Phase II trial of nivolumab with chemotherapy as neoadjuvant treatment in inflammatory breast cancer (IBC)

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Funding Sponsor: Bristol-Myers Squibb, Inc

Study Product: Nivolumab (Opdivo®)

Protocol Number: CA209-8NL

IND Number: 141788

Study Number: **s17-00890**

ClinicalTrials.gov Identifier: NCT03742986

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ClinicalTrials.gov Number: NCT03742986

Initial version: BMS 7/13/2018
Protocol Development & Progress Monitoring Unit / Clinical Trials Office 10/4/2018
FDA 11/28/2018
PRMC 1/4/2019

Amended: 06/11/2019
Amended: 2/4/2020
Amended: 8/4/2020
Amended: 10/1/20

PROTOCOL APPROVAL SIGNATURES

Protocol Title: PHASE II TRIAL OF NIVOLUMAB WITH CHEMOTHERAPY AS NEOADJUVANT TREATMENT IN INFLAMMATORY BREAST CANCER (IBC)

Protocol Number: s17-00890

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and applicable regulatory requirements.

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Abbreviations

AC	Doxorubicin and cyclophosphamide
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALN	Axillary lymph nodes
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AUC	Area under the curve
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BC360	Breast Cancer 360 Panel
BMS	Bristol-Myers Squibb
BOR	Best overall response
C	Clinical
CAP	College of American Pathologists
Cavgss	Time averaged steady state concentration
CBRD	Center for Biospecimen Research and Development
CHF	Congestive heart failure
cHL	classical Hodgkin Lymphoma
CI	Confidence interval
CL	Clearance
CLss	Steady state clearance
Cmaxss	Maximum plasma concentration
CMF	Cyclophosphamide, methotrexate, fluorouracil
Cmin	Minimum serum concentration
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
CV	Coefficient of variation
DFS	Disease-free survival
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic Acid
DSMC	Data and Safety Monitoring Committee
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EC	Epirubicin and cyclophosphamide
EC	Ethics Committee
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EKG	Electrocardiogram
ER	Estrogen receptor
FAC	5-fluorouracil, doxorubicin, and cyclophosphamide
FEC	5-fluorouracil, epirubicin, and cyclophosphamide
FDA	United States Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FISH	Fluorescence in situ hybridization

G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HR	Hormone receptor
IB	Investigator's Brochure
IBC	Inflammatory Breast Cancer
ICF	Informed consent form
IFN	Interferon
IHC	Immunohistochemistry
INR	Internationalized Normalized Ratio
IP	Investigational product
irAESI	immune related adverse events of special interest
IRB	Institutional Review Board
IRFI	Invasive recurrence-free survival
IV	Intravenous
Kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LFT	Liver function test
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MDACC	MD Anderson Cancer Center
mcL	Microliter
Mg	Milligram
MP	Multiplexing
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MUGA	Multigated acquisition
N	Number
NCI	National Cancer Institute
NCT	ClinicalTrials.gov registry number
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
NYULH	NYU Langone Health
ORR	Overall response rate
OS	Overall survival
PCC	NYU Perlmutter Cancer Center
pCR	Pathologic complete response
PCR	Polymerase chain reaction
PD	Progression of disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1
PD-L2	Programmed cell death-ligand 2
PET	Positron Emission Tomography
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic
PPK	Population pharmacokinetic (s)
PR	Partial response
PR	Progesterone receptor

PS	Performance status
PT	Prothrombin Time
Q2W	Every two weeks
Q3W	Every three weeks
Q4W	Every four weeks
QA	Quality assurance
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	QT interval corrected for heart rate
RCC	Clear-cell renal cell carcinoma
SAE	Serious adverse event
SD	Stable disease
T	Tumor
TBD	To be determined
T-DM1	Ado-trastuzumab emtansine
TFT	Thyroid function test
TIL	Tumor infiltrating lymphocytes
TMB	Tumor mutation burden
TNBC	Triple negative breast cancer
TTE	Transthoracic echocardiogram
UC	Urothelial carcinoma
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VP	Vincristine and prednisone
Vss	Volume of distribution at steady state

Study Summary

Title	Phase II trial of nivolumab with chemotherapy as neoadjuvant treatment in inflammatory breast cancer (IBC)
Brief Summary	Study of efficacy of nivolumab with neoadjuvant chemotherapy in patients with IBC
Protocol Number	CA209-8NL
Study Number	S17-00890
Phase	Phase II
Methodology	Multi-center open label, phase II study
Study Duration	6 years
Participant Duration	Up to 24 months
Study Center(s)	Multi-center: NYU Perlmutter Cancer Center, Bellevue Hospital and Indiana University
Objectives	**Primary Objective** • To determine whether the addition of nivolumab to chemotherapy improves pathologic complete response (pCR) in the breast and post-therapy lymph nodes evaluated histologically (ypT0/Tis ypN0) in patients with inflammatory breast cancer (IBC). **Secondary Objectives** • To evaluate the safety and tolerability of the combination of nivolumab with neoadjuvant chemotherapy in IBC. • To evaluate the invasive recurrence-free interval (IRFI) [time frame: up to 24 months after study entry]. **Correlative Studies** • To explore predictive markers of response/sensitivity as well as markers of resistance to therapy. • To assess the frequency of mutational and neoantigen load and to explore mutational and neoantigen load as predictive markers of response. • To assess changes in expression levels of biomarkers or biomarker panels before, during, and after treatment.
Number of Subjects	52
Diagnosis and Main Inclusion Criteria	Patients ≥18 years with newly diagnosed inflammatory breast cancer without distant metastases and have not received prior chemotherapy or immunotherapy. All breast cancer subtypes are allowed: ❖ Triple negative breast cancer (TNBC) ❖ Hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative ❖ HR-positive or HR-negative and HER2-positive

Treatment Product, Dose, Route	**<u>Cohort 1: TNBC or HR-positive/HER2-negative</u>:** (n=26) 1. Cycle 1-4, 21 day cycle • Nivolumab 360 mg IV on Day 1 x 4 cycles and Paclitaxel 80 mg/m^2 IV on Day 1, 8, and 15 x 4 cycles, followed by 2. Cycle 5-8, 14 day cycle • Doxorubicin 60 mg/m^2 IV on Day 1 x 4 cycles and Cyclophosphamide 600 mg/m^2 IV on Day 1 x 4 cycles **<u>Cohort 2: HR-positive/HR-negative and HER2-positive</u>**: (n=26) 1. Cycle 1-4, 21 day cycle • Nivolumab 360 mg IV on Day 1 x 4 cycles, + Docetaxel* 75 mg/m^2 IV on Day 1 x 4 cycles, + Trastuzumab** 8 mg/kg IV on Day 1 of Cycle 1 and then 6 mg/kg IV on Day 1 of Cycle 2-4, + Pertuzumab 840 mg IV on Day 1 of Cycle 1 and then 420 mg IV on Day 1 of Cycle 2-4, followed by 2. Cycle 5-8, 14 day cycle • Doxorubicin 60 mg/m^2 IV on Day 1 x 4 cycles and Cyclophosphamide 600 mg/m^2 IV on Day 1 x 4 cycles *Paclitaxel 80 mg/m^2 IV weekly x 12 (Cycle 1-4) may be substituted **Trastuzumab biosimilar may be used
Statistical Analysis	Summary statistics (percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. Sequential boundaries will be used to monitor dose-limiting toxicity rate. There will be an interim safety analysis in Cohort 2. Monitoring for toxicity will follow a Bayesian-based rule for the probability that the rate of DLT exceeds a maximal tolerated level of 30%. We will assume a Beta(1,2) prior, which is prior information equivalent to one DLT observed in three treated patients. The association between biomarkers and best overall response (responder versus non-responder primary) will be described by response rate in subgroups, and assessed using the mid-p adjustment to Fisher's exact test. The association between biomarkers and response will be described by graphical summaries and assessed using a two-sample t-test with transformation as needed.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with United States government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

1.1.1 Inflammatory Breast Cancer (IBC) and Current Therapies

Inflammatory breast cancer (IBC) is the most aggressive form of breast cancer, and the incidence in the United States ranges from 1 to 5%[1]. IBC is a clinical presentation that is characterized by diffuse erythema, rapid enlargement of the breast, and a characteristic peau d'orange appearance of the skin[2]. Pathologically, tumor emboli are often present in dermal lymphatics of the involved skin, however dermal lymphatic involvement itself is not required for a diagnosis of IBC. IBC is characterized by younger age of onset, rapid disease progression, local and distant metastases, and worse overall survival (OS) when compared to non-IBC. The prognosis remains poor, with a 5-year OS of approximately 50%[3], despite multimodality treatment. The median OS duration of patients with IBC compared to those with non-IBC tumors for stage III disease is 4.75 years versus 13.40 years,[4] and for stage IV disease, it is 2.27 years versus 3.40 years[5]. IBC is usually hormone receptor (HR)-negative and is more frequently human epidermal growth factor receptor 2 (HER2)-positive compared to the more common ductal breast cancer. Gene expression profiling studies of IBC have shown a greater frequency of basal and HER2 overexpression.

The multidisciplinary approach to treatment of IBC without distant metastases involves neoadjuvant (primary) systemic chemotherapy followed by definitive surgery with mastectomy and axillary lymph node dissection and radiotherapy[6,7]. Before the use of systemic chemotherapy, the 5-year OS rate using surgery and/or radiation therapy ranged from 0 to 5%. After the introduction of combination chemotherapy as part of a multimodality approach, survival has improved, with 15-year OS in 20%-30% of patients. Because IBC is a rare disease, there are no large randomized trials evaluating the optimal preoperative systemic therapy. The current systemic therapy recommendations are based on results from retrospective studies, smaller prospective studies, and data from locally advanced non-inflammatory breast cancer. A retrospective analysis demonstrated the benefit of preoperative systemic therapy followed by mastectomy compared to preoperative systemic therapy alone in which lower local recurrence rates and longer disease-free survival (DFS) were reported for the combined modality approach[8]. A large retrospective study of patients with IBC at The University of Texas MD Anderson Cancer Center (MDACC) showed that initial treatment with anthracycline-based chemotherapy followed by local therapy—with radiation, mastectomy, or both—and additional post-operative chemotherapy resulted in a 15-year DFS rate of 28%[9].

Achieving a pathologic complete response (pCR) to neoadjuvant therapy is associated with favorable outcomes in earlier stage breast cancer. A retrospective study demonstrated that the addition of a taxane to an anthracycline-based chemotherapy regimen improved progression-free survival (PFS) and OS in patients with hormone receptor (HR)-negative IBC[10]. A study of patients with IBC and metastasis to axillary lymph nodes who were treated with anthracycline-based chemotherapy with or without taxanes revealed that more patients receiving the combination achieved a pCR compared to those that only received anthracycline-based chemotherapy[11]. Furthermore, those with a pCR in the axillary lymph nodes had improved DFS and OS compared to those with residual axillary disease.

For the initial treatment of patients with IBC, preoperative systemic therapy with an anthracycline-based regimen with taxane is recommended. For patients with HER2-positive IBC, the addition of trastuzumab to systemic chemotherapy is associated with improvement in response rates. A prospective study that randomized patients with locally advanced breast cancer, including IBC, to neoadjuvant anthracycline-based chemotherapy with or without trastuzumab for one year demonstrated that the addition of trastuzumab significantly improved overall response rate (ORR) and event free survival[12,13]. The inclusion of trastuzumab in the chemotherapy regimen is recommended for patients with HER2-positive IBC. In addition, a phase II trial of patients with HER2-positive breast cancer including IBC showed improvement

in pCR with the addition of another HER2-targeting agent, pertuzumab[14]. Pertuzumab may therefore be included in the preoperative systemic therapy in patients with HER2-positive IBC. All patients with HR-positive IBC are recommended to receive endocrine therapy sequentially after completion of planned preoperative systemic therapy and surgery.

The response to preoperative chemotherapy is an important prognostic factor. A retrospective analysis at MDACC looked at treatment efficacy in 527 patients with IBC by HR- and HER2-defined subtypes[15]. The patients had received neoadjuvant chemotherapy, and the overall pCR rate was 15.2%. Based on subtype, the pCR rates were 7.4% in HR-positive/HER2-negative, 12.4% in triple negative breast cancer (TNBC), 15% in HR-positive/HER2-positive, and 30.5% in HR-negative/HER2-positive[15]. Features that were associated with improvement in DFS and OS were achieving a pCR, no evidence of vascular invasion, non-TNBC subtype, and adjuvant hormonal therapy and radiotherapy.

In summary, neoadjuvant systemic therapy, modified radical mastectomy and axillary lymph node dissection, post-mastectomy radiotherapy, adjuvant targeted therapy (as indicated) and hormonal therapy (as indicated) are the current recommended multimodality treatments for IBC[6,7], however pCR rates are low and overall outcomes are poor, signifying an important need for better therapies.

1.1.2 IBC Biology and PD-L1 Expression

Several studies have documented a higher frequency of negative HR status in IBC tumors compared to non-IBC tumors, with some reporting up to 50% of tumors being estrogen receptor (ER)-negative[16]. Lack of expression of hormone receptors has been shown to be associated with a more aggressive clinical course and decreased breast cancer-specific and overall survival. A higher incidence of HER2-positive tumors has also been reported among IBC[17]. Tumor infiltrating lymphocytes (TILs) have been shown to be prognostic in the more highly proliferative and aggressive breast cancer subtypes, such as TNBC which lacks ER/PR expression, and HER2-positive breast cancer[18-20]. The degree of infiltrating immune cells in the tumor microenvironment has correlated with response to treatment and clinical outcome in these two subtypes, providing important prognostic and possibly predictive information. IBC comprises similar molecular subtypes as other types of breast cancer, but may contain a more important role for the tumor microenvironment, including immune cell infiltration[21].

Advances in cancer immunotherapy and a growing body of research have focused on the role of the antitumor response in breast cancer. There is strong evidence that TILs have prognostic value and are associated with clinical outcome and improved survival. Immunotherapy studies have focused on the role of the programmed cell death-1 (PD-1) receptor/programmed death-ligand 1 (PD-L1) pathway in maintaining immunosuppression in the tumor microenvironment. PD-1 is a member of the T-cell co-regulatory receptor family and, when it binds to its ligands, PD-L1 and PD-L2, it attenuates T-cell function, survival, and expansion, thereby mediating immune tolerance. PD-L1 is expressed on activated T cells within the tumor microenvironment; however, tumors can also express PD-L1, which has been demonstrated in breast cancer, melanoma, lung cancer, and renal cell cancer, among other malignancies. This expression of PD-L1 enables inhibition of the local immune response. Blockade of the PD-1/PD-L1 axis has emerged as a promising therapeutic option to enhance antitumor immunity and is actively being investigated in breast cancer, in particular TNBC, with encouraging results. Atezolizumab (an anti-PD-1 antibody), in combination with nab-paclitaxel, was recently granted accelerated approval by the FDA for patients with metastatic TNBC whose tumors express PD-L1[22].

