening and Day 1 of each cycle. If TSH is abnormal, free T4 should be tested

[8] Serum or urine test for females of child-bearing potential (FOCBP) within 72 hours of registration. FOCBP are also required to have a negative pregnancy test within 24 hours of starting nivolumab and Day 1 of each cycle.

[9] Nivolumab will be administered IV at 240mg over 30 minutes every two weeks in combination with ipilimumab as follows:
Cycle 1, C2D1, & C2D15: 240mg over 30 minutes (-5 / +15 minutes) every 14 days.
Starting with Cycle 2 Day 29: 480mg over 60 minutes (-10 / +15 minutes) every 28 days until PD, intolerability, or withdrawal of consent.

[10] Ipilimumab will be administered IV at 1mg/kg over 90 minutes every six weeks in combination with nivolumab. Dosing will be based on body weight measured every 6 weeks, prior to each ipilimumab infusion. Nivolumab will be given before ipilimumab.

[11] Archival tissue (or fresh tissue if not available) will be collected at baseline for all patients. If the patient agrees, additional tissue may be collected during biopsies performed as standard of care during study participation. Please see separate lab manual for details.

[12] Treatment will start within 14 days of registration, and continue until confirmed disease progression, unacceptable toxicity, or withdrawal of consent.

[13] Study procedures may take place within 24 hours prior to study treatment.

[14] End of Treatment visit will occur 30 days (± 7 days) after stopping nivolumab or combination treatment, or before the patient starts new treatment, whichever occurs first. Adverse events will be recorded for up to 12 weeks after stopping treatment.

[15] Patients will be followed and assessed for adverse events every 4 weeks (±7 days) by routine clinic visit for the first 12 weeks after treatment. Thereafter, patients will be followed (either by routine clinic visit or by phone) every 3 months for up to 2 years while off treatment to document survival and disease progression.

[16] Photographs for disease assessments will be taken by study staff on a study-supplied digital camera. It is preferred that these photos be taken on a white background (wall of patient room) using a ruler measurement when possible. Photographs should not include any identifying characteristics

6.0 ENDPOINT ASSESSMENT

6.1 Definitions

For the purposes of this study, patients should be re-evaluated for response every 12 weeks (±1 week). In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response greater than Stable Disease (SD). Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [46]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

High resolution CT with oral/intravenous contrast or contrast-enhanced MRI is the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 28 days of registration. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is required during screening in all eligible subjects. All known or suspected sites of disease (including CNS if history of CNS metastases) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

6.2 Primary Endpoint

Progression free survival defined as time in months from the date of first study treatment to the date of disease progression or death from any cause, whichever comes first. All patients who receive at least one dose of nivolumab/ipilimumab combination will be included in the primary analyses of PFS. The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment (when disease is measurable and non-measurable).[46]

- Patients with IBC often do not have measurable disease. For example, patients will sometimes have just recurrent skin involvement, pleural effusions, or bone disease. Measurable disease is not a requirement for enrollment on the study.
- For patients who have only non-measurable disease, unequivocal progression or response will be defined after consideration if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD or tumor response for measurable disease. Complete response will be defined as disappearance of non-measurable disease.
- Clinical and radiological assessments will be performed every 8 weeks (+- 7 days) while on treatment and patients will be followed for up to 2 years after completion of treatment.

6.3 Secondary Endpoints

- Overall response rate (ORR, defined as Complete Response (CR) + Partial Response (PR)),and Clinical Benefit Rate (CBR, defined as CR + PR + Stable Disease (SD)) in patients with newly recurrent IBC treated with nivolumab and ipilimumab
- Overall survival defined as time in months from the date of first study treatment to the date of death.
- The number, frequency, and severity of adverse events will be collected from the time of consent until 12 weeks after study treatment to evaluate safety of nivolumab and ipilimumab in patients with IBC. Adverse events will follow National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

6.4 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with nivolumab and or ipilimumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one dose of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Evaluable non-target disease response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one dose of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.5 Disease parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam (such measurements must be clearly documented). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.6 Response Criteria

6.6.1 Evaluation of target lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

6.6.2 Evaluation of Non-Target Lesion

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.6.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Responses will be assessed using CT scans or magnetic resonance imaging according to standard RECIST 1.1 criteria in order to assess disease progression. These criteria will also allow for patients who experience an initial disease flare, and as some patients who will have a delayed response may experience an initial disease flare, we will allow patients to continue receiving nivolumab beyond progression (see section 4.4).

6.6.4 Duration of response

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

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

6.7 Evaluable patients

All patients who receive at least one dose of nivolumab/ipilimumab combination will be evaluable for the secondary endpoints of safety and overall survival (OS). All patients who have at least one on-study scan after baseline will be evaluable for the primary endpoint of PFS, and secondary endpoints of ORR and CBR.

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 Intensity 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 v4.03 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 12 weeks after the last administration of study drug, must be reported upon discovery or occurrence (see section 7.4.3.4 for reporting details). 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 associated with an overdose.
  For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for nivolumab or ipilimumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of nivolumab or ipilimumab. In the event of overdose, nivolumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
  If an adverse event(s) is associated with ("results from") the overdose of a BMS product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
  If a dose of BMS's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."
  All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to BMS Global Safety.
- **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.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others (UPIRSO)

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.

7.3 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 Event 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 Monitoring Committee (DMC) 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/DMC

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 DMC at their next meeting.

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 the FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.4.3.4 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 209-782). 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
Facsimile Number: 609-818-3804

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 (100mg/vial) is a sterile, non-pyrogenic single-use, isotonic aqueous solution formulated at 10mg/mL. Vials must be stored in a secure, limited-access location at 2ºC to 8ºC (36ºF to 46 ºF) 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 preparation can be further diluted with

normal saline or 5% Dextrose 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. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Nivolumab infusion must be completed within 24 hours of preparation. 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 2ºC to 8ºC (36ºF to 46ºF) for no more than 24 hours from the time of infusion preparation.
- Do not freeze

8.1.5 Protocol dose specifics

240mg q2weeks or 480mg q4weeks

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 paticulate matter other than a few translucent-to-white, amorphous particles.