A study analyzed PD-L1 mRNA expression in 306 breast cancer tumor samples, including 112 samples from IBC[23]. IBC patients were younger than non-IBC patients and tumor samples were more often associated with poor prognosis features: higher grade and stage, ER and progesterone (PR)-negative, HER2-positive and aggressive molecular subtypes (basal, HER2-enriched). The 5-year metastasis-free survival was 49% (95% confidence interval [CI]: 37–64%) in IBC patients and 82% (95% CI: 76–88%) in non-IBC patients (p= 2.7E-9; log-rank test). Of the IBC samples, the frequency of PD-L1 mRNA overexpression was 38% (42 of 112), and in comparison, 28% of non-IBC samples showed PD-L1 overexpression. In IBC, PD-L1 expression was associated with ER-negative status, basal and HER2-enriched subtypes, as well as $CD8^+$ T-cell specific gene signatures. Pathologic response to neoadjuvant

anthracycline-based chemotherapy was found in 66 out of 112 patients with IBC, of which 22 (33%) had achieved pCR. Expression in tumors (T) was measured as discrete value after comparison with mean expression in normal breast samples (NB): overexpression, designated as 'PD-L1-high', was defined by a T/NB ratio ≥ 2 and no overexpression, or 'PD-L1-low', was designated by a T/NB ratio <2. Higher PD-L1 expression correlated with improved pathological response to neoadjuvant anthracycline-based chemotherapy (pCR rate was 50% in the 'PD-L1 high' group and 20% in the 'PD-L1 low' group). Tumors with high PD-L1 expression also showed a more dense T-cell infiltration, with positive correlation between PD-L1 expression and the presence of elevated TILs, higher expression of T-cell-specific and CD8+ T-cell-specific gene expression signatures, and higher expression of genes coding proteins related to the T-cell receptor.

1.1.3 Study Rationale and Hypothesis

IBC remains frequently resistant to standard treatment approaches, including neoadjuvant chemotherapy, and shows a predictable pattern of early recurrence and systemic spread of disease with poor prognosis. There is therefore an unmet need for identification of new therapeutic targets and novel systemic therapeutic approaches in this aggressive type of breast cancer. Blockade of the PD-1/PD-L1 axis has emerged as a promising option to enhance anti-tumor immunity and clinical responses. PD-L1 expression in IBC is frequent and may predict for improved response to chemotherapy and should be investigated in the neoadjuvant setting. Achieving a pCR to neoadjuvant therapy is associated with favorable disease-free survival and OS. We **hypothesize** that PD-1 blockade with nivolumab in combination with standard neoadjuvant (primary) systemic chemotherapy will be well tolerated and will increase the rate of pCR and reduce risk of recurrence in patients with IBC compared to known efficacy of neoadjuvant chemotherapy alone.

1.2 Investigational Agent

1.2.1 Nivolumab and Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes[24]. Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the downregulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. OPDIVO™ (nivolumab) is approved for the treatment of several types of cancer and is also being investigated in various other types of cancer as monotherapy or in combination with other therapies.

1.2.2 Preclinical Data for Nivolumab

Nivolumab has been shown to bind specifically to the human PD-1 receptor and inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro.[25-27] Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1. In a mixed lymphocyte reaction, nivolumab promoted a reproducible concentration-dependent enhancement of IFN-γ release[28]. In intravenous repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg administered twice weekly for 27 doses. In addition, an enhanced pre- and postnatal development study in pregnant cynomolgus monkeys with nivolumab was conducted[29]. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys.

1.2.3 Nivolumab Pharmacokinetic Data in Humans

The pharmacokinetics (PK), clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, clear-cell renal cell carcinoma (RCC), classical Hodgkin

Lymphoma (cHL), urothelial carcinoma (UC), squamous cell carcinoma of the head and neck (SCCHN), in addition to other tumor types. Nivolumab monotherapy is approved in the United States for unresectable or metastatic melanoma, previously treated metastatic NSCLC, previously treated recurrent or metastatic SCCHN, previously treated advanced RCC, previously treated relapsed or refractory cHL, and previously treated advanced or metastatic UC. In addition, nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies for the treatment of several types of cancer.

The PK of nivolumab was studied in subjects with cancer over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) was 6.8 L (27.3%), and geometric mean elimination half-life ($t^{1/2}$) was 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Additionally, nivolumab has a low potential for drug-drug interactions. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 status, solid tumor type, baseline tumor size, and hepatic impairment.

PPK and exposure response analyses have been performed to support use of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W dosing regimens in subjects with cancer in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients, while the nivolumab 360 mg Q3W and 480 mg Q4W regimens allow flexibility of dosing with less frequent visits and in combination with other agents using alternative dosing schedules to Q2W.

Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either nivolumab 3mg/kg or 240 mg Q2W. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cavgss are expected to be similar to those following nivolumab 3 mg/kg or 240 mg Q2W, while Cminss are predicted to be 6% and about 16% lower, respectively, and are not considered to be clinically relevant. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cmaxss are predicted to be approximately 23% and about 43% greater, respectively, relative to that following nivolumab 3 mg/kg Q2W dosing. However, the range of nivolumab exposures (median and 90% prediction intervals) following administration of 240 mg flat Q2W, 360 mg Q3W, and 480 mg Q4W regimens across the 35 to 160 kg weight range are predicted to be maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosing regimen.

1.2.4 Nivolumab Clinical Efficacy

Nivolumab has demonstrated durable responses exceeding six months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cHL, small cell lung cancer, gastric cancer, SCCHN, urothelial cancer, hepatocellular carcinoma, and colorectal cancer. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma.

1.2.5 Nivolumab Clinical Safety

The overall safety experience with nivolumab, as monotherapy or in combination with other therapeutics, is based on experience in approximately 16,900 subjects treated to date. For monotherapy, the safety

profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care. In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve.

1.3 Clinical Data to Date

1.3.1 Combined Modality Treatment with Anthracycline-based Chemotherapy in IBC

Between May 1973 and September 1993, 178 previously untreated patients with IBC without distant metastasis were treated at MDACC by a combined-modality approach under four different protocols[30]. Each protocol included induction chemotherapy, then local therapy (radiotherapy or mastectomy), then adjuvant chemotherapy, and if mastectomy was performed, adjuvant radiotherapy. Chemotherapy consisted of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) with or without vincristine and prednisone (VP). In one protocol, patients received an alternate adjuvant chemotherapy regimen, methotrexate and vinblastine (MV), if they did not achieve a complete response (CR) to induction chemotherapy. Results of the study showed that 28% of patients were currently free of disease beyond 15 years. An important prognostic factor was initial response to induction chemotherapy. At 15 years, DFS was 44% in patients who had a CR to induction chemotherapy, 31% in those who had a partial response (PR), and 7% in those who had less than a PR. These long-term follow-up data show that with a combined modality approach a significant fraction of patients (28%) remained free of disease beyond 15 years. In contrast, single-modality treatments had a DFS of less than 5%. Therefore, using combined-modality treatment is recommended as a standard of care for IBC.

1.3.2 Addition of Taxanes to Preoperative Systemic Therapy in IBC

A later retrospective study at MDACC demonstrated that the addition of paclitaxel to anthracycline-based therapy resulted in a statistically significant improvement in outcome in patients with ER-negative IBC[10]. A total of 240 patients treated between 1973 and 2000 in six consecutive trials were included in the analysis. Group 1 (n= 178) consisted of patients treated in the first 4 trials (1973-1993) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide). Group 2 (n= 62) consisted of patients treated in the last 2 trials (1994-2000) with FAC followed by paclitaxel given every 3 weeks or given in a high-dose weekly schedule. The two groups differed with respect to median follow-up durations, which were 148 months (range, 85-283 months) in Group 1 and 45 months (range, 21-99 months) in Group 2. ER status was negative in 58 cases (33%) in Group 1 and 40 cases (65%) in Group 2. The objective response rates were similar (Group 1, 74%; Group 2, 82%). The median overall PFS and OS were improved in the patients treated with paclitaxel, and these differences reached statistical significance in the patients with ER-negative disease (median OS: Group 1, 32 months; Group 2, 54 months; p= 0.03; median PFS: Group 1, 18 months; Group 2, 27 months; p= 0.04).

A systematic review of 27 studies of IBC totaling 1232 patients found that pCR rates after no anthracycline induction, low-dose anthracycline induction, moderate-dose anthracycline induction, and neoadjuvant high-dose chemotherapy subgroups were 4% (95% CI, 1%-18%), 11% (95% CI, 7%-17%), 14% (95% CI, 8%-22%), and 32% (95% CI, 24%-41%), respectively[31]. The criteria and reporting of IBC and treatment response was notably variable, with significant potential for subject heterogeneity. pCR rates appeared to be related to intensity of neoadjuvant treatment.

Metastases to axillary lymph nodes (ALN) is a known prognostic factor in breast cancer, with pCR in ALN after chemotherapy being associated with significantly higher recurrence-free survival (RFS) and OS rates. A study evaluated the long-term outcome in patients with IBC achieving a pCR of cytologically proven ALN

metastases after primary chemotherapy[11]. Patients with cytologically documented ALN metastases from IBC were treated in three prospective primary chemotherapy trials. After surgery, patients were subdivided into those with and without residual ALN carcinoma. Of 175 patients treated, 61 had cytologically confirmed ALN metastases. Fourteen patients (23%) achieved a pCR of the ALNs after primary chemotherapy. The 5-year OS and RFS rates were found to be improved in those patients achieving a pCR of the ALNs (82.5% [95% CI, 62.8-100], and 78.6% [95% CI, 59.8-100], respectively, vs. 37.1% [95% CI, 25.4-54.2] and 25.4% [95% CI, 15.5-41.5], respectively) (p=0.01 [for OS] and p=0.001 [for RFS]). In addition, combination anthracycline and taxane-based primary chemotherapy resulted in significantly more patients achieving an ALN pCR (45% vs. 16%; p=0.01).

1.3.3 Targeted Therapies in HER2-positive IBC

HER2-positive IBC is associated with an overall poor prognosis[17], although the introduction of HER2-targeting antibodies has improved outcomes. The phase III NOAH trial compared one year of treatment with trastuzumab (given as neoadjuvant and adjuvant treatment; n=117) with no trastuzumab (n=118), in patients with HER2-positive locally advanced or IBC receiving neoadjuvant chemotherapy with doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and fluorouracil[13]. A total of 62 patients with IBC were included in the study, of which 32 patients received trastuzumab and 31 did not. The primary endpoint was event-free survival [12]. The 5-year EFS was 58% (95% CI, 48–66) in the trastuzumab group and 43% (95% CI, 34–52) in the chemotherapy alone group; the unadjusted hazard ratio (HR) for event-free survival between the two randomized HER2-positive treatment groups was 0.64 (95% CI, 0.44-0.93; two-sided log-rank p=0·016). EFS was strongly associated with pCR in patients given trastuzumab. Of the 68 patients with a pCR (45 with trastuzumab and 23 with chemotherapy alone), the HR for EFS between those with and without trastuzumab was 0.29 (95% CI, 0.11-0.78). Generally, patients with inflammatory disease or negative hormonal receptors had a more pronounced benefit from trastuzumab. For the patients with IBC who received trastuzumab, the 5-year EFS was 64% versus 24% for those who did not receive trastuzumab (HR 0.34; 95% CI, 0.15-0.80). The 5-year OS for the patients with IBC was 74% versus 44%, respectively (HR 0.38; 95% CI, 0.15-0.95)[32].

There was multicenter open-label, phase 2 neoadjuvant study (NeoSphere, NCT00545688), of women with locally advanced HER2-positive breast cancer and IBC who were randomly assigned to receive four cycles of: trastuzumab plus docetaxel (group A), or pertuzumab and trastuzumab plus docetaxel (group B), or pertuzumab and trastuzumab (group C), or pertuzumab plus docetaxel (group D)[14]. Pertuzumab is a monoclocal antibody that binds to a different epitope on HER2 and blocks the formation of HER2 and HER3 heterodimers. The primary endpoint of this study was pCR in the breast. Of 417 eligible patients, 107 were randomly assigned to group A (7 with IBC), 107 to group B (10 with IBC), 107 to group C (7 with IBC), and 96 to group D (5 with IBC). Patients who were given pertuzumab and trastuzumab plus docetaxel (group B) had a significantly improved pCR rate (49 of 107 patients; 45.8% [95% CI, 36.1-55.7]) compared with those given trastuzumab plus docetaxel (group A; 31 of 107; 29.0% [95% CI, 20.6-38.5]; p=0.0141). There were no substantial differences in tolerability or toxicity with the addition of pertuzumab to trastuzumab and docetaxel, including the risk of cardiac adverse events. The mean maximum decrease in left ventricular ejection fraction (LVEF) measurement was 4-5% and was balanced across the four treatment groups. No significant change was detected when pertuzumab was added to trastuzumab and no patient had an LVEF decrease to less than 40% at any time during the study.

The main objective of the phase II TRYPHAENA trial (NCT00976989) was to evaluate tolerability, with a focus on cardiac safety, of pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive locally advanced or IBC[33]. A total of 225 patients (13 with IBC) were randomized to 5-fluorouracil, epirubicin, cyclophosphamide [FEC] followed by docetaxel, with trastuzumab and pertuzumab starting either concurrently with FEC (Arm A) or upon initiation of docetaxel (Arm B) or to docetaxel, carboplatin, trastuzumab, and pertuzumab (Arm C). The combination of trastuzumab and pertuzumab was generally well tolerated regardless of whether it was given sequentially or concomitantly with anthracycline-based chemotherapy, or combined with carboplatin-based chemotherapy. During neoadjuvant treatment, two patients (2.7%; Arm B) experienced symptomatic left ventricular systolic dysfunction (LVSD) and 11 patients (Arm A: 4 [5.6%]; Arm B: 4 [5.3%]; Arm C: 3 [3.9%]) had declines in LVEF of ≥10% points from

baseline to <50%. Safety outcomes at 3 years were recently reported and no new safety signals were identified[34].

The phase III APHINITY trial (NCT01358877) assessed the combination of pertuzumab and trastuzumab with chemotherapy in the adjuvant setting[35]. The 3-year rate of invasive-disease-free survival were 94.1% in the pertuzumab group and 93.2% in the placebo group. In patients with node-positive disease, the 3-year rate of invasive-disease-free survival was 92.0% in the pertuzumab group, as compared with 90.2% in the placebo group (HR for an invasive-disease event, 0.77; 95% CI, 0.62 to 0.96; p= 0.02). In the cohort of patients with node-negative disease, the 3-year rate of invasive-disease-free survival was 97.5% in the pertuzumab group and 98.4% in the placebo group (HR for an invasive-disease event, 1.13; 95% CI, 0.68 to 1.86; p= 0.64).

1.3.4 Neoadjuvant Treatment with Bevacizumab in IBC

IBC is molecularly associated with high vascularity, increased microvessel density, and high expression of angiogenic factors such as vascular endothelial growth factor (VEGF)[36]. Bevacizumab is a humanized monoclonal antibody that targets VEGF-A. The multicenter, single-arm, phase II BEVERLY-1 study (NCT00820547) showed that the addition of bevacizumab to neoadjuvant and adjuvant chemotherapy did not provide clinical benefit to patients with HER2-negative IBC[37]. A total of 101 patients were enrolled. Patients underwent 3-week treatment cycles, receiving neoadjuvant fluorouracil, epirubicin, cyclophosphamide (FEC), and bevacizumab during cycles 1-4, then docetaxel and bevacizumab during cycles 5–8. Two to four weeks after surgery, the patients received adjuvant radiotherapy, hormone therapy (if they had a HR-positive tumor), and adjuvant bevacizumab. The primary endpoint was pCR in breast and axillary lymph nodes after neoadjuvant treatment. After neoadjuvant therapy, 19 (19% [95% CI 12–28]; p=0·16) of 100 patients achieved a pCR. The most frequent grade 3-4 events during the neoadjuvant phase were neutropenia (89 [89%] of 100 patients), febrile neutropenia (37 [37%]), and mucositis (23 [23%]) and during the adjuvant phase the most frequent grade 3-4 adverse event was proteinuria (5 [7%] of 75 patients). Overall, the proportion of patients achieving a pCR was inferior or equal to that which has been reported without bevacizumab.

Similarly, the phase 2 multicenter open label single arm BEVERLY-2 trial (NCT00717405) evaluated neoadjuvant and adjuvant bevacizumab in combination with chemotherapy for patients with HER2-positive inflammatory breast cancer[38]. A total of 52 patients were enrolled. One year of treatment with bevacizumab plus a trastuzumab and anthracycline-taxane-based regimen was well tolerated and 33 of 52 patients had a pCR (63.5%, 95% CI 49.4-77.5). The most common adverse events were asthenia and nausea (both occurred in 36 [69%] of 52 patients). A total of 25 (48%) patients had grade 3-4 neutropenia, which was the most common grade 3-4 adverse event. Only one grade 3 or worse adverse event regarded as related to bevacizumab was reported (hypertension, one patient). Four patients (8%) had cardiac failure. Survival rates at three years were encouraging, with 68% disease-free survival (DFS) and 90% overall survival (OS)[9]. Furthermore, a pooled analysis of the BEVERLY-1 and BEVERLY-2 trials looking at the predictive and prognostic role of circulating tumor cells (CTCs) showed that the detection rate of CTCs was 39% with independent prognostic value for survival[39]. After neoadjuvant therapy, the combination of pCR with no CTC detection at baseline yielded a subgroup of patients with IBC with improved prognosis (3-year OS of 94%). Further larger and randomized studies evaluating the potential benefit of antiangiogenic therapy in this setting, as well as the role of CTCs as part of IBC stratification, are needed.

A recently published phase II trial studied the clinical efficacy of neoadjuvant treatment with weekly carboplatin and paclitaxel plus oral metronomic cyclophosphamide in association with bevacizumab for patients with primary or recurrent IBC who were candidates for locoregional treatment[40]. Patients with HER2-positive IBC tumors received trastuzumab. Patients with HR-positive disease received concomitant endocrine therapy. Oral metronomic capecitabine and cyclophosphamide was continued for 6 months after surgery in those patients with a response. Thirty-four patients with IBC were included and treatment was well tolerated and safe. The overall response rate (ORR) was 88%, and the pCR rate was 29%, with the most significant effect of neoadjuvant therapy observed in patients with HER2-positive cancer. The achievement of pCR was associated with longer DFS and OS.

1.3.5 Neodjuvant Therapy with Carboplatin in TNBC

The efficacy of the addition of carboplatin to neoadjuvant therapy for patients with previously untreated state II or III TNBC and HER2-positive breast cancer was assessed in the randomized phase II GeparSixto trial (NCT01426880)[41]. Patients were treated for 18 weeks with paclitaxel and non-pegylated liposomal doxorubicin. Those with TNBC received simultaneous bevacizumab. Patients with HER2-positive disease received simultaneous trastuzumab and lapatinib. Patients were randomly assigned at the same to either carboplatin (AUC 1.5 [2.0 for the first 329 patients] once a week) or no carboplatin. A total of 296 patients received carboplatin and another 296 patients did not receive carboplatin. A total of 129 patients (95% CI, 43.7; 38.1-49.4) in the carboplatin group achieved a pCR, compared with 108 patients (95% CI, 36.9; 31.3-42.4) without carboplatin (odds ratio 1.33, 95% CI, 0.96-1.85; p=0.107). For the patients with TNBC, 84 (53.2%, 54.4-60.9) of 158 patients achieved a pCR with carboplatin, compared with 58 (36.9%, 29.4–44.5) of 157 without carboplatin (p=0.005). However, responses were not increased in patients with HER2-positive breast cancer. Toxicities were significantly more common in the carboplatin group than in the non carboplatin group including grade 3 or 4 neutropenia, anemia, thrombocytopenia, and diarrhea. Carboplatin was also more often associated with dose discontinuations (141 [48%] with carboplatin and 114 [39%] without carboplatin; p=0.031).

The CALGB 40603 (Alliance) trial was a 2x2 factorial, open-label, randomized phase II trial that evaluated the impact of adding carboplatin and/or bevacizumab to neoadjuvant paclitaxel followed by doxorubicin and cyclophosphamide in TNBC[42]. Patients (n=443) with stage II to III TNBC received paclitaxel once per week for 12 weeks followed by doxorubicin plus cyclophosphamide once every 2 weeks for four cycles, and were randomly assigned to concurrent carboplatin (AUC 6) once every 3 weeks for four cycles and/or bevacizumab 10 mg/kg once every 2 weeks for nine cycles. Results showed that patients assigned to either carboplatin or bevacizumab were less likely to complete weekly paclitaxel and doxorubicin plus cyclophosphamide without dose modification, skipped doses, or early discontinuation due to toxicity. Grade 3 or 4 neutropenia and thrombocytopenia were more common with carboplatin, and hypertension, infection, thromboembolic events, bleeding, and postoperative complications were more common with bevacizumab. The addition of either carboplatin (60% v 44%; p=0.0018) or bevacizumab (59% v 48%; p=0.0089) significantly increased pCR in the breast, whereas only carboplatin (54% v 41%; p=0.0029) significantly increased pCR in the breast/axilla. More-than-additive interactions between the two agents could not be demonstrated.

Of note, these trials did not show specific results for patients with IBC (GeparSixto) or excluded IBC patients (CALGB 40603). Per international consensus on the clinical management of IBC from the Morgan Welch Inflammatory Breast Cancer Research Program 10th Anniversary Conference held at MDACC in 2017, although neoadjuvant carboplatin has been shown to increase pCR rates in TNBC, there is still not enough evidence supporting long term clinical efficacy at this time to recommend routine use in IBC[6].

1.3.6 Neoadjuvant Therapy with Anti-PD-1/PD-L1 Antibodies in TNBC

No neoadjuvant chemoimmunotherapy trial has been reported for IBC patients, however trials in TNBC are being conducted and early results have shown promise. The recently reported phase 2 randomized, multicenter I-SPY2 study (an adaptive trial platform to test novel agents) achieved an increase in pCR in patients who had locally advanced (stage II/III) TNBC or HR-positive/HER2-negative breast cancer when pembrolizumab was added to the taxane segment of the standard neoadjuvant regimen, followed by doxorubicin and cyclophosphamide (NCT01042379)[43]. In total, 249 patients were randomized, of whom 69 were to receive pembrolizumab in combination with paclitaxel, 180 were to receive paclitaxel alone in the control arm, and all patients then continued to receive neoadjuvant doxorubicin and cyclophosphamide. The findings indicated that the estimated pCR rate (negative pathologic post-treatment tumor classification/tumor in situ and negative pathologic post-treatment lymph node status [ypT0/Tis ypN0]) was significantly higher with the addition of pembrolizumab in patients who had TNBC (60% vs 20%, respectively) and in those who had HR-positive/HER2-negative breast cancer (34% vs 13%) compared with

standard therapy, and the predictive probability of success in a phase 3 trial was 99%. No additive toxicities were observed except for an excess of adrenal insufficiency in the pembrolizumab arm, which appeared to be greater than that reported from chemoimmunotherapy trials conducted in other cancer types. This finding is significant, because management requires long-term steroid replacement for patients who are treated in the curative setting.

Preliminary results from additional randomized neoadjuvant trials in TNBC combining standard cytotoxic regimens with immunotherapy also recently were reported. The phase 1b KEYNOTE-173 study evaluated pembrolizumab plus chemotherapy as neoadjuvant therapy for locally advanced TNBC in 2 cohorts (NCT02622074)[44]. Preliminary data were reported from 10 patients in cohort A (single-dose pembrolizumab, followed by 4 cycles of pembrolizumab every 3 weeks in combination with weekly nab-paclitaxel, followed by 4 cycles of pembrolizumab in combination with doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks) and 10 patients in cohort B (the same treatment as in cohort A plus carboplatin at an area under curve (AUC) of 6 every 3 weeks was added to pembrolizumab and nab-paclitaxel). The ypT0/Tis ypN0 pCR rate (no invasive residual disease in the breast and lymph nodes) was 60% (90% CI, 30%-85%) in cohort A and 90% (90% CI, 61%- 100%) in cohort B.

In the randomized phase 2 GeparNuevo study, durvalumab, a monoclonal antibody that binds to PD-L1, was added to an anthracycline-containing and taxane- containing neoadjuvant regimen for patients with TNBC (NCT02685059)[45]. The patients received durvalumab or placebo monotherapy for the first 2 weeks (window phase), followed by durvalumab or placebo plus nab-paclitaxel weekly for 12 weeks, followed by durvalumab or placebo plus dose-dense epirubicin and cyclophosphamide every 2 weeks for 4 cycles. Of the 50 patients enrolled, the addition of immune checkpoint blockade to standard neoadjuvant chemotherapy did not identify unexpected toxicity, and most AEs included chemotherapy-related toxicities. In the recently reported phase 2 portion, a total of 174 patients were enrolled and all had completed treatment[46]. Median age was 49.5 years [range 23.0-76.0], and 44.5% of patients had cT1, 49.7% cT2, 3.5% cT3, and 2.3% cT4 tumors. Eighty-three percent of the tumors were grade 3. Approximately 31% were cN-positive tumors. Overall, the addition of durvalumab increased the pCR from 44.2 to 53.4%, although this was not statistically significant (OR 1.53). As per subgroup analysis, the patients who started with durvalumab were found to have the greatest benefit with pCR of 61%. Additionally, patients with stage IIA or higher tumors and those who were 40 years of age or younger achieved a pCR rate of greater than 60%. A total of 86 serious adverse events (SAEs) and 65 immune related AEs of special interest (irAESI) were reported; 34.5% of pts had at least one SAE and 27.6% had at least one irAESI. The irAESI were related to endocrine disorders of the thyroid gland. In addition, the safety of administering durvalumab concomitant with sequential taxane and anthracycline neoadjuvant chemotherapy was studied in a phase 1/2 single-arm trial of stage I through III TNBC (NCT02489448). Patients received durvalumab in combination with weekly nab-paclitaxel, followed by dose-dense doxorubicin and cyclophosphamide with durvalumab. The phase 1 portion established the safety of the combination[47].

In summary, while there appears to be efficacy in terms of increased pCR rates in TNBC with the addition of immunotherapy to standard neoadjuvant chemotherapy, toxicity has been observed and may be worse with the combination with anthracycline. Therefore at this time, only patients with poor prognosis—such as those with IBC—should be considered for these types of clinical studies, and concurrent therapy with immunotherapy should be given during the non-anthracycline containing segment.

1.3.7 Treatment with Anti-PD-1/PD-L1 Antibodies in HER2-positive Advanced Breast Cancer

The phase Ib/II PANACEA trial (BIG 4-13/IBCSG 45-13) (NCT02129556) evaluated the combination of pembrolizumab and trastuzumab in 58 patients with HER2-positive advanced breast cancer who had progressed on a prior trastuzumab-based therapy[48]. Tumors were assessed centrally for HER2-positivity and programmed cell death ligand 1 (PD-L1) status, and for quantity of tumor-infiltrating lymphocytes (TILs). The phase Ib portion was a dose-escalation study of pembrolizumab, an anti-PD-1 antibody, in conjunction with the standard dose of trastuzumab. No dose-limiting toxicities were observed. In the phase II portion, 40 patients and 12 patients were enrolled to the PD-L1–positive and PD-L1–negative cohorts, respectively. Patients received 200mg of pembrolizumab every 3 weeks in combination with the standard dose of

trastuzumab for 24 months or until disease progression. In the PD-L1–positive intent-to-treat population, the trial met its primary endpoint with an objective response rate of 15% and disease control rate of 25%. In a subgroup of PD-L1–positive patients with 5% or more TILs present in the metastatic lesion, the objective response rate was 39% and the disease control rate was 47%. No responses were observed in the PD-L1–negative cohort. Pembrolizumab with trastuzumab was well tolerated, with grade 1 to 2 fatigue as the most commonly reported adverse event (21%). The most common immune-related adverse events reported were hyper- and hypo-thyroidism (grade 1–2 at 6.7%) and pneumonitis (grade 3-4 at 3.4%).

1.3.8 Select Ongoing Neoadjuvant Studies in IBC

Table 1 lists select ongoing neoadjuvant clinical trials in IBC.