Note: 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 study drug as an IV push or bolus injection.

When the dose is based on patient weight (i.e. mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% sodium chloride injection, USP or 5% dextrose injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g. 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent. “Channel” or tube systems should not be used to transport prepared infusions of nivolumab.

8.1.7 Route of administration for this study

Intravenous infusion. Do not administer as an IV push or bolus injection.

Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter.

At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

8.1.8 Incompatibilities

No incompatibilities between nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed.

8.1.9 Availability & Supply

The supply for this study will be investigational – not commercially available. Supply will be provided by BMS free of charge. Nivolumab will be supplied as 100 mg/vial (10mg/mL) packaged in cartons of 5 or 10 vials. Drug is protocol specific, but not patient specific.

Drug can be ordered using the Drug Request Form provided by BMS. The form is provided as a separate document and should be submitted electronically at least 7 business days for initial order and at least 14 days for re-supply before the expected delivery date. The initial order should be limited to 20 vials. Contact and submission details can be found directly on the Drug Request Form. Deliveries will be made Tuesday through Friday.

8.1.10 Side effects

Immune-related adverse events have been associated with nivolumab is administered intravenously.

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).

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.1.11 Safety and monitoring plan

All participants will be carefully followed for safety. Participants are seen by their study doctor and research nurse before each dose of nivolumab (every 2 weeks). Safety evaluations at this time include a physical exam, vital signs, performance status assessment, and safety laboratory tests. The study team will continuously monitor participants for treatment side effects. Participants are instructed to inform their study doctor right away if they notice or feel anything different so the study doctor can check for side effects. The study doctor may be able to provide treatment for side effects. The study doctor may temporarily hold the study drug to reduce side effects. The study doctor will permanently stop the study drug if side effects are too severe and/or long lasting. All participants will be followed for side effects for 12 weeks from their last dose of nivolumab. Participants with ongoing side effects will continue to be followed until resolution or stabilization of

the side effects. Because it is not known if nivolumab will be effective against anal cancer, to enrollment will stop after 12 participants are treated with nivolumab if none of them have their tumors shrink. Study team conferences will be held monthly or more frequently if needed.

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 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.

8.2 Ipilimumab

8.2.1 Other names

MDX-CTLA-4, MDX-010, Yervoy

8.2.2 Classification and type agent

Human IgG1 Kappa anti-CTLA-4monoclonal antibody

8.2.3 Mode of action

Ipilimumab acts as an immunomodulator by blocking the interaction between of the CTLA-4 receptor and its ligands CD80/CD86. CTLA-4 has been shown augment T-cell proliferation and activation.

8.2.4 Storage and stability

Ipilimumab solution for infusion (50mg and 200mg vials) is a sterile, non-pyrogenic single-use, isotonic aqueous solution formulated at 5mg/mL.
Vials must be stored in a secure, limited-access location at 2ºC to 8ºC (36ºF to 46 ºF) 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 preparation 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. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Ipilimumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours under refrigeration conditions (2ºC to 8ºC) and used within 4 hours for up to 24 hours. Ipilimumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of solution in vials, room temperature storage of prepared solution in the syringe and the duration of drug administration.

8.2.5 Protocol dose specifics

1mg/Kg

8.2.6 Preparation

Ipilimumab 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 paticulate matter other than a few translucent-to-white, amorphous particles.
Note: Mix by gently inverting several times. Do not shake.
Aseptically withdraw the required volume of ipilimumab 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 study drug as an IV push or bolus injection
Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. It is acceptable to add ipilimumab solution from the vials into an appropriate pre-filled bag of diluent.
Ipilimumab infusion concentration must be between 1 mg/mL to 2 mg/mL per package insert. Mix diluted solution by gentle inversion.“Channel” or tube systems should not be used to transport prepared infusions of ipilimumab.

8.2.7 Route of administration for this study

Intravenous infusion. Do not administer using IV push or bolus. Administer through a volumetric pump with a 0.2 to 1.2 micron in-line filter (non pyrogenic and low-protein binding). At the end of the infusion, flush the line with a sufficient quantity of approved diluents.

8.2.8 Incompatibilities

No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab

8.2.9 Availability & Supply

The supply for this study will be investigational – not commercially available. Supply will be provided by BMS free of charge. Ipilimumab will be supplied as 50mg or 200mg/vial (5mg/mL) packaged in cartons of 5 or 10 vials. Drug is protocol specific, but not patient specific.

Drug can be ordered using the Drug Request Form provided by BMS. The form is provided as a separate document and should be submitted electronically at least 7 business days for initial order and at least 14 days for re-supply before the expected delivery date. The initial order should be limited to 20 vials. Contact and submission details can be found directly on the Drug Request Form. Deliveries will be made Tuesday through Friday.

8.2.10 Side effects

Immune-related adverse events have been associated with ipilimumab is administered intravenously.

Below are safety data from 131 patients with metastatic melanoma who received ipilimumab as monotherapy in a phase 3 trial.

Very Frequent – Expected to occur in more than 20% of people (more than 20 out of 100 people):Fatigue (42%), Pruritus (24.4%), Decreased appetite (26.7%) Diarrhea (32.8%), Nausea (35.1%),Constipation (20.6%), Vomiting (23.7%),

Frequent - Expected to occur in 10% to 20% of people (10 to 20 out of 100 people): Abdominal pain (15.3%), pyrexia(12.2%), headache (14.5%), Cough (16%), dyspnea (14.5%), anemia (11.5%), rash (19.1)

Not Frequent – Expected to occur in less than 10% of people (less than 10 out of 100 people): vitiligo, colitis, hypothyroidism, hypopituitarism and adrenal insufficiency, increased aspartate aminotransferase and alanine aminotransferase

Deaths thought to be related to ipilimumab when given alone were reported in approximately 3 % of subjects treated (approximately 4 out 131 people).