Study Phase and Title	Study Agents	Population	Enrollment	Primary Endpoint	NCT ID No.
Randomized, phase II open label PELICAN: Immunotherapy in combination with chemotherapy in HER2-negative IBC	FEC (if HR-positive IBC)→ weekly paclitaxel dose-dense EC (if HR-negative IBC) → weekly paclitaxel Experimental arm will receive pembrolizumab q 3 weeks during neoadjuvant chemotherapy	HER2-negative IBC	81/ongoing	pCR (ypT0/is, ypN0)	NCT03515798
Single arm, phase II open label Panitumumab, nab-paclitaxel and carboplatin for HER2-negative IBC	PNC (panitumumab + nab-paclitaxel + carboplatin) + FEC (5-fluorouracil, epirubicin, and cyclophosphamide)	HER2-negative IBC	40/completed	pCR (ypT0, ypN0)	NCT01036087
Single arm, phase II open label Eribulin followed by doxorubicin and cyclophosphamide as preoperative therapy for HER2-negative IBC	Eribulin → AC	HER2-negative IBC	25/ongoing	pCR (will be reported as residual cancer burden [RCB])	NCT02623972
Randomized, phase II open label Ruxolitinib (INCB018424) with preoperative chemotherapy for triple negative IBC	Paclitaxel +/- Ruxolitinib → AC	HR-/HER2-IBC	64/ongoing	Assess JAK inhibition with Ruxolitinib on pStat3+ expression	NCT02876302

Randomized, phase II open label Carboplatin/ paclitaxel versus panitumumab/ carboplatin/ paclitaxel followed by anthracycline-containing regimen for newly diagnosed primary triple-negative IBC	Carboplatin/Paclitaxel →AC versus Panitumumab/Carboplatin/ Paclitaxel → AC	HR-/HER2- IBC	72/ongoing	pCR	NCT02876107
Single arm, phase II open label Paclitaxel combined with trastuzumab and pertuzumab as pre-operative therapy for IBC	Paclitaxel +Trastuzumab +Pertuzumab → Mastectomy → Option 1: AC → Trastuzumab +Pertuzumab to complete one year of therapy Option 2: Trastuzumab +Pertuzumab to complete one year of therapy	HER2+ IBC	23/completed	pCR	NCT01796197

1.4 Dose Rationale and Schedule

The treatment to be used in this trial is outlined below and in **Table 2/3 and Table 4/5.**

Cohort 1: TNBC or HR-positive/HER2-negative

1. Cycle 1-4, 21 day cycle
   - Nivolumab 360 mg IV on Day 1 x 4 cycles and Paclitaxel 80 mg/m^2 IV on Day 1, 8, and 15 x 4 cycles, followed by

2. Cycle 5-8, 14 day cycle
   - Doxorubicin 60 mg/m^2 IV on Day 1 x 4 cycles and Cyclophosphamide 600 mg/m^2 IV on Day 1 x 4 cycles

Table 2

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Use
Nivolumab	360 mg	Day 1 of every 21 day cycle (Cycle 1-4)	Intravenous (IV)	Experimental
Paclitaxel	80 mg/m2	Day of 1, 8, 15 of every 21 day cycle (Cycle 1-4)	IV	Standard
Doxorubicin	60 mg/m2	Day of 1 of every 14 day cycle (Cycle 5-8)	IV	Standard
Cyclophosphamide	600 mg/m2	Day of 1 of every 14 day cycle (Cycle 5-8)	IV	Standard

Table 3

	Cycle 1-4	Cycle 5-8
Nivolumab	X	
Paclitaxel	X	
Doxorubicin		X
Cyclophosphamide		X

Cohort 2: HR-positive/HR-negative and HER2-positive:

1. Cycle 1-4, 21 day cycle
   - Nivolumab 360 mg IV on Day 1 x 4 cycles, + Docetaxel 75 mg/m^2 IV on Day 1 x 4 cycles or Paclitaxel 80 mg/m^{2}IV on Day 1, 8, and 15 x 4 cycles, + Trastuzumab* 8 mg/kg IV on Day 1 of Cycle 1 and then 6 mg/kg IV on Day 1 of Cycle 2-4, + Pertuzumab 840 mg IV on Day 1 of Cycle 1 and then 420 mg IV on Day 1 of Cycle 2-4, followed by

2. Cycle 5-8, 14 day cycle
   - Doxorubicin 60 mg/m^2 IV on Day 1 x 4 cycles and Cyclophosphamide 600 mg/m^2 IV on Day 1 x 4 cycles

*Trastuzumab biosimilar is allowed

Table 4

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Use
Nivolumab	360 mg	Day 1 of every 21 day cycle (Cycle 1-4)	Intravenous (IV)	Experimental
Docetaxel (or Paclitaxel)	75 mg/m^2 (80 mg/m^2)	Day 1 of every 21 day cycle (Day 1, 8, 15 of every 21 day cycle) (Cycle 1-4)	IV	Standard
Trastuzumab (biosimilar is allowed)	8 mg/kg IV on Day 1 of Cycle 1 and then 6 mg/kg IV on Day 1 of Cycle 2-4	Day 1 of Cycle 1 and then Day 1 of subsequent cycles (2-4) (Cycle 1-4) Each cycle is 21 days	IV	Standard
Pertuzumab	840 mg on Day 1 of Cycle 1 and then 420 mg IV on Day 1 of Cycle 2-4	Day 1 of Cycle 1 and then Day 1 of subsequent cycles (2-4) (Cycle 1-4) Each cycle is 21 days	IV	Standard
Doxorubicin	60 mg/m^2	Day 1 of every 14 day cycle (Cycle 5-8)	IV	Standard
Cyclophosphamide	600 mg/m^2	Day 1 of every 14 day cycle (Cycle 5-8)	IV	Standard

Table 5

	Cycle 1-4	Cycle 5-8
Nivolumab	X	
Docetaxel (or Paclitaxel)	X	
Trastuzumab	X	
Pertuzumab	X	
Doxorubicin		X
Cyclophosphamide		X

Postoperative Therapy:

- After mastectomy and axillary lymph node dissection, radiation therapy is recommended as per institutional guidelines.
- Patients with HR-positive tumors should receive a minimum of 5 years of adjuvant endocrine therapy. Choice of endocrine therapy is at the discretion of the investigator.
- For HER2-positive tumors, patients with residual disease after neoadjuvant therapy may receive ado-trastuzumab emtansine (T-DM1) in the adjuvant setting for 14 cycles[49]. Another option is to continue trastuzumab with or without pertuzumab to complete one year of HER2-directed therapy[35]. For patients with pathologic complete response (no residual disease), adjuvant trastuzumab can be continued with or without pertuzumab to complete one year of HER2-directed therapy. Treatment regimen is at the discretion of the investigator.

- Use of adjuvant capecitabine for 6-8 cycles (permissible after surgery) for patients with TNBC with residual disease is at the discretion of the investigator[50].

1.4.1 Rationale for Nivolumab Dose and Schedule

The FDA approved dose of nivolumab is 240 mg IV (flat dose) every 2 weeks or 480 mg IV (flat dose) every 4 weeks in malignancies such colorectal cancer (microsatellite instability-high or mismatch repair deficient), recurrent or metastatic squamous cell head and neck cancer, hepatocellular carcinoma, melanoma, metastatic NSCLC, metastatic renal cell cancer, or urothelial carcinoma. This is equal to 120 mg IV weekly. PPK and exposure response analyses have been performed to support use of nivolumab 360 mg every three weeks. The phase III CheckMate-227 trial evaluated the combination of nivolumab and ipilimumab versus chemotherapy in treatment-naïve patients with NSCLC with high tumor mutation burden (TMB)[51]. Patients with a PD-L1 expression level of less than 1% were randomly assigned (in a 1:1:1 ratio), with stratification according to tumor histologic type, to receive nivolumab (3 mg per kilogram every 2 weeks) plus ipilimumab (1 mg per kilogram every 6 weeks), platinum doublet chemotherapy based on tumor histologic type every 3 weeks for up to four cycles, or nivolumab (360 mg) plus platinum doublet chemotherapy based on tumor histologic type every 3 weeks for up to four cycles. The combination schedule was overall tolerated and safety was similar to previous reported results[52].

In the current study, nivolumab will be administered every three weeks, therefore the dosing of nivolumab will be 360 mg IV every three weeks for four cycles. Nivolumab will be given at the same time as standard taxane chemotherapy with paclitaxel and docetaxel or with HER2-targeted therapy with trastuzumab and pertuzumab. It will not be given at the same time as the anthracycline-based therapy (doxorubicin and cyclophosphamide) due to a potential increased risk of cardiotoxicity. Of note, combination therapies of PD-1/PD-L1 checkpoint inhibitors and taxane chemotherapy have not identified excessive toxicity. A phase Ib study evaluated atezolizumab (anti-PD-1 antibody) plus nab-paclitaxel in patients with metastatic TNBC, and the combination was well-tolerated without additive toxicity[53]. In the randomized IMpassion 130 trial (n=902) with nab-paclitaxel and atezolizumab or placebo, grade ≥3 adverse events occurred in 49% of patients receiving atezolizumab and 42% of patients receiving placebo, with grade 3 or 4 neuropathy occurring more frequently among those receiving atezolizumab (5.5% versus 2.8%)[22]. A phase Ib/II trial studied pembrolizumab (anti-PD-1 antibody) and HER2-directed agent, trastuzumab, in advanced HER2-positive breast cancer, and the combination was also found to be safe without excess cardiac toxicity[48].

1.4.2 Rationale for Chemotherapy Dose and Schedule

Anthracycline and taxane based chemotherapy

For patients with HER2-negative breast cancer who are candidates for neoadjuvant therapy, standard therapy consists of anthracycline- and taxane-based chemotherapy regimens. The meta-analysis of adjuvant chemotherapy trials from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated benefit for anthracycline-based regimens over cyclophosphamide, methotrexate, plus fluorouracil (CMF)[54]. In addition, adding taxanes to anthracyclines further improved outcomes in the adjuvant setting. Further rationale for the use of anthracyclines and taxanes in the preoperative setting comes from clinical trials of neoadjuvant treatment. In this setting, multiple studies have shown that addition of a taxane to an anthracycline-based regimen is associated with increased response rates[55-58].

The Neo-tAnGo neoadjuvant trial assessed the sequencing of chemotherapy by evaluating epirubicin and cyclophosphamide and paclitaxel (with or without gemcitabine)[59]. A total of 831 patients were randomized; 207 received epirubicin and cyclophosphamide then paclitaxel; 208 were given paclitaxel then epirubicin and cyclophosphamide; 208 had epirubicin and cyclophosphamide followed by paclitaxel and gemcitabine; and 208 received paclitaxel and gemcitabine then epirubicin and cyclophosphamide. 828 patients were eligible for analysis. Median follow-up was 47 months, and 207 (25%) patients had inflammatory or locally advanced disease, 276 (33%) patients had estrogen receptor (ER)-negative disease, and 191 (27%) patients had HER2-positive disease. Addition of gemcitabine did not increase pCR: 70 (17%, 95% CI 14–21) of 404 patients in the epirubicin and cyclophosphamide then paclitaxel group achieved pCR compared

with 71 (17%, 14–21) of 408 patients who received additional gemcitabine (p=0·98). Receipt of a taxane before the anthracycline was associated with improved pCR: 82 (20%, 95% CI 16–24) of 406 patients who received paclitaxel with or without gemcitabine followed by epirubicin and cyclophosphamide achieved pCR compared with 59 (15%, 11–18) of 406 patients who received epirubicin and cyclophosphamide first (p= 0.03). Although addition of gemcitabine to paclitaxel and epirubicin and cyclophosphamide chemotherapy does not improve pCR, sequencing chemotherapy so that taxanes are received before anthracyclines may improve pCR with standard neoadjuvant chemotherapy for breast cancer.

In the current study, the taxane-based chemotherapy (paclitaxel or docetaxel) will be given prior to the anthracycline-based chemotherapy (doxorubicin and cyclophosphamide). Standard dose and schedule of paclitaxel, docetaxal, doxorubicin, and cyclophosphamide will be used (Section 1.4).

HER2-targeted therapy with trastuzumab and pertuzumab

For patients with HER2-positive breast cancer that are candidates for preoperative systemic therapy, chemotherapy and trastuzumab-based therapy are recommended. Chemotherapy and dual anti-HER2 blockade associated with trastuzumab plus pertuzumab have shown significant improvements in the pCR rate when compared with chemotherapy and one anti-HER2 agent in the preoperative setting. In the NeoSphere trial, the addition of pertuzumab to trastuzumab and docetaxel preoperatively led to a statistically significant increase in pCR in the breast (16.8% increase; 95% CI, 3.5–30.1; p= 0.0141)[14]. In the TRYPHAENA trial, preoperative therapy with pertuzumab and trastuzumab given alone with or without anthracycline-containing chemotherapy regimens demonstrated pCR rates in all treatment arms ranging from 57% to 66%[33]. The mean change in LVEF was similar in all treatment arms. The FDA granted accelerated approval in 2013 for the addition of pertuzumab to neoadjuvant chemotherapy and trastuzumab for patients with HER2-positive locally advanced, inflammatory, or early-stage (either greater than 2 cm in diameter or node positive) breast cancer.

In the current study, the standard dose and schedule of trastuzumab and pertuzumab will be used (Section 1.4). Use of trastuzumab biosimilar is allowed.

1.5 Research Risks & Benefits

1.5.1 Risk of Study Drug

Dose modifications for nivolumab are described in 5.3. While this is a greater than minimal risk study, combination therapies of PD-1/PD-L1 checkpoint inhibitors with taxane chemotherapy or HER2-directed therapy with trastuzumab were found to be safe[48,53]. The safety of the addition of nivolumab to standard chemotherapy will be closely monitored in this study, as described in Sections 4.3.11 and 6.1.

1.5.2 Other Risks of Study Participation

Additional risks to study participation are listed in the consent form and include breach of confidentiality, not deriving benefit from the study treatment, and procedures performed for research only (peripheral blood draws and tumor tissue biopsies for correlative studies). Privacy protection procedures are in place and good clinical practice guidelines are followed for the study to minimize risks associated with research procedures and participation.

1.5.3 Potential Benefits

It is not known if participation in the study will be beneficial for the patient, although it is anticipated that patients will derive clinical benefit from treatment with the combination of nivolumab and chemotherapy.

2 Study Objectives and Hypotheses

2.1 Study Objectives

Primary Objective

- To determine whether the addition of nivolumab to chemotherapy improves pathologic complete response (pCR) in the breast and post-therapy lymph nodes evaluated histologically in patients with inflammatory breast cancer (IBC). *This is defined as no histologic evidence of invasive tumor cells in the surgical breast specimen, axillary nodes, or sentinel node identified after neoadjuvant chemotherapy (ypT0/Tis ypN0).*

Secondary Objectives

- To evaluate the safety and tolerability of the combination of nivolumab with neoadjuvant chemotherapy in IBC.
- To evaluate the invasive recurrence-free interval (IRFI) [time frame: up to 24 months after study entry]. *This is assessed as the time from study entry until diagnosis of the first invasive local, regional, or distant breast cancer recurrence during the 24 months after study entry.*

Correlative Objectives

- To evaluate PD-L1 expression on tumor and tumor-infiltrating immune cells as a predictor for pCR following treatment with neoadjuvant nivolumab and chemotherapy.
- To assess the frequency of mutational and neoantigen load and to explore mutational and neoantigen load as predictive markers of response.
- To assess changes in expression levels of biomarkers or biomarker panels before, during, and after treatment.

2.2 Hypotheses

Primary Hypothesis

- For HER2-negative cohort (including TNBC or HR-positive), the combination of nivolumab with neoadjuvant chemotherapy will result in a pCR rate greater than 10% in IBC.
- For HER2-positive cohort (independent of HR status), the combination of nivolumab with neoadjuvant chemotherapy will result in a pCR rate greater than 25% in IBC.

Secondary Hypotheses

- Treatment with the combination of nivolumab and chemotherapy is safe and well tolerated.
- The combination of nivolumab and chemotherapy will be active (as determined by ORR and IRFI) in patients with IBC.
- Subjects with tumoral PD-L1 expression will demonstrate improved pCR rate, clinical response, and IRFI compared to subjects without PD-L1 expression.

Exploratory Hypotheses

- Patients with tumors containing higher expression of PD-L1 and TILs will have higher pCR rate and IRFI compared with patients with tumors with little or no expression.
- Predictive biomarkers in tumor tissue and peripheral blood can be detected.

- Changes in biomarkers during therapy are predictive of clinical response or resistance in patients treated with the combination of nivolumab and chemotherapy.

3 Study Design

3.1 General Design

This is an open label, multicenter, phase II clinical trial designed to study the efficacy and safety of nivolumab in combination with neoadjuvant chemotherapy for patients with IBC (n=52).

- **Cohort 1:** HER2-negative, including TNBC or HR-positive (26 patients)
- **Cohort 2:** HER2-positive, independent of HR status (26 patients)

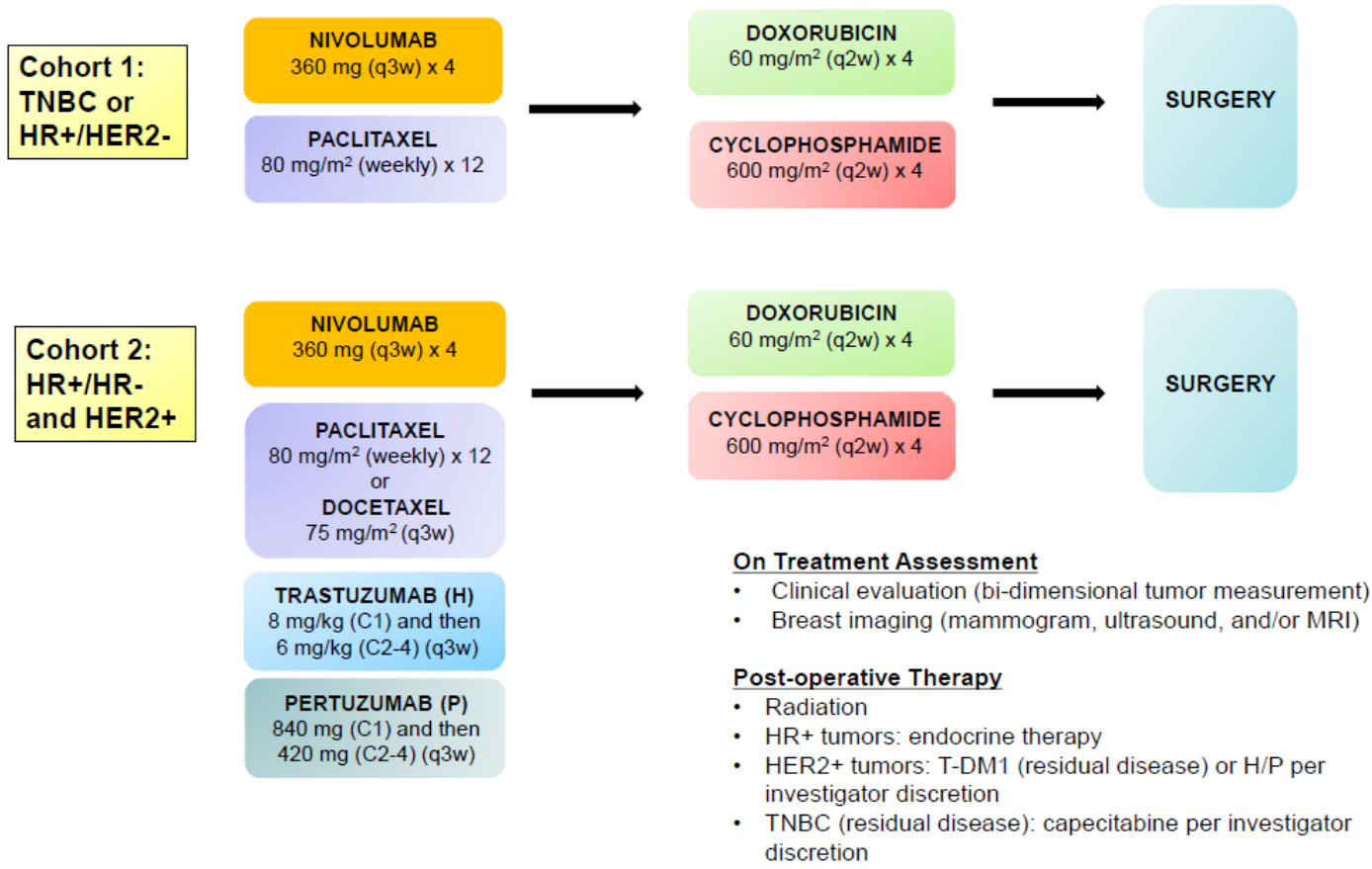
Expression of tumoral PD-L1 is not required for study entry.

There will be an interim safety analysis in Cohort 2 with 13 patients. If no more than 5 DLT is observed, then enrollment will continue to complete Cohort 2. The subjects from the interim safety analysis will be included in the final analysis. In all patients in both cohorts, safety will be closely monitored to confirm tolerability and to assess long-term impact of PD-1 blockade on immune function which remain to be established.

We plan to open the study at three sites. Two of the locations will be at NYU Perlmutter Cancer Center and its public hospital affiliate, Bellevue Hospital Center. Bellevue Hospital Center is the oldest public hospital in the United States, and the majority of patients cared for are underserved minorities and the indigent population. The breast cancer patients that are seen tend to be younger and with more aggressive disease biology including IBC. The third site will be at Indiana University. Guidelines for affiliate institutions in multicenter studies are described in Appendix 1.

After completion of neoadjuvant therapy, patients will undergo surgery with mastectomy and axillary lymph node dissection. Post-mastectomy radiotherapy (per institutional guidelines) is warranted and targets should include the chest wall and supraclavicular, infraclavicular, and internal mammary chain nodes. Patients with HR-positive tumors should receive a minimum of 5 years of adjuvant hormonal therapy. Choice of hormonal therapy is at the discretion of the investigator. For HER2-positive tumors, patients with residual disease after neoadjuvant therapy may receive ado-trastuzumab emtansine (T-DM1) in the adjuvant setting for 14 cycles[49]. Another option is to continue trastuzumab with or without pertuzumab to complete one year of HER2-directed therapy[35]. For patients with pathologic complete response (no residual disease), adjuvant trastuzumab can be continued with or without pertuzumab to complete one year of HER2-directed therapy. Treatment regimen is the discretion of the investigator. The use of adjuvant capecitabine for 6-8 cycles for patients (permissible after surgery) with TNBC with residual disease is at the discretion of the investigator[50].

Study Schema (n=52)



3.2 Primary Study Endpoint

Pathologic complete response (pCR), which is defined as no histologic evidence of invasive tumor cells in the surgical breast specimen, axillary nodes, or sentinel node(s) identified after neoadjuvant chemotherapy (ypT0/Tis ypN0).

3.3 Secondary Study Endpoints

a) Patient tolerability and safety with the combination will be assessed using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.

b) To estimate the invasive recurrence-free interval (IRFI) [time frame: up to 24 months after study entry]. This is assessed as the time from study entry until diagnosis of the first invasive local, regional, or distant breast cancer recurrence during the 24 months after study entry (would exclude contralateral new primaries).

3.4 Correlative Endpoints

A variety of factors that could potentially predict clinical response to nivolumab will be investigated in tumor specimens and peripheral blood. These will provide important information regarding biological effects of this combination therapy in IBC, and changes in patterns based on response to or resistance to therapy.

- Baseline tumoral expression of PD-L1 and expression of PD-L1 during and following treatment with nivolumab and chemotherapy as a predictor for pCR and IRFI will be evaluated. Composition of immune response will be investigated, including T cell repertoire, macrophage response, select cytokine, transcription factor, and protein kinase responses (e.g. JAK2, mTORC1, IL8, STAT3).
- The frequency of mutational and neoantigen load will be studied as predictive markers of response.
- Changes in expression levels of biomarkers or biomarker panels before, during, and after treatment will be evaluated.

4 Subject Selection and Study Assessments

4.1 Inclusion Criteria

Patients must meet ALL of the following inclusion criteria to be eligible for study entry:

- Histological diagnosis of invasive adenocarcinoma of the breast and a clinical diagnosis of IBC based on presence of inflammatory changes in the involved breast, including erythema and edema (peau d'orange), with or without an underlying palpable mass involving a third or more of the skin of the breast (T4d according to American Joint Committee on Cancer (AJCC) breast cancer staging, 8th ed.). Pathological evidence of dermal lymphatic invasion should be noted but is not required for diagnosis of IBC.
- In case of bilateral cancer, the investigator should decide prospectively which side will be evaluated for the primary endpoint.
- Local CLIA-certified laboratory testing on the tumor tissue specimen for ER, PR, and HER2 must be performed:
    - Hormone Receptor (HR)-positive: defined as estrogen receptor (ER) and/or progesterone receptor (PR) ≥1% per ASCO-CAP guidelines[60]
    - HER2-positive: IHC 3+ or 2+ with HER2/CEP17 ratio >2.0 or average HER2 copy number >6.0 signals/cell per ASCO-CAP guidelines[61]
    - TNBC: defined as ER/PR<1% and HER2-negative per ASCO-CAP guidelines[60]
- Age ≥ 18 years, individuals of all races and ethnic groups are eligible
- Eastern Cooperative Group (ECOG) performance status of 0 or 1 (see Appendix 2)
- LVEF assessment performed by echocardiogram or MUGA scan based on institutional preferences. Results must be at or above the normal limit of the institution and/or ≥50%.
- All patients with disease that is deemed by the treating Investigator as safely accessible to biopsy are required to undergo research biopsies as outlined in this protocol
- Ability to understand and willingness to sign a written informed consent document or if appropriate, have an acceptable surrogate capable of giving consent on the subject's behalf
- Adequate hematologic and end-organ function, as evidenced by the following local laboratory results obtained within 28 days prior to the first study treatment (Cycle 1, Day 1):

Table 6: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥ 1,500/mcL
Platelets	≥ 100,000/mcL (without transfusion within 1 week prior to Cycle 1, Day 1)
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L (without transfusion or EPO dependency within 1 week prior to Cycle 1, Day 1)
Renal	
Serum creatinine **OR**	≤ 1.5 X upper limit of normal (ULN)

Measured or calculated creatinine clearance[a] (can also be used in place of creatinine or CrCl)	**OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST and ALT	≤ 2.5 X ULN
Albumin	≥ 2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard	

- For women of childbearing potential (pre-menopausal women and women less than 12 months after the onset of menopause): must have a pregnancy test every 4 weeks and must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive measures (barrier methods, intrauterine contraceptive devices, sterilization) during study treatment and for a total of 5 months post-treatment completion. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm

4.2 Exclusion Criteria

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

- Definitive clinical or radiologic evidence of distant metastases
- Has a known additional malignancy that progressed within the last five years
- Cardiac disease (history of and/or active disease) that would preclude the use of the drugs included in the treatment regimens
- Patients known to be HIV positive
- Neuropathy ≥ Grade 2, per the NCI CTCAE v5.0
- History of allogeneic stem cell or solid organ transplantation
- Has active clinically significant autoimmune disease where in the opinion of the Investigator would preclude the use of immunotherapy
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), or evidence of active pneumonitis
- Patients with clinically active tuberculosis
- Pregnancy or lactation at the time of enrollment
- Prior treatment with CD137 agonists or immune checkpoint−blockade therapies, including anti-CD40, anti−CTLA-4, anti−PD-1, and anti−PD-L1 therapeutic antibodies
- Treatment with systemic immunosuppressive medications (including but not limited to interferons, IL-2) within 28 days or 5 half-lives of the drug, whichever is longer, prior to study entry

- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis [anti-TNF] factor agents) within 2 weeks prior to randomization or anticipation of need for systemic immunosuppressive medications during the study.
- CardiopuImonary dysfunction as defined by:
    - Inadequate LVEF at baseline, <50% by either TTE or MUGA
    - History of symptomatic congestive heart failure (CHF): Grade ≥ 3 per NCI CTCAE version 5.0 or Class ≥ II per New York Health Association
    - History of a decrease in LVEF to <40% or symptomatic CHF
    - Myocardial infarction or unstable angina within 6 months of start of study treatment
    - Current dyspnea at rest due to complications of malignancy, or other disease requiring continuous oxygen therapy
    - Corrected QT interval (QTc) >450 msec on screening EKG
- Clinically significant history of liver disease, including cirrhosis, autoimmune hepatic disorders, HIV infection, or active Hepatitis B or Hepatitis C
    - Active infection requiring treatment with antiviral therapy or presence of positive test results for Hepatitis B (e.g. Hepatitis B surface antigen and/or total Hepatitis B core antibody) or HCV antibody.
    - HBV and HCV assessments are required at screening.
    - Patients who test positive for Hepatitis B core antibody are eligible if polymerase chain reaction (PCR) is negative for HBV DNA
    - Patients who are positive for HCV serology are only eligible if testing for HCV RNA is negative
- Subject is pregnant or nursing
- Known documented or suspected hypersensitivity to the components of the study drugs(s)

4.3 Subject Recruitment/Screening and Clinical Procedures/Assessments

Target enrollment for this study is 52 patients. Patients will be recruited from physicians at the NYU Perlmutter Cancer Center and its nearby public hospital affiliate, Bellevue Hospital Center, as well as through outside referrals. In addition, patients will be recruited at Indiana University.

Consenting, screening and treatment will take place under the supervision of the Investigator. Prospective subjects receive detailed information about this study and its investigational nature, required study procedures, alternative treatments, risks, and potential benefits of the study. They also receive the informed consent document to read. All questions are answered by the PI and qualified research personnel. Recruitment and consenting will take place in a private area such as an exam room to protect the patient's privacy.

Prior to study entry, a patient's eligibility must be approved in writing (email is allowed) by the NYU CTO study coordinator.

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.

2. Determine patient eligibility (See Section 4.1 and 4.2).

3. Submit registration to NYU Perlmutter Cancer Center CTO.

4. Receive registration confirmation from NYU Perlmutter Cancer Center CTO, including unique study identification number assigned to the patient that will be distributed to the study team upon registration of the patient.

The informed consent process and documentation follows established procedures of the NYU Langone Health Perlmutter Cancer Clinical Trials Office.

4.3.1 Informed Consent

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

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the NYU Institutional Review Board's (IRB) approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to NYU IRB requirements, applicable laws and regulations, and Sponsor requirements.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies.

For patients who cannot read, a witness, not related to the research study, will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The Investigator will ask the patient questions to ensure s/he understands the study. If the Investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

4.3.2 Documentation of Consent

The Principal Investigator or IRB approved sub-Investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

4.3.3 Multi-Site Surveillance

As the lead investigator in a multi-site trial, the Overall Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's quarterly Data and Safety Monitoring reports to the Data Safety and Monitoring Committee (DSMC) to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's quarterly review to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PCC Clinical Trial Office, Quality Assurance Unit will provide a remote extensive monitoring including real-time review of all eCRF's to ensure completeness and compliance with the protocol (100% source documentation verification). Additionally, a first subject audit is to be completed

with four weeks of enrollment.