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.2.11 Safety and monitoring plan

All participants will be carefully followed for safety. Participants are seen by their study team before each dose of ipilimumab (every 2 weeks). Safety evaluations at this time include a physical exam, vital signs, performance status assessment, and safety laboratory tests. The study team will continuously monitor participants for treatment side effects. Participants are instructed to inform their study doctor right away if they notice or feel anything different so the study doctor can check for side effects. The study doctor may be able to provide treatment for side effects. The study doctor may temporarily hold the study drug to reduce side effects. The study doctor will permanently stop the study drug if side effects are too severe and/or long lasting. All participants will be followed for side effects for 12 weeks from their last dose of ipilimumab. Participants with ongoing side effects will continue to be followed until resolution or stabilization of the side effects. Because it is not known if ipilimumab will be effective against anal cancer, to enrollment will stop after 12 participants are treated with ipilimumab if none of them have their tumors shrink. Study team conferences will be held monthly or more frequently if needed.

8.2.12 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 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.

9.0 CORRELATIVES/SPECIAL STUDIES

The Win trial correlative studies will identify genomic alterations that mechanistically contribute to oncogenic signaling in IBC. The information from the correlative studies will provide genetic and genomic information that may be relevant for the development of targeted and combination therapeutic strategies. The correlative studies will use next-generation sequencing (NGS) technologies to characterize tumor genetics and to identify gene expression profiles that may contribute to IBC. The genetic analysis will be used to study the relationship between mutation frequency and immune response. The expression analysis will focus on genes that are related to immune cell signaling, with the goal of identifying an immune expression signature that may be useful in identifying potential immunotherapy responders.

The archival diagnostic tissue biopsy performed as part of the standard of care approach to recurring breast cancer will be obtained for all patients; if no tissue is available, patients will need to undergo a biopsy to provide fresh tumor tissue. The sample will be sent for NGS, and evaluation of iScore (baseline assessment). The same specimen will be assessed for immune

infiltrates and PDL-1. Details on sample collection, shipping, and processing are available in a separate lab manual.

Repeated tissue biopsy samples will be performed optionally at time of disease progression and partial or complete response and only performed when clinically indicated as part of standard of care approach. When performed, specimens will be sent for NGS and iScore and PDL-1 staining. See separate lab manual for details on processing and shipping of samples.

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. 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. William Gradishar 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 is a single open label phase II clinical trial; “window of opportunity” study of nivolumab in association with ipilimumab in patients with newly recurrent HER2 negative IBC. We believe that a *Window of Opportunity trial* design is the more appropriate for this population inasmuch as it allows to assess the efficacy of immunotherapy in IBC when the tumor is still unperturbed by other systemic treatments routinely used the metastatic setting.[48]

10.1.1 Primary:

To determine progression free survival (PFS) in patients with newly recurrent HER2 negative IBC treated with nivolumab and ipilimumab

10.1.2 Secondary:

- To assess the overall response rate (ORR, defined as Complete Response (CR) + Partial Response (PR)),and Clinical Benefit Rate (CBR, defined as CR + PR + Stable Disease (SD)) in patients with newly recurrent IBC treated with nivolumab and ipilimumab
- To assess the safety and tolerability of nivolumab and ipilimumab in patients with newly recurred IBC
- To assess overall survival (OS).

10.1.3 Exploratory endpoints:

- To assess the predictive value of baseline iSCORE and PDL-1 expression using archival tissue samples as well as any standard of care tissue obtained during study treatment.

10.2 Sample Size and Accrual

We previously identified 44 patients who were included in a retrospective study of the prognostic significance of HER2 status in IBC. These patients had both HER2 negative and HER2 positive disease, developed metastases, and experienced a disease progression. The median time from the first progression of their metastatic disease to the second progression event or death was approximately 3 months. These patients will be considered our historical control group.

Nivolumab ipilimumab combination will be considered of interest for further study if the median PFS time is increased to at least 6 months. We will test the null hypothesis that median PFS is at most 3 months versus the alternative that it is at least 6 months. The null corresponds to 25% PFS at 6 months under the exponential distribution of PFS versus an alternative 6 month PFS rate of 50%. The null corresponds to 50% PFS at 3 months and the alternative corresponds to 70.71% PFS at 3 months under the same conditions.

We will initially recruit and treat 15 patients. If 7 or fewer initial cohort patients are progression free at 3 months the study will be terminated for lack of efficacy. If at least 8/15 are progression-free at 3 months then we will recruit an additional 14 patients for a total of 29.

The patients free of progression at 3 months from the initial cohort will remain on study until either progression or 6 months evaluation. Second cohort patients will be evaluated at 6 months only. If at least 11/29 patients are progression free at 6 months the null hypothesis will be rejected.

The chance of early study termination (3 months follow up with 15 patients) is 50% under the null and 4.4% under the alternative. Study power is 90% with overall type I error of 7%. The design follows: Early stopping designs based on progression-free survival at an early time point in the initial cohort.[49]

10.3 Data Analyses Plans

Response rates and 95% confidence intervals will be calculated using exact binomial probability distributions. Progression-free survival and overall survival will be analyzed using Kaplan-Meier curves. Adverse events will be summarized descriptively using frequencies and percentages. Statistics will be given on type, severity, frequency and attribution of adverse events. Sample size considerations are described above.

An intention to treat analysis will be done. In a single group Phase II study, intention to treat means that all patients who are evaluated and registered for the study are followed and analyzed regardless of (a) whether they were subsequently found to be protocol ineligible and (b) the amount of study treatment (nivolumab/ipilimumab) they received. To calculate progression-free and overall survival in patients who received nivolumab/ipilimumab, times will be taken from the time of study registration. This definition parallels the definition of intention to treat in randomized clinical trials.

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. 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. Training on eCRF completion will be provided at the time of site activation.

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)

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). Generally, all data are due at the end of each cycle.

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 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.

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 NOTIS 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.

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).

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 Promptly Reportable Non-Compliance (PRNC) 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

This section should be removed if the trial is not rated as a high intensity trial.
All potential publications and/or data for potential publications (e.g. manuscripts, articles, data, text, digrams, abstracts, posters, charts, slides, picture, or clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. For trials that require high intensity monitoring, the assigned QAM will prepare a preliminary data summary (to be approved by the DMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

NU shall provide BMS with a copy of each Publication at the earliest practicable time, but in any event not less than thirty (30) days prior to its submission to a journal, publisher or meeting or fifteen (15) days prior to any public disclosure of any manuscript or other public disclosure (e.g., presentations). To the extent applicable, BMS personnel shall be acknowledged (including authorship where applicable) in accordance with customary scientific practice.

REFERENCES

1. Factsheets SCS. Breast Cancer. National Cancer Institute. Bethesda, MD. 2015.
2. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. *J Natl Cancer Inst.* 2005;97(13):966-975.
3. Haagensen CD. Diseases of the female breast. *Trans N Engl Obstet Gynecol Soc.* 1956;10:141-156.
4. Walshe JM, Swain SM. Clinical aspects of inflammatory breast cancer. *Breast Dis.* 2005;22:35-44.
5. Jaiyesimi IA, Buzdar AU, Hortobagyi G. Inflammatory breast cancer: a review. *J Clin Oncol.* 1992;10(6):1014-1024.
6. Panades M, Olivotto IA, Speers CH, et al. Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. *J Clin Oncol.* 2005;23(9):1941-1950.
7. Guidelines N. NCCN Clinical Practical Guidelines in Oncology (NCCN Guidelines) Breast Cancer Version 3.215.
8. Network NCC. Breast Cancer Version 3.2015. 2015.
9. Veyret C, Levy C, Chollet P, et al. Inflammatory breast cancer outcome with epirubicin-based induction and maintenance chemotherapy: ten-year results from the French Adjuvant Study Group GETIS 02 Trial. *Cancer.* 2006;107(11):2535-2544.
10. Cristofanilli M, Valero V, Buzdar AU, et al. Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. *Cancer.* 2007;110(7):1436-1444.
11. Matro JM, Li T, Cristofanilli M, et al. Inflammatory breast cancer management in the national comprehensive cancer network: the disease, recurrence pattern, and outcome. *Clin Breast Cancer.* 2015;15(1):1-7.
12. Masuda H, Brewer TM, Liu DD, et al. Long-term treatment efficacy in primary inflammatory breast cancer by hormonal receptor- and HER2-defined subtypes. *Ann Oncol.* 2014;25(2):384-391.
13. Paradiso A, Tommasi S, Brandi M, et al. Cell kinetics and hormonal receptor status in inflammatory breast carcinoma. Comparison with locally advanced disease. *Cancer.* 1989;64(9):1922-1927.
14. Nguyen DM, Sam K, Tsimelzon A, et al. Molecular heterogeneity of inflammatory breast cancer: a hyperproliferative phenotype. *Clin Cancer Res.* 2006;12(17):5047-5054.
15. Guerin M, Sheng ZM, Andrieu N, Riou G. Strong association between c-myb and oestrogen-receptor expression in human breast cancer. *Oncogene.* 1990;5(1):131-135.
16. Li J, Gonzalez-Angulo AM, Allen PK, et al. Triple-negative subtype predicts poor overall survival and high locoregional relapse in inflammatory breast cancer. *Oncologist.* 2011;16(12):1675-1683.
17. Gogas H, Pectasides D, Kostopoulos I, et al. Paclitaxel and carboplatin as neoadjuvant chemotherapy in patients with locally advanced breast cancer: A phase II Trial of the Hellenic Cooperative Oncology Group. *Clin Breast Cancer.* 2010;10(3):230-237.
18. Kleer CG, van Golen KL, Merajver SD. Molecular biology of breast cancer metastasis. Inflammatory breast cancer: clinical syndrome and molecular determinants. *Breast Cancer Res.* 2000;2(6):423-429.
19. Turpin E, Bieche I, Bertheau P, et al. Increased incidence of ERBB2 overexpression and TP53 mutation in inflammatory breast cancer. *Oncogene.* 2002;21(49):7593-7597.
20. Gonzalez-Angulo AM, Sneige N, Buzdar AU, et al. p53 expression as a prognostic marker in inflammatory breast cancer. *Clin Cancer Res.* 2004;10(18 Pt 1):6215-6221.
21. Van Laere SJ, Van der Auwera I, Van den Eynden GG, et al. Nuclear factor-kappaB signature of inflammatory breast cancer by cDNA microarray validated by quantitative real-time reverse transcription-PCR, immunohistochemistry, and nuclear factor-kappaB DNA-binding. *Clin Cancer Res.* 2006;12(11 Pt 1):3249-3256.
22. van Golen KL, Wu ZF, Qiao XT, Bao L, Merajver SD. RhoC GTPase overexpression modulates induction of angiogenic factors in breast cells. *Neoplasia.* 2000;2(5):418-425.
23. Kleer CG, Zhang Y, Pan Q, et al. WISP3 is a novel tumor suppressor gene of inflammatory breast cancer. *Oncogene.* 2002;21(20):3172-3180.
24. Norma A Palma SMA, Kai Wang, Juliann Chmeleiki, Gary Palmer, Deborah Morosini, Jeffrey S Ross, Vincent A Miller, Phil J Stephens, Massimo Cristofannilli. Genomic profiling by FoundationOne® analysis of inflammatory breast cancer cases reveals a high frequency of

clinically relevant genomic alterations (GA) [abstract]. *In: Proceedings of the Thirty-Seventh Annual CTRC-AACR San Antonio Breast Cancer Symposium: 2014 Dec 9-13; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res.*75(9 Suppl).