4.3.4 Patient Informed Consent at Additional Sites

See Appendix 1.

4.3.5 Inclusion/Exclusion Criteria

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

4.3.6 Medical History

A medical history will be obtained by the Investigator or qualified designee. Medical history will include all active conditions, including cardiac history, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

4.3.7 Prior Medications

The Investigator or qualified designee will review prior medication use and record prior medication(s) taken by the subject within 30 days before enrolled in this study. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

4.3.8 Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable serious adverse events (SAE) and events of clinical interest (ECI) should be recorded as defined in Section 8.2.

4.3.9 Disease Details

The Investigator or qualified designee will obtain prior and current details regarding disease status as per AJCC 8th edition.

Clinical Procedures/Assessments

4.3.10 Adverse Event (AE) Monitoring

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Study Schedule of Events (Section 6.1) and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

4.3.11 Full Physical Exam

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

4.3.12 Directed Physical Exam

At subsequent visits (or as clinically indicated), directed physical examinations can be performed. Changes from baseline abnormalities should be recorded in the patient notes.

4.3.13 Vital Signs

The Investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, and at treatment discontinuation as specified in the Study Schedule of Events (Section 6.1). Vital signs should include temperature, pulse, respiratory rate, weight, height (Screening only) and blood pressure.

4.3.14 Eastern Cooperative Oncology Group (ECOG) Performance Status

The Investigator or qualified designee will assess ECOG performance status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in Study Schedule of Events (Section 6.1) and Appendix 2.

4.3.15 Collection of Tumor Tissue Prior To Treatment

Collection of formalin-fixed paraffin-embedded (FFPE) tumor tissue from diagnostic core biopsy within 60 days prior to enrollment (Cycle 1 Day 1) is required. If available, a fresh biopsy sample is preferred. Testing by a CLIA-certified local laboratory on the tumor tissue specimen for ER, PR, and HER2 must be performed.

4.3.16 Tumor Imaging/ Cardiac Imaging

Initial imaging assessments must include bilateral mammogram and/or bilateral ultrasound. Bilateral breast MRI is optional. Imaging must also be performed at screening to rule out distant disease. CT scans (with IV contrast and oral contrast unless contraindicated) of the chest, abdomen, and pelvis or Positron emission tomography (PET)/CT may be used. If a CT scan for tumor assessment is performed as part of a PET/CT, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. MRI scans of the chest, abdomen, and pelvis may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). A bone scan or PET scan should be performed to evaluate for bone metastases if there is clinical suspicion for osseous metastases. Imaging assessments should be done within 60 days prior to enrollment (Cycle 1 Day 1).

LVEF assessment by echocardiogram (TTE) or by MUGA scan is required within 60 days prior to enrollment (Cycle 1 Day 1).

4.3.17 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided in the Study Schedule of Events (Section 6.1).

Laboratory tests for screening or entry into the study should be performed within 30 days prior to enrollment (Cycle 1 Day 1). For subsequent cycles after Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the treating Investigator and found to be acceptable prior to each dose of trial treatment.

4.3.18 Tumor Assessment during Study Treatment

Clinical evaluation, with a bidimensional measurement of the tumor, will be performed every three weeks during Cycle 1-4 and every two weeks during Cycle 5-8. For subjects with no palpable mass, changes in clinically evaluable skin criteria (such as erythema, edema, peau d'orange) will be considered as response criteria. Patients should also have re-evaluation of the primary tumor by imaging with either mammography,

breast ultrasound, and/or breast MRI after the end of Cycle 8 (prior to surgery). In the case of progressive disease, see Section 6.2.

4.3.19 Screening Period

The screening phase is the interval between the signing of the Informed Consent Form (ICF) and the day the subject is enrolled in the study (Cycle 1 Day 1). Informed consent must be obtained prior to performing any study-specific procedures. Assessments that are required to demonstrate eligibility may be performed over 1 or more days during this phase.

Screening procedure timeline:

- Laboratory tests and EKG may be performed within 30 days prior to enrollment.
- Women of reproductive potential must have a negative urine or serum pregnancy test within 24 hours prior to first dose of study treatment.
- Tumor tissue biopsy may be obtained within 60 days prior to enrollment
- Tumor imaging assessment may be done within 60 days prior to enrollment.
- Echocardiogram or MUGA assessment may be done within 60 days prior to enrollment.

Results of tests done as standard of care prior to signing consent may be used for screening and confirmation of eligibility information if performed within the specified time frame.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility prior to enrollment/administration of study drug via investigator and CTO personnel. Tests with results that fail eligibility requirements may be repeated once during the screening phase, if the Investigator believes the results to be in error or not representative. Additionally, a subject who fails screening may repeat the screening process one time, if the Investigator believes there has been a change in eligibility status (e.g. following recovery from an infection).

Additionally, the screening period will be utilized to determine the baseline assessments of clinical condition and disease status. Tumor assessments appropriate to the type of malignancy will be performed and recorded in the case report form (CRF).

4.4 Registration Procedures

4.4.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care. Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU PCC Clinical Trials Office. The following materials must be submitted to the CTO for subject registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist
3. All supporting documentation verifying each eligibility criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration.

Once eligibility is verified, a unique patient study number will be issued within 48 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study.

4.4.2 Patient Registration at Other Participating Institutions

See Appendix 1.

4.5 Early Withdrawal of Subjects

Subjects may be withdrawn from the study prior the expected completion of that subject for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent
- Disease progression or occurrence of a secondary malignancy which requires systemic therapy or radiotherapy for treatment.
- Unacceptable adverse events as described in Section 5.3
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up

4.5.1 When and How to Withdraw Subjects

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 4.5.

The End of Treatment and Follow-up visit procedures are listed in the Study Schedule of Events (Section 6.1) and Section 6.4. After the end of treatment, each subject will be followed for 100 days for adverse event monitoring. This monitoring may be done remotely. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up after last dose of treatment for disease recurrence, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up.

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such subjects throughout the protocol defined follow-up period for that subject. Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study, attempts should be made to obtain permission to record survival data up to the protocol-described end of subject follow-up period.

5 Study Drug

5.1 Description

Nivolumab, also referred to as BMS-936558-01 or BMS-936558, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. The physical and chemical properties of nivolumab are:

Molecular Weight:	146,221 daltons (143,619.17 daltons, protein portion)
Appearance:	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may

	be present
Solution:	pH 5.5 to 6.5

5.1.1 Pharmaceutical Properties and Formulation

Nivolumab Injection, 100 mg/10 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), at pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

5.1.2 Drug Product Preparation

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered 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 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4mL per kg of patient weight.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection is available in current Investigator Brochure and Prescribing Information. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride or polyolefin containers and infusion sets, and glass bottles.

5.1.3 Recommended Storage and Use Conditions

Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

5.2 Treatment Regimen

Treatment will be administered on an outpatient basis. Nivolumab is the *investigational product (IP)* of this trial and will be provided by Bristol-Myers Squibb (BMS). Chemotherapy with docetaxel, paclitaxel, doxorubicin, cyclophosphamide, trastuzumab, or pertuzumab is considered *Non-IP* as it represents routine or standard of care treatment for the respective patient population. Chemotherapy will not be provided by BMS and must be selected by the Investigator as part of standard of care therapy.

IP treatment

Nivolumab: Nivolumab will be given at 360mg intravenously (IV) on Day 1 of every 21 day cycle during

Cycle 1-4.

Non-IP treatment

Cohort 1: TNBC or HR-positive/HER2-negative:

Paclitaxel: Paclitaxel will given at 80 mg/m^2 IV weekly x 12 during Cycle 1-4.
Doxorubicin: Doxorubicin will be given at 60 mg/m^2 IV every two weeks x 4 during Cycle 5-8.
Cyclophosphamide: Cyclophosphamide will be given at 600 mg/m^2 IV every two weeks x 4 during Cycle 5-8.

Doxorubicin and Cyclophosphamide will be administered with G-CSF support.

Cohort 2: HR-positive/HR-negative and HER2-positive:

Docetaxel: Docetaxel will be given at 75 mg/m^2 IV every three weeks x 4 during Cycle 1-4.
Paclitaxel (may be substituted for Docetaxel): Paclitaxel will be given at 80 mg/m^2 IV weekly x 12 during Cycle 1-4.
Trastuzumab*: Trastuzumab will be given at 8 mg/kg IV on day 1 of Cycle 1 and then 6 mg/kg IV on day 1 of Cycle 2-4 every three weeks.
Pertuzumab: Pertuzumab will be given at 840 mg IV on day 1 of Cycle 1 and then 420 mg IV on day 1 of Cycle 2-4 every three weeks.
Doxorubicin: Doxorubicin will be given at 60 mg/m^2 IV every two weeks x 4 during Cycle 5-8.
Cyclophosphamide: Cyclophosphamide will be given at 600 mg/m^2 IV every two weeks x 4 during Cycle 5-8.

Doxorubicin and Cyclophosphamide will be administered with G-CSF support.
*Trastuzumab biosimilar is allowed.

5.2.1 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it has a low incidence of 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 as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 5.0) guidelines.

Treatment recommendations are provided below:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated).

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30

minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.

- For future infusions, the following prophylactic pre-medications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor 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).

5.3 Dosage Modification

Dose reductions or dose escalations for nivolumab are not permitted.

5.3.1 Nivolumab Dose Delay Criteria for Study Treatment

Study drug administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
- Any adverse event, laboratory abnormality, or intercurrent illness, which in the judgment of the investigator, warrants delaying the dose of study medication.
- Dose delay for AST, ALT, or Total Bilirubin abnormalities should be managed as follows:
  - If a participant has a baseline AST, ALT, or Bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a participant has baseline AST, ALT, or Bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
  - If a participant has baseline AST, ALT, or Bilirubin within the Grade 2 toxicity range, delay dosing for a 2-fold drug-related increase in AST, ALT or Bilirubin, or for AST, ALT or bilirubin values 8 x ULN (whichever is lower)

Participants who require delay of study treatment should be re-evaluated weekly or more frequently if clinically indicated and resume study treatment when re-treatment criteria are met (See Section 5.3). See also Appendix 3 (Algorithms for Management of Side Effects of Nivolumab) for guidance on appropriate management and follow-up of adverse events.

5.3.2 Criteria for Discontinuation of Nivolumab

Study treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related AE lasting >7 days or recurs:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
    - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation
            - AST or ALT >10 x ULN for >2weeks
            - AST or ALT >15 x ULN irrespective of duration
            - Total bilirubin >5 x ULN for those participants with normal total bilirubin at entry or >8 x ULN for participants with elevated bilirubin at study entry, irrespective of duration
- 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 or asymptomatic amylase or lipase
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Sponsor's Medical Monitor or designee.
- Any event that leads to delay in dosing lasting >6 weeks from the previous dose requires discontinuation, with the following exceptions:
    - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
    - Dosing delays lasting >6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor's Medical Monitor or designee.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued study treatment.

5.3.3 Criteria To Resume Treatment with Nivolumab

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

- Participants with baseline Grade 1 AST, ALT, or Total Bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or Total Bilirubin.
- Participants who require dose delays for drug-related increased AST, ALT, or Total Bilirubin may resume treatment when hepatic parameters are at baseline or Grade 1 and after discussion with Sponsor's Medical Monitor or designee.
- Participants with AST, ALT, or Total Bilirubin values meeting discontinuation should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by Sponsor's Medical Monitor or designee.
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with Sponsor's Medical Monitor or designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

5.3.4 Recommendations for Chemotherapy Delays and Modifications

In the opinion of the investigator, if a toxicity is considered to be attributable solely to one component of the study treatment and the dose of that component is delayed or modified in accordance with the guidelines below, the other component may be administered if there is no contraindication.

Table 7 Dose Modification Levels for Docetaxel / Paclitaxel

Level	Dose Level 0 (starting dose) (mg/m^2)	Dose Level -1 (mg/m^2)	Dose Level -2 (mg/m^2)	Dose Level -3 (mg/m^2)
Docetaxel (mg/m^2)	75	60	50	Discontinue
Paclitaxel (mg/m^2)	80	60	50	Discontinue

General dose modification guidelines:

- If a taxane-related hypersensitivity reaction occurs despite pre-medication, treatment as medically indicated will be instituted.
    - ❖ For hypersensitivity reaction less than CTCAE Grade 3, continuation of docetaxel/paclitaxel is at the Investigator's discretion.
    - ❖ If Grade 4 hypersensitivity is experienced, docetaxel/paclitaxel must be permanently discontinued.
    - ❖ If the taxane is discontinued, an alternative taxane may be substituted (nab-paclitaxel or docetaxel if paclitaxel was discontinued). Dosing and schedule of alternative taxane is as per institutional standard of care.
- Taxane-related fluid retention will be treated as per the Investigator's discretion.
- For HER2-positive tumors, if the taxane must be discontinued before completion of the scheduled cycles, the remaining trastuzumab and pertuzumab can be administered.
- For patients who are dose reduced due to Grade 2 or Grade 3 toxicity, they may return to the starting dose level if the AE returns to baseline or Grade 1, per discretion of the Investigator.
- Dose level reductions that are below the recommended level in the tables can be made per discretion of the Investigator.

See Table 8 for the management of taxane-related neurosensory toxicity and Table 9 for taxane-related musculoskeletal pain. Instructions for management of all other toxicities related to docetaxel/paclitaxel are listed in Table 11.

Table 8 Dose modifications for taxane-related neurosensory toxicity

Paresthesias/Dysesthesias	**1 – 7 Days Duration**	**Persistent for >7 Days**
Grade 1	Maintain *docetaxel/paclitaxel* dose	Maintain *docetaxel/paclitaxel* dose
Grade 2	Maintain *docetaxel/paclitaxel* dose	Decrease *docetaxel/paclitaxel* one dose level
Grade 3[a]	First episode: Decrease *docetaxel/paclitaxel* one dose level Second episode: Decrease *docetaxel/paclitaxel* *two dose levels*	Decrease *docetaxel/paclitaxel* *two dose levels* *OR* Discontinue *docetaxel/paclitaxel*

[a] For persistent paresthesias/ dysesthesias that are disabling or life-threatening, docetaxel/paclitaxel should be discontinued.

Table 9 Dose modifications for taxane-related musculoskeletal pain *not controlled by analgesics*[a]

Musculoskeletal pain	**1 – 7 Days Duration**	**Persistent for >7 Days**
Grade 1	Maintain *docetaxel/paclitaxel* dose	Maintain *docetaxel/paclitaxel* dose
Grade 2	Maintain *docetaxel/paclitaxel* dose	Decrease *docetaxel/paclitaxel* one dose level
Grade 3	First episode: Decrease *docetaxel/paclitaxel* one dose level Second episode: Decrease *docetaxel/paclitaxel* *two dose levels*	First episode: Decrease *docetaxel/paclitaxel* one dose level OR Decrease *docetaxel/paclitaxel* *two dose levels* Second episode: Discontinue *docetaxel/paclitaxel*

[a] Use of analgesics can be used to maintain dose of docetaxel/paclitaxel if possible.