25. Diarmuid Moran CAH, Kakuturu Rao, Patricia Bacon-Trusk, Karen Pry, Victor Velculescu, Massimo Cristofanilli, Sarah S. Bacus. . Genomic analysis identifies drug targetable pathways and predicts immune infiltration in inflammatory breast cancer tumors. *In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18-22; Philadelphia, PA. Philadelphia (PA): AACR;.* 2015.
26. Champiat S, Ferte C, Lebel-Binay S, Eggermont A, Soria JC. Exomics and immunogenics: Bridging mutational load and immune checkpoints efficacy. *Oncoimmunology.* 2014;3(1):e27817.
27. Rosenberg SA. Decade in review-cancer immunotherapy: entering the mainstream of cancer treatment. *Nat Rev Clin Oncol.* 2014;11(11):630-632.
28. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med.* 2015;372(26):2509-2520.
29. Nanda R CL, Dees EC, et al. A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer. *San Antonio Breast Conference.*
30. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med.* 2015;373(2):123-135.
31. McDermott DF, Drake CG, Sznol M, et al. Survival, Durable Response, and Long-Term Safety in Patients With Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab. *J Clin Oncol.* 2015;33(18):2013-2020.
32. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med.* 2015;372(21):2006-2017.
33. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* 2013;369(2):122-133.
34. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science.* 1996;271(5256):1734-1736.
35. van Elsas A, Sutmuller RP, Hurwitz AA, et al. Elucidating the autoimmune and antitumor effector mechanisms of a treatment based on cytotoxic T lymphocyte antigen-4 blockade in combination with a B16 melanoma vaccine: comparison of prophylaxis and therapy. *J Exp Med.* 2001;194(4):481-489.
36. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711-723.
37. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med.* 2011;364(26):2517-2526.
38. Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci U S A.* 2010;107(9):4275-4280.
39. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 2015;373(1):23-34.
40. Gettinger SN, Horn L, Gandhi L, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol.* 2015;33(18):2004-2012.
41. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. *J Clin Oncol.* 2015;33(13):1430-1437.
42. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2015;373(19):1803-1813.
43. Naiyer Rizvi SNG, Jonathan Goldman, Matthew D. Hellmann, Laura Q. Chow, Rosalyn Juergens, Hossein Borghaei, Julie Brahmer, Yun Shen, Christopher Harbison, Faith Nathan, Neal E. Ready, Scott J. Antonia. Safety and Efficacy of First-line Nivolumab (Anti-programemed Death-1 [PD-1]) and Ipilimumab in Non-small cell lung cancer (NSCLC). *16th World conference on Lung cancer September 6-0,2015. Denver Colorado USA.* 2015.
44. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26):2443-2454.
45. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature.* 2014;515(7528):563-567.

46. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
47. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol.* 2013;31(31):3997-4013.
48. Glimelius B, Lahn M. Window-of-opportunity trials to evaluate clinical activity of new molecular entities in oncology. *Ann Oncol.* 2011;22(8):1717-1725.
49. S. Litwin Y-NWaGH. Early stopping designs based on progression-free survival at an early time point in the initial cohort. *Statistics in Medicine.* 2007;26:4400-4415.

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. 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

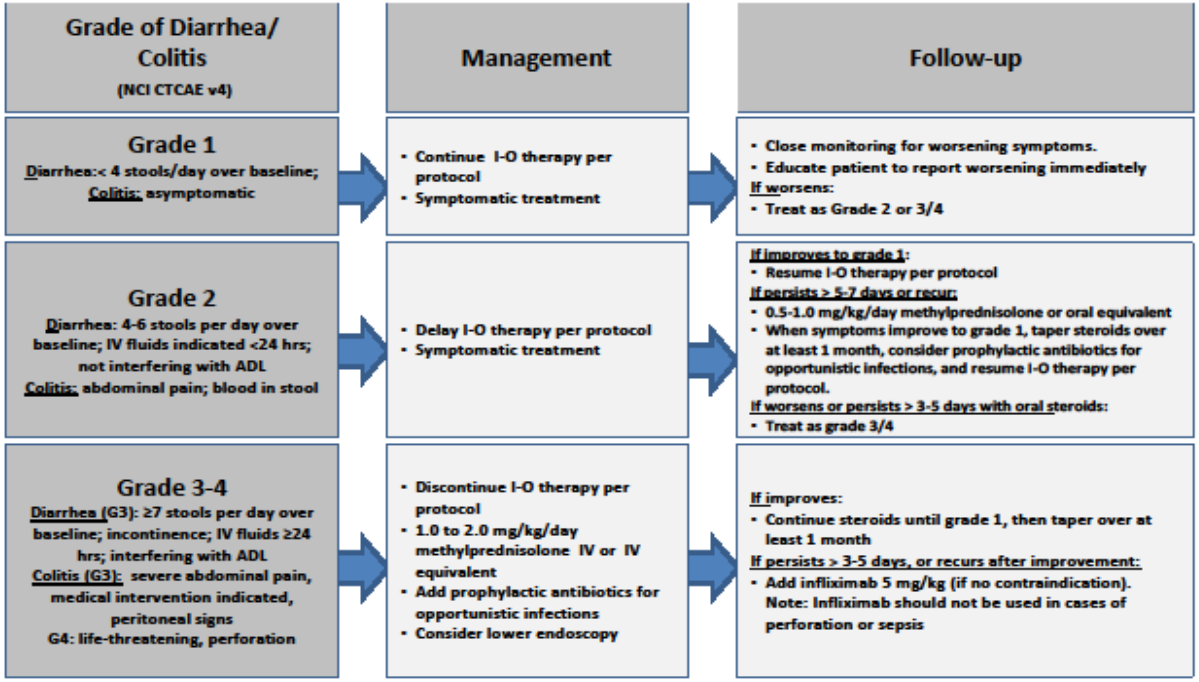
a) Diaphragm with spermicide
b) Cervical cap with spermicide
c) Vaginal sponge
d) Male Condom without spermicide*
e) Progestin only pills by FOCBP subject or male subject's FOCBP partner
f) Female Condom*

*A male and female condom must not be used together

Appendix D – Immune-Mediated Adverse Event Management
Recommended management algorithms for suspected nivolumab related endocrinopathy, gastrointestinal toxicity, hepatotoxicity, neurologic toxicity, pulmonary toxicity, renal toxicity and skin toxicity