Table 10 Dose Modification Levels for Doxorubicin / Cyclophosphamide

Level	**Dose Level 0 (starting dose) (mg/m^2)**	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3 (mg/m^2)**

Doxorubicin (mg/m^2)	60	50	40	Discontinue
Cyclophosphamide (mg/m^2)	600	500	400	Discontinue

- For patients who are dose reduced due to Grade 2 or Grade 3 toxicity, they can return to the starting dose if the AE returns to baseline or Grade 1, per discretion of the Investigator
- Dose level reductions that are below the recommended level in the tables can be made per discretion of the Investigator.

Table 11 Dose modifications and delays for docetaxel / paclitaxel / doxorubicin / cyclophosphamide

NCI CTCAE v 5.0 [Category] Grade		**Modifications for AEs[b]**
HEMATOLOGICAL:		
Neutrophil count decreased		
Grades 2, 3, 4		*Hold until ≥ 1500/mm^3* *If recovery takes:* • 1-3 wks: maintain dose and add G-CSF *If previously receiving G-CSF and recovery takes:* • 1 wk: maintain dose • 2-3 wks: decrease one dose level
Platelet count decreased		
Grades 2, 3		*Hold until ≥ 75,000/mm^3.* *If recovery takes:* • 1 wk: maintain dose • 2-3 wks: decrease one dose level
Grade 4		Decrease one dose level
BLOOD AND LYMPHATIC SYSTEM DISORDERS:		
Febrile Neutropenia		
Grade 2		Maintain dose
Grade 3 (first episode)		Maintain dose and add G-CSF
Grade 3 (subsequent episodes)		Decrease one dose level
Grade 4 (first episode)		Decrease one dose level
Grade 4 (subsequent episodes_		Decrease two dose levels or discontinue
GASTROINTESTINAL DISORDERS *(if related to chemotherapy):*		
Diarrhea		
Grade 2		Maintain dose
Grade 3		Decrease one dose level

Grade 4		Decrease two dose levels or discontinue
Mucositis		
Grade 2		Maintain dose
Grade 3		Decrease one dose level
Grade 4		Decrease two dose levels or discontinue
Vomiting (despite antiemetics)		
Grade 2		Maintain dose
Grade 3		Decrease one dose level
Grade 4		Decrease two dose levels or discontinue
HEPATIC FUNCTION:		
Bilirubin or AST or ALT increased		
Grade 2		*Hold until bilirubin returns to baseline and AST and ALT have returned to ≤ grade 1.* Then decrease one dose level.
Grade 3		*Hold until bilirubin returns to baseline and AST and ALT have returned to ≤ grade 1.* Then decrease one dose level.
Grade 4		Discontinue
OTHER CLINICALLY SIGNIFICANT AEs:		
Grade 3		Decrease one dose level
Grade 4		Decrease two dose levels or discontinue

Table 12 ***Left ventricular dysfunction***

Adverse Event	**Grade**			
	1	**2**	**3**	**4**
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated

For symptomatic heart failure, treatment includes management per standard evidence-based guidelines and management of any concurrent conditions (such as hypertension) and fluid management with diuretic therapy as needed.

For asymptomatic decline to an LVEF <40% and at least 15 percentage points to LVEF <50%, doxorubicin and cyclophosphamide should be held and repeat imaging with TTE or MUGA performed in two to four weeks. If LVEF is improved to ≥50%, then treatment can be resumed.

Dose modifications for trastuzumab and pertuzumab

No dose reduction is recommended. In case of severe toxicity probably related to these compounds, treatment should be discontinued. If toxicity is recovered within three weeks to Grade 1, a restart of

treatment should be considered at the discretion of the treating investigator.

If the patient misses a dose of trastuzumab or pertuzumab for any cycle, i.e., the two sequential administration times are 6 weeks or more apart, a re-loading dose of 8 mg/kg of trastuzumab and pertuzumab 840 mg IV should be given. If re-loading is required for a given cycle, the study therapies should be given at the same schedule.

Refer to algorithm in Appendix 5 to assist in the decision as to whether to initiate, continue or discontinue therapy based on LVEF assessment in asymptomatic patients.

5.4 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that the investigational produce is only dispensed to study participants. The investigational product must only be dispensed from official study sites by authorized personnel according to local regulations. The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS or designee immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration, and as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required dilutents, administration sets).

5.5 Subject Treatment Compliance Monitoring

Study treatment will be administered in the clinical facility. Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF.

5.6 Concomitant Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study treatment discontinuation visit. All such medications must be reported to the Investigator and recorded in the Concomitant Medications CRF.

Subjects must be instructed not to take any additional medications during the study without prior consultation with the Investigator. Any medications including herbal supplements, vitamins, or treatment taken by the subject from 30 days prior to the start of study treatment and up to 30 days following the last dose of investigational products and the reason for their administration must be recorded on the CRF.

5.6.1 Prohibited Therapies with Nivolumab

The following medications are prohibited during the study (unless authorized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids
- Traditional herbal medicines: These therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity
- Concurrent use if antiviral therapy containing IFN

- Excessive alcohol intake should be avoided (occasional to moderate use is permitted)

5.6.2 Permitted Therapies with Nivolumab

The following therapies are permitted as concomitant medications in the study:

- Prophylactic or therapeutic anticoagulation therapy (such as low-molecular weight heparin or warfarin at a stable dose level)
- Inactive influenza vaccinations during influenza season
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids for subjects with orthostatic hypotension or adrenocortical insufficiency
- Bisphosphonates for prevention of skeletal related events

Subjects who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2-receptor antagonist per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists).

6 Study Procedures

6.1 Study Calendar/Study Schedule of Events

See Study Schedule of Events on next page.

Study Activity	Screening Phase[a]	Treatment Phase (Cycle 1-4 = 21 days; Cycle 5-8 = 14 days)[b]								After End of Treatment and Prior to Surgery	Time of Surgery	Post Surgery[l]	End of Study Follow-up[j]
Treatment Cycle	-60 to -1 (days)	1	2	3	4	5	6	7	8		≤ 12 weeks after last treatment		
Scheduling Window		± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days				
Clinical Procedures/Assessments													
Informed Consent[c]	X												
Inclusion/Exclusion Criteria[d]	X												
Demographics and Medical History[e]	X												
Prior and Concomitant Medications Review[f]	X	X	X	X	X	X	X	X	X				
Physical Examination[g]	X	X	X	X	X	X	X	X	X				
ECOG Performance Status	X	X	X	X	X	X	X	X	X				

Vital Signs and Weight[g]	X	X	X	X	X	X	X	X	X				
Height[g]	X												
Neoadjuvant Treatment Administration[h]		X	X	X	X	X	X	X	X				
Review Adverse Events[i]		X	X	X	X	X	X	X	X				
Follow-up for recurrence-free survival[j]													X (up to two years)
Laboratory Procedures/Assessments													
Pregnancy Test – Urine or Serum β-HCG (women of childbearing potential)[k]	X (within 24 hours prior to start of nivolumab)	X	X	X	X	X	X	X	X				
CBC with Differential[l]	X	X	X	X	X	X	X	X	X				
Comprehensive Serum Chemistry Panel (Blood Chemistry and Liver Function Tests)[l]	X	X	X	X	X	X	X	X	X				
TSH, free T3 (or total T3), and free T4[l]	X					X							
HBV and HCV testing[l]	X												
Urinalysis[l]	X												

12-Lead EKG[m]	X												
Cardiac echo (TTE) or MUGA scan[n]	X (within 60 days)	Continue q 3 months											
Treatment													
Nivolumab (Day 1 of Cycle 1-4)[o]		X	X	X	X								
Chemotherapy[p]		X	X	X	X	X	X	X	X				
Radiation[q]												X	
Adjuvant therapy[r]												X	
Tumor Assessment and Imaging Procedures													
Clinical tumor assessment[s]	X	X	X	X	X	X	X	X	X				
Imaging tests[t]	X (within 60 days)									X			
Tumor Biopsies/Archival Tissue Collection/Blood for Correlative Studies													
Archival or Newly Obtained Tissue Collection[u]	X (within 60 days)				X (optional)						X (if residual disease)		
Peripheral Blood Collection[v]		X				X			X				

1 Within 3 months (± 14 days) post-surgery

a Screening Phase: All screening evaluations must be completed and reviewed to confirm that subjects meet all inclusion criteria and do not meet any of the exclusion criteria.

b Treatment Phase: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. For Cycle 1-4, a cycle is defined as 21 days, starting with the first dose of treatment drug at baseline (Cycle 1, Day 1) and following the pre-defined visit schedule throughout the treatment period (± 3 days). For Cycle 5-8, a cycle is defined as 14 days, starting with the first dose of treatment drug at baseline (Cycle 1, Day 1) and following the pre-defined visit schedule throughout the treatment period (± 3 days).

c Informed Consent: Informed consent must be obtained prior to any protocol required screening assessments being performed, which is not performed as part of standard routine care.

d Inclusion Criteria: See Section 4.1 for inclusion criteria and Section 4.2 for exclusion criteria.

e Demographics and Medical History: Medical history includes clinically significant diseases that are currently active or that were active, including major surgeries, within the previous 10 years, any cancer history (including prior cancer therapies and procedures) and reproductive status. Demographic data includes age, sex, stratification factors, and self-reported race/ethnicity.

f Any concomitant medications and treatments will be recorded from 30 days prior to starting treatment and up the end of the Treatment Phase.

g At screening, a physical examination including palpation of breast/chest wall, axilla, supra- and infraclavicular region, height, weight, blood pressure and pulse rate is required. This should be done within 30 days prior to enrollment (Cycle 1 Day 1). Directed physical examinations including clinical assessment of tumor, blood pressure, weight and pulse rate can be performed at subsequent visits.

h. See Section 1.4 for dose and schedule of treatment administration with nivolumab (IP), chemotherapy, and/or HER2-targeted therapy. At each visit, prior to IP dispensation, an AE and laboratory-based assessment must be performed by the Investigator for evaluation of potential dose delay, reduction, or discontinuation according to the protocol.

i AEs/SAEs must be reported from the date of signature of informed consent form for all enrolled patients until a minimum of 100 days following the last dose of study treatment. Adverse Events that occur during the screening phase and are deemed to be serious and related to any study specific procedure should be reported to the Study Sponsor. SAEs must be reported within 24 hours of site awareness (see Section 8.3 for further instructions). AEs fulfilling the criteria for expedited reporting have to be treated according to the reporting procedures described in Section 8.3 including a submission to the Sponsor within 24 hours of awareness.

j After surgery, subjects will be followed every 3 months (± 14 days) thereafter until end of study which is up to 2 years. Subjects will be followed for the occurrence of local or distant recurrence and/or death. If an in-person visit is unable to be performed, a telemedicine encounter (video or telephone) is allowed.

k Women of child-bearing potential must have a pregnancy test every 4 weeks and must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.

l Laboratory tests: Hematology includes hemoglobin, WBC, absolute neutrophil count, and platelet count. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (or urea), serum creatinine, and albumin. Hepatitis B and C screening is required. Thyroid Stimulating Hormone (TSH), free T3 (or total T3), and free T4 will be checked at screening and during Cycle 5. Abnormal endocrine results should be followed up per standard of care, and may require an endocrine consult and additional testing. Additional hematology/chemistry panels may be performed as clinically indicated. INR and aPTT will be done during screening period and afterward as clinically indicated. Laboratory tests for screening or entry into the study should be performed within 30 days prior to enrollment (Cycle 1 Day 1).

l Urinalysis will be done at screening and afterward as clinically indicated. Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood. Laboratory tests for screening or entry into the study should be performed within 30 days prior to enrollment (Cycle 1 Day 1).

m A 12-lead EKG is required within 30 days prior to enrollment (Cycle 1 Day 1). Subsequent EKGs may be performed as clinically indicated. EKGs for each subject should be obtained from the same machine wherever possible. EKG recordings must be performed after the subject has been resting in a supine position for at least 10 minutes.

n LVEF assessment by TTE or by MUGA scan within 60 days prior to enrollment (Cycle 1 Day 1). The same method should be used throughout the study for each subject if possible. LVEF assessment will be performed every three months (±7 days), during study treatment (Cycle 1-8). For subjects with HER2-positive tumors, LVEF assessment will continue every three months (±7 days) thereafter while receiving adjuvant T-DM1, trastuzumab, and/or pertuzumab.

o Nivolumab (IP) will be administered at each Day 1 (±3 days) onsite visit during Cycle 1-4. At each visit, prior to IP dispensation, an AE and laboratory-based assessment must be performed by the Investigator for evaluation of potential dose delay or discontinuation.

p See Section 1.4 for dose and schedule of treatment administration with chemotherapy and/or HER2-targeted therapy. At each visit, prior to IP dispensation, an AE and laboratory-based assessment must be performed by the Investigator for evaluation of potential dose delay, reduction, or discontinuation according to the protocol.

q Radiation: Post-mastectomy radiotherapy as per institutional guidelines

r See Section 1.4 for postoperative adjuvant therapy (regarding endocrine therapy, capecitabine, T-DM1, trastuzumab, and pertuzumab)

s Clinical evaluation, with a bidimensional measurement of the tumor, will be performed every three weeks during Cycle 1-4 and every two weeks during Cycle 5-8. The presence of erythema, edema, and/or peau d'orange should also be noted. For subjects with no palpable mass, changes in clinically evaluable skin criteria (erythema, edema, peau d'orange), will be considered as response criteria.

t Tumor assessments performed as standard of care and within 60 days prior to enrollment (Cycle 1 Day 1). Initial imaging assessments must include bilateral mammogram and/or bilateral ultrasound. Bilateral breast MRI is optional. Imaging must also be performed at screening to rule out distant disease. CT scans (with IV contrast and oral contrast unless contraindicated) of the chest, abdomen, and pelvis or Positron emission tomography (PET)/CT may be used. If a CT scan for tumor assessment is performed as part of a PET/CT, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. MRI scans of the chest, abdomen, and pelvis may be used in subjects for whom CT scans with contrast are contraindicated (i.e., subjects with contrast allergy or impaired renal clearance). A bone scan or PET scan should also be performed to evaluate for bone metastases if there is clinical suspicion for osseous metastases. Re-evaluation of the primary tumor by imaging with either mammography, breast ultrasound, and/or breast MRI should be performed after the end of Cycle 8 (prior to surgery).

u FFPE archival tumor specimen or a fresh core biopsy (preferred) (optimally at least 2 cores) within 60 days prior to enrollment (Cycle 1 Day 1) is required. An optional core biopsy can be obtained at end of Cycle 4 (± 7 days) for correlatives. Tissue specimen will be obtained at the time of surgery if there is residual disease. A tumor block is preferred, however if a block is not feasible, a minimum of 15-20 unstained slides from the resected tumor is allowed.

v Correlative studies blood collection: Maximum of 40 cc collected per time point

6.2 Treatment discontinuation due to early progression or toxicity

If a subject shows progressive disease (increase in tumor area by 25% or detection of new lesion) or treatment has to be discontinued due to toxicity, subjects wish, or other reasons, further treatment decisions have to be made individually by the Investigator.