GI Adverse Event Management Algorithm

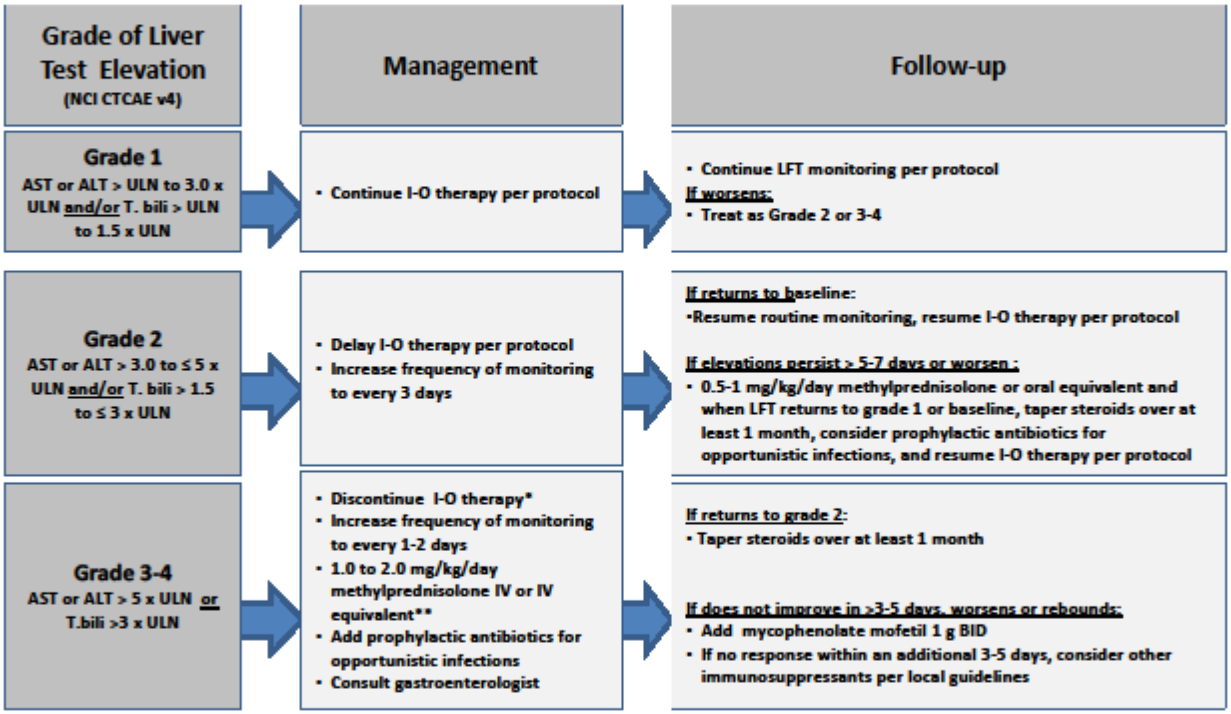
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Hepatic Adverse Event Management Algorithm

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



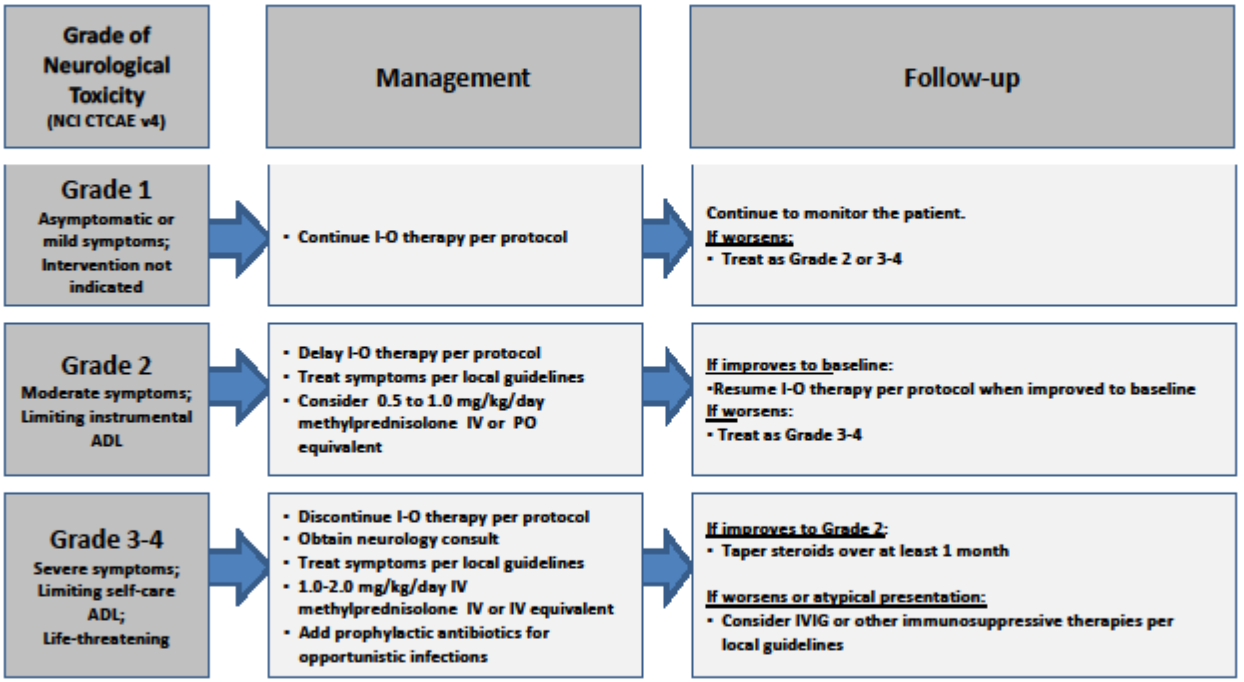
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

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



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

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

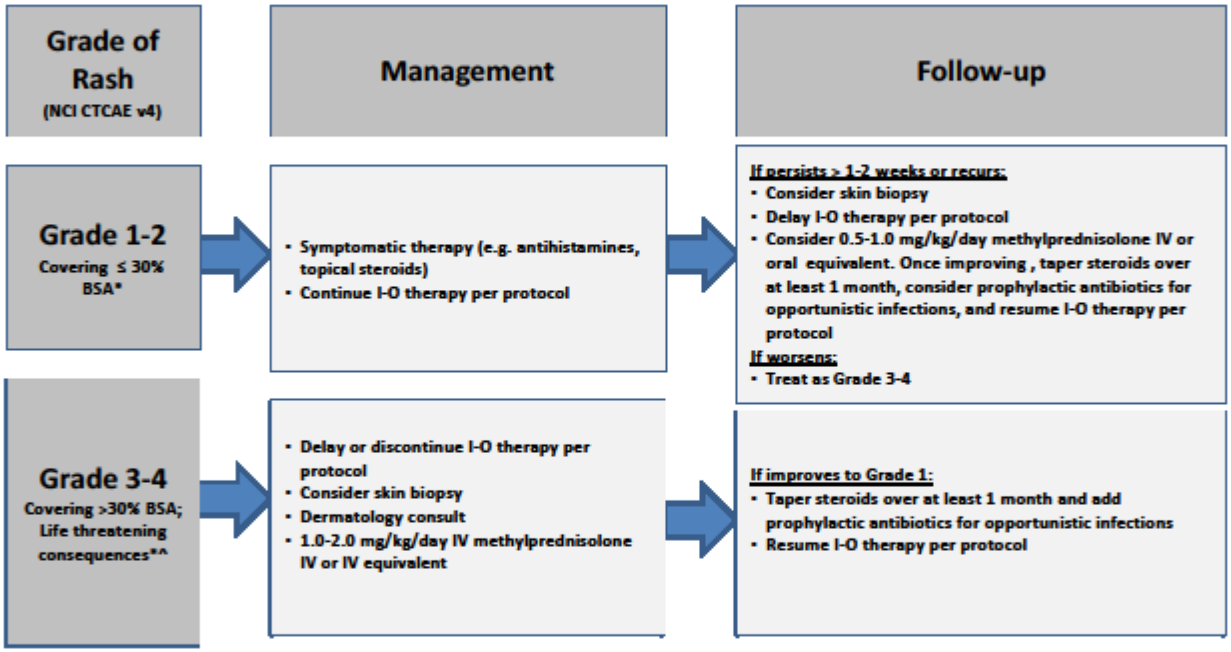
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

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

Amendment 1 – September 28, 2016 *Approved by Scientific Review Committee October 31, 2016*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover Page	Lists "n/a" for IND number/holder	Adds "Exempt" for IND number/holder Adds Kalliopi Siziopikou as sub-I	Clarification Administrative; Kalliopi is involved in relevant pathology
Study Schema; Study Summary; 4.1 (Overview); 4.2 (Treatment Administration); 4.2.1 (Nivolumab); 5.0 (Study Procedures); 6.1 (Definitions); 8.1.5 (Protocol dose specifics)	Nivolumab was to be administered at 240mg every 2 weeks throughout the study 1 cycle = 2 weeks Scans every 8 weeks for the first 13 months and 12 weeks thereafter	Nivolumab will now be administered at 240mg every 2 weeks for the first 16 weeks and 480mg every 4 weeks thereafter (starting with C2D29) 1 cycle = 12 weeks Scans every 12 weeks throughout study	To align with new BMS dosing strategy for nivolumab which is under investigation
Eligibility Criteria (3.1.9, 3.2.1, 3.2.3, 3.2.8, 3.2.14)	n/a	Replaces ambiguous wording with ≤ or ≥ symbols for windows Replaces # weeks with # days for windows Adds "prior to registration" to unclear windows	Simplifications for clarity
4.2.2 (Ipilimumab)	"Subjects may be dosed no less than 12 days from the previous dose"	Removes statement	Statement was invalid; dosing takes place every 6 weeks, and PI does not feel that a minimum window between doses is necessary
4.3.1 (Dose Delays: Ipilimumab and/or Nivolumab)	"Both drugs can be held for a maximum of **28 days**. If the patient is receiving clinical benefit in the opinion of the investigator, this period can be extended up to 56 days with approval from the DMC"	"Both drugs can be held for a maximum of **56 days."** Removes allowable extension	After 16 weeks, nivolumab doses are always given 28 days apart, so a dose hold will allow for another 28 days.
4.3.1 (Dose Delays: Ipillimumab and/or Nivolumab); Appendix D	n/a	Adds management algorithms for immune-mediated adverse events.	Algorithms were provided by BMS as they were developed specifically for immune-oncology drugs
5.0 (Study Procedures)	#2: Listed respirations as part of vitals #4 & 5: CBC & Chem to be collected on Day 1 of each cycle	#2: Removes respirations #4 & 5: CBC & Chem to be collected before each dose (Day 1, 29, 43, and 57 after Cycle 2)	To avoid deviations; respiration are not clinically relevant To align with new treatment schedule
7.2.3 (SAEs)	SAE's were to be reported through 30 days after the last study drug	SAE's are to be reported for 12 weeks after the last study drug	Corrects discrepancy

		Adds reference to section 7.4.3.4 for reporting instructions	
7.4.3.4 (Reporting to BMS)	n/a n/a Listed incorrect reporting email for BMS	Adds that SAE's are to be reported regardless of attribution to study drug and including death by any cause BMS study number should be included in the SAE report Corrects BMS email	Clarification Clarification Discrepancy
8.1.11 & 8.2.11 (Safety and Monitoring Plan)	"All participants will be followed for side effects for **100 days** from their last dose of nivolumab"	"All participants will be followed for side effects for **12 weeks** from their last dose of nivolumab"	Corrects discrepancy
Amendment 2 – November 22, 2016 *Approved by Scientific Review Committee: December 1, 2016*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Title Page	Lists excess sub-Investigators	Removes the following sub-investigators: Sunandana Chandra Maria Matsangou Jason Kaplan Aparna Kalyan Mark Agulnik	Administrative; sub-I's no longer need to include all investigators at the Developmental Therapeutics Program. Current listing only includes those who will work with breast cancer patients
4.4 (Treatment with ipilimumab and/or nivolumab beyond progression)	"Patients must provide separate consent to continue treatment despite radiological scans indicating PD. Separate consent must be obtained when progression is first detected."	Removes this statement to require consent beyond progression.	A consent is not available for patients to sign in this situation. Aligns with other protocols, which do not require consent to treat beyond progression.
5.0 (Study Procedures)	#3: Scans were to take place every 4 cycles for the first 13 months and every 6 cycles thereafter. Amylase and lipase will be assessed at screening every 2 cycles starting with Cycle 2.	#3: Scans will take place day 1 of each cycle (every 12 weeks) Amylase and lipase will be assessed at screening and Day 1 of each.	#3: Correction for discrepancy; protocol previously included 2-week cycles. Cycle length and scan frequency has since been changed, and the update was not changed in this footnote. #6: Correction for discrepancy; protocol previously included 2-week cycles. Cycle length has since been changed, and the update was not changed in this footnote.

Amendment 3 – May 30, 2017 *Approved by Scientific Review Committee: April 25, 2017 and June 28, 2017*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Cover Page; 3.0 (Patient Eligibility); 3.2.5 (Exclusion Criteria); 9.4 (Specimen Banking)	Listed Ricardo Costa as the study PI	Removes Ricardo Costa and adds William Gradishar as PI	Administrative faculty transition; Dr. Costa's last day at Northwestern is 4/30/17
Cover Page	Listed Kalliopi Siziopikou as a sub-Investigator	Removes Kalliopi Siziopikou as a sub-Investigator and lists her as a "collaborator"	Administrative
List of Abbreviations; 1.4 (Exploratory Studies); 2.3.2 (Exploratory Objectives & Endpoints); 5.0 (Study Procedures #11); 9.0 (Correlatives/ Special Studies); 9.0 (Correlatives/ Special Studies); 10.1.3 (Exploratory Endpoints)	Listed objective of analyzing ctDNA with Guardant Health Laboratory performing the ctDNA analysis	Removes references to Guardant Health Laboratory and all correlative blood samples	Logistical issues with Guardant Health Laboratories
3.0 (Patient Eligibility)	Specified that the study would be conducted at Northwestern Medicine Developmental Therapeutics Institute (NMDTI)	Removes reference to NMDTI, stating generally that the study will take place at Northwestern	Administrative; it is possible that patients will be seen at locations other than NMDTI
3.1.4 (Inclusion Criteria); 3.2.6 (Exclusion Criteria)	Leptomeningeal disease was listed as non-measurable	Removes leptomeningeal disease as an example of non-measurable disease and adds it as an autoimmune disease, thus excluding leptomeningeal disease	Per PI, leptomeningeal disease should be excluded and is not an example of non-measurable disease
3.2.5 (Exclusion Criteria)	Included a reference to cancer.gov	Removes cancer.gov reference	Inaccurate reference
3.2.11 (Exclusion Criteria)	Prior cancer was excluded "unless patient has been disease free for 3 years"	Changes language to state more clearly that cancers are only excluded if within 3 years	Clarification
4.2.1 (Nivolumab); 5.0 (Study Procedures #9)	Infusion window for nivolumab was ±5 minutes	Updates infusion windows as follows: 30-minute (-5 / +15 minutes) 60-minutes (-10 / +15 minutes)	To align with updated drug information per BMS
4.2.2 (Ipilimumab); 5.0 (Study Procedures #9)	n/a	Adds an infusion window for ipilimumab (-5 / +15 minutes) and states that dosing will be based on actual body weight on the day of the infusion	Clarifications

4.3.2 (Treatment Discontinuation: Ipilimumab and/or nivolumab)	"Upon resolution of the adverse event, the unrelated study drug may be continued"	Removes statement	Statement is irrelevant and misleading; there was no mention in this section of delaying the unrelated study drug
5.0 (Study Procedures)	n/a	Adds visit window of ±3 days	Clarification
	n/a	Adds a legend to identify "T" as 240mg nivolumab and "F" as 480mg nivolumab	Clarification
	#2: n/a	#2: Adds smoking history as part of the physical exam at baseline	PI would like to collect smoking history as data
	n/a	Adds an activity for "Lesion Photos" and footnote 16 to specify that photos will be taken by study staff on a study-supplied digital camera, preferably on a white background	Photos are part of standard IBC lesion measurement, and a study-supplied camera will allow for consistency in study measurements.
6.6.4 (Duration of Response)	Contained a run-on sentence to describe the timeframe of a CR	Removes language: "category when no lesions can be measured is not advised"	Language included inadvertently
9.0 (Correlative Studies)	Samples for NGS and iScore were to be sent to American Molecular Laboratories (AML)	Removes AML references; samples will now be sent to GoPath Laboratories	Administrative – change in outside collaboration
Amendment 4– November 1, 2017 *IRB-Requested Changes: October 31, 2017*			
Section(s) Affected	***Prior Version***	***Changes***	***Rationale***
8.1.4 (Storage and Stability)	Nivolumab could be stored at room temperature for a maximum of 4 hours	Nivolumab can be stored at room temperature for a maximum of 8 hours	Updated to align with new IB, version 16, per IRB request
8.1.6 (Preparation)	Included dilution instructions with concentrations only relevant to weight-based dosing	Now includes dilution instructions and concentrations for both weight-based and flat dosing.	Updated to align with new IB, version 16, per IRB request. Flat dosing is a new strategy available for investigational use of nivolumab.
Amendment 5 – March 1st, 2018 *Approved by Scientific Review Committee:*			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Cover Page	Sarika Jain and Cesar Santa-Maria were listed as study sub-I's	Removes Sarika Jain and Cesar Santa-Maria as sub-I's	Administrative due to faculty leaving institution
3.2 (Exclusion Criteria)	Numbering for exclusion criteria skipped #3.2.9	Renumbers exclusion criteria to correct numbering error	To correct typographical error
9.0 (Correlative/ Special Studies)	Specified locations for sample analysis, including GoPath Laboratories.	Removes specific locations of sample analysis instead referring to separate lab manual	Protocol language did not align with the plan to have IHC for PD-L1 analysis performed externally. For

			simplicity, the protocol will remain vague, and the lab manual will specify exactly where to send each sample.
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.