Immediate surgery (in the case of given operability), radiotherapy (in the case of inoperability) or continuation of systemic treatment have to be discussed with the subject. It is recommended to the investigator to follow as closely as possible protocol guidelines for surgical or radiation treatment as well as for postsurgical systemic treatment as the subject still remains a study participant and will be included in the intent-to-treat analysis. Only a subject who has withdrawn her consent for data collection will be excluded from the analysis.

With regard to continuation of neoadjuvant systemic therapy, the following recommendations are made:

For HER2-negative disease, if tumor progression or intolerable toxicity occurs during the taxane-based cycles (paclitaxel or docetaxel), subjects may skip the remaining taxane cycles and continue with doxorubicin and cyclophosphamide),

For HER2-positive disease, if tumor progression or intolerable toxicity occurs during the taxane-based cycles (paclitaxel or docetaxel), subjects may skip the remaining taxane cycles and continue with trastuzumab or pertuzumab.

For HER2-positive disease, if tumor progression or intolerable toxicity occurs during treatment with trastuzumab and pertuzumab, subjects may skip the remaining cycles of trastuzumab and pertuzumab and continue with the taxane (paclitaxel or docetaxel).

For both HER2-negative and HER2-positive disease, if tumor progression or intolerable toxicity occurs during the anthracycline-based cycles (doxorubicin and cyclophosphamide), systemic treatment should be discontinued and subjects should undergo immediate local treatment.

The reason and date of chemotherapy discontinuation for all subjects will be documented on the Case Report Form (e.g. progressive disease, death, adverse event, withdrawal of consent, lost to follow-up, etc.).

6.3 Surgery and Post-operative Therapy

After completion of neoadjuvant therapy, subjects will undergo surgery with mastectomy and axillary lymph node dissection, performed within 12 weeks after the last infusion of neoadjuvant therapy. Surgery will not be done in case of metastatic progression.

The third phase (adjuvant treatment) will include radiotherapy according to institutional practice. Radiotherapy targets should include the chest wall and supraclavicular, infraclavicular, and internal mammary chain nodes.

Subjects with HR-positive tumors should receive a minimum of 5 years of adjuvant endocrine therapy. Choice of endocrine therapy is at the discretion of the investigator.

For HER2-positive tumors, patients with residual disease after neoadjuvant therapy may receive ado-trastuzumab emtansine (T-DM1) in the adjuvant setting for 14 cycles[49]. Another option is to continue trastuzumab with or without pertuzumab to complete one year of HER2-directed therapy[35]. For patients with pathologic complete response (no residual disease), adjuvant trastuzumab can be continued with or without pertuzumab to complete one year of HER2-directed therapy. The choice of adjuvant therapy is at the discretion of the investigator.

The use of adjuvant capecitabine for 6-8 cycles for subjects with TNBC with residual disease at the time of surgery is at

the discretion of the investigator[50].

6.4 Post-Treatment Follow-up/End of Treatment/End of Study Visits

6.4.1 End of Treatment

See the criteria in Section 4.4 for stopping treatment prematurely.

6.4.2 Post-Treatment Follow-up and End of Study

Post-Treatment Follow-up Assessment

Adverse events will be collected for a minimum of 100 days following last dose of study treatment. The study subject will be contacted by telephone call by a member of the study team (unless there is a clinic visit in the same time frame).

After neoadjuvant treatment and surgery, all subjects will be followed up to two years for the occurrence of local or distant recurrence and death. A visit at the trial site should be performed and documented every three months (±14 days) up to two years. If an in-person visit is unable to be performed, a telemedicine (video or telephone) encounter is allowed.

End of Study Visit

Subject's end of study visit is the last formal study visit or last formal contact or an unscheduled study visit in case of early withdrawal from the study for treatment and follow-up. End of study (EOS) is defined as 24 months after study treatment.

Subjects will no longer be formally followed after completion of the end of study visit, unless adverse event(s) occur that require subsequent follow-up (i.e. unresolved AEs). All adverse events, both serious and non-serious, and deaths that are encountered during the study and within 100 days of the last study intervention should be followed.

6.4.3 Subjects Lost to Follow Up

During the duration of the study, sites will be expected to continue efforts to contact all subjects as well as regularly consult publicly available information to ascertain vital status of the subject if permissible per local regulation. In cases where sites cannot successfully contact a subject and is not able to receive appropriate publicly available information for greater than two years, the subject will be noted as lost to follow up.

Efforts will be made to contact the subject via phone calls and next of kin. If this approach is unsuccessful, then certified letters to the address on record will be sent requesting follow up via an in person visit. After two unsuccessful calls and one certified letter with no response, a subject is considered lost to follow-up; survival data will be obtained by public record.

6.4.4 Post-Study Access

At the end of the study period, BMS will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgment of the Investigator to treat the condition under study.

6.5 Correlative Studies

Associations of correlative biomarkers with pCR, other efficacy parameters, and sensitivity or resistance to therapy with the combination of nivolumab and chemotherapy will be studied. Changes in the tumor microenvironment will be evaluated[62]. This tumor tissue will be used to study possible mechanisms of resistance to study treatment. Subsequent biopsies should be taken from the same lesion, if feasible.

6.5.1 Tumor Tissue Samples

Collection of pretreatment and on treatment tumor biopsies[17]

Archived FFPE specimens from the original diagnostic tumor biopsy may be utilized. If they do not provide sufficient material for study, then new biopsies will be performed. Optimally, at least 2 core needle biopsies are preferred (prior to first dose of nivolumab and chemotherapy). Another optional core biopsy will be obtained during treatment at end of Cycle 4 (completion of nivolumab therapy). A tumor block is preferred, however if a block is not feasible, a minimum of 15-20 unstained slides are allowed. Slides should have a recommended tissue thickness of 5-10 microns.

If only minute tissue is present (recuts listed in order of priority):
1 USS 5 microns for H&E
2 USS 5 microns for PD-L1 IHC (Charged slide)
1 USS 5 microns for MP (Charged slide)
6 USS 10 microns for BC360

If optimal tissue is present, i.e. separate cores/separate blocks with good cellularity (recuts listed in order of priority):
1 USS 5 microns for H&E
2 USS 5 microns for PD-L1 IHC (Charged slide)
1 USS 5 microns for MP (Charged slide)
6 USS 10 microns for BC360
4 USS 5 microns (back up IHC and MP Charged slide)

For biopsies performed at NYULMC, the pathologist may verify the presence of leftover clinical recuts to be used for the study in case of limited samples.

Operative specimens

Tissue specimens will be obtained at the time of surgery if there is residual disease after neoadjuvant therapy. A tumor block is preferred, however if a block is not feasible, a minimum of 15-20 unstained slides from the resected tumor are allowed. Slides should have a recommended tissue thickness of 5-10 microns.

Select the area with highest tumor cellularity, (recuts listed in order of priority):
1 USS 5 microns for H&E
2 USS 5 microns for PD-L1 IHC (Charged slide)
1 USS 5 microns for MP (Charged slide)
6 USS 10 microns for BC360
4 USS 5 microns (back up IHC and MP, Charged slide)

For surgical resections performed at NYULMC, the pathologist may verify the presence of leftover clinical recuts to be used for the study in case of limited samples.

6.5.2 Characterization of Tumor Immune Cells

Immunohistochemistry (IHC) will be used to assess the number and composition of immune cells present

within FFPE tumor tissue before therapy, during treatment, and at the time of surgery[19]. Expression of PD-L1 will be measured on tumor and tumor-infiltrating immune cells. IHC analyses may include, but is not necessarily limited to, the following markers: MHC class I/II, CD8, CD-20 (active B-cells)[63], CD4 (helper T cells, regulatory T cells), FoxP3 (regulatory T cells), CD86 (M1 macrophages), CD163 (M2 macrophages), IL8 (associated with IBC)[64], and CD68 (total macrophages).

6.5.3 Tumor Genomic Analysis

RNA will be extracted from tumor samples for analysis with Nanostring assay (BC360 panel). The BC360 panel includes 776 genes across 23 key breast cancer pathways and provides information about the breast tumor microenvironment and immune response. Analysis of data will provide information about 33 biological signatures including signatures based upon the validated PAM50 and Tumor Inflammation Signature (TIS) assays. DNA will be extracted from tumor samples for analysis with a 580 genes NGS hybrid capture assay. Tumor mutational burden (TMB), defined as the number of somatic, coding base substitutions and short insertions and deletions per megabase of genome examined, will be evaluated. Blockade of PD-1 by nivolumab from binding to its ligands PDL-1 and PDL-2 may result in expansion of tumor-specific T cells. TCR sequencing will be used to determine the effect of nivolumab on the T-cell repertoire in tumor specimens. In addition, analyses of mTOR and JAK/STAT pathways, as well as inflammatory cytokines, and tumor-associated macrophages (TAMs)[65] will be performed.

6.5.4 Peripheral Blood Samples

Blood samples will be drawn at the time points identified in the Study Calendar (Section 6.1).

Key immune biomarkers will be evaluated on circulating leukocytes to evaluate changes during PD-1 blockade. In addition, the immune cell subset frequencies and expression of key receptors on PBMC will be studied to identify changes that occur after PD-1 blockade. Included in the analysis are CD4/CD8 and Th1/Th2 profiles, immunosuppressive regulatory T cells (Tregs), the development of which is promoted by PD-1/PD-L1 ligation, dendritic cells (DC), which are important APCs, and inhibitory receptors PD-1, CTLA4, TIM-3, and LAG-3, which can contribute to T cell exhaustion. Flow cytometry will be used to quantify these biomarkers. Sequential samples of PBMCs will be analyzed from subjects before and during treatment with nivolumab.

Liquid biopsy enables analysis of tumor cells and tumor DNA directly from blood. We will perform a comprehensive liquid biopsy evaluation in which whole tumor cells as well as cell-free tumor DNA are captured from blood and profiled. Genetic heterogeneity is analyzed on a single cell level and compared with the levels of cell-free tumor DNA to determine response to therapy and predict disease recurrence. DNA from circulating leukocytes is used as a control for DNA NGS and methylation.

6.5.5 Banked Biospecimens

To protect subject's confidentiality, banked biospecimens and data generated from them will be coded with the subject's study ID number. Samples will be kept in the Center for Biospecimen Research and Development (CBRD) accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the Investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. Subjects are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the Investigator.

6.5.6 Specimen Shipment

See laboratory manual for full details on specimen shipment.

7 Statistical Plan

7.1 Primary Endpoint and Sample Size Determination

The *primary endpoint* is pathological complete response (pCR). pCR is defined as no histologic evidence of invasive tumor cells in the surgical breast specimen, axillary nodes, or sentinel node identified after neoadjuvant chemotherapy. In a retrospective analysis of 527 patients with IBC at MDACC, the pCR rates after neoadjuvant chemotherapy by hormone receptor and HER2-defined subtypes were: 7.4% in HR-positive/HER2-negative, 12.4% in TNBC, 15% in HR-positive/HER2-positive, and 30.5% in HR-negative/HER2-positive[15].

For Cohort 1 (HER2-negative, including TNBC and HR-positive), a total sample size of 26 subjects with newly diagnosed IBC will be enrolled to evaluate the anti-tumor activity of the combination of nivolumab and chemotherapy in the neoadjuvant setting. With a sample size of 26 for Cohort 1, we can detect a 20% increase in pCR in patients who will be treated with the combination of nivolumab and neoadjuvant chemotherapy compared to the 10% baseline pCR in patients treated with only neoadjuvant chemotherapy[15] with two-sided alpha of 0.05 and power of 80% based on Fisher's exact test.

For Cohort 2 (HER2-positive, independent of HR status), a total sample size of 26 subjects with newly diagnosed IBC will be enrolled to evaluate the anti-tumor activity of the combination of nivolumab and chemotherapy in the neoadjuvant setting. With a sample size of 26 for Cohort 2, we can detect a 25% increase in pCR in patients who will be treated with the combination of nivolumab and neoadjuvant chemotherapy compared to the 25% baseline pCR in patients treated with only neoadjuvant chemotherapy[15] with two-sided alpha of 0.05 and power of 80% based on Fisher's exact test.

Descriptive statistics will be provided for efficacy endpoints. An estimated 70 subjects will be screened for eligibility to reach a goal of 52 participants.

The two analysis populations will be defined as:

- interim safety analysis population: all subjects in Cohort 2 who receive any amount of study drug (i.e. nivolumab).
- efficacy evaluable population: all subjects in Cohorts 1 and 2 who receive any amount of study drug (i.e. nivolumab) (i.e. All-Treated Population (AT)). Analysis of efficacy endpoints will be performed on the efficacy evaluable population. Supportive and correlative analysis will be based on AT as well.

7.2 Statistical Methods

Definition of primary outcomes/endpoint:

The primary endpoint will be pathological complete response (pCR). pCR is defined as no histologic evidence of invasive tumor cells in the surgical breast specimen, axillary nodes, or sentinel node identified after neoadjuvant chemotherapy (ypT0/Tis ypN0).

Definition of secondary outcomes/endpoints:

Safety and tolerability of the combination of nivolumab and chemotherapy will be determined using the

Common Terminology Criteria for Adverse Events (CTCAE) v5. Dose-limiting toxicity (DLT) is defined as any toxicity requiring discontinuation of nivolumab as defined in Section 5.3.2. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs, and/or AEs/SAEs leading to discontinuation will be tabulated as per NCI CTCAE v 5.0 criteria by system organ class and preferred term.

Invasive recurrence-free interval (IRFI) will be assessed [time frame: up to 24 months after study entry]. *This is defined as the time from study entry until diagnosis of the first invasive local, regional, or distant breast cancer recurrence during the 24 months after study entry.* If a subject has no event/death but the last known date alive is earlier than 24 months since study entry, then subject's IRFI should be censored (at last known alive date or date of last assessment).

Analytic plan for primary objective:

The response rate and associated 95% confidence interval will be estimated using a uniformly minimum variance unbiased estimator as per Clopper-Pearson method.

Analytic plan for secondary objectives:

a) Safety monitoring will occur continuously in the study. The safety endpoints are AEs graded using CTCAE (Version 5.0) criteria. Safety will be assessed by quantifying the toxicities by type and grade experienced by subjects who have received therapy, including serious adverse events (SAEs). Summary statistics (percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. Sequential boundaries will be used to monitor dose-limiting toxicity rate. There will be an interim safety analysis in Cohort 2. Monitoring for toxicity will follow a Bayesian-based rule for the probability that the rate of DLT exceeds a maximal tolerated level of 30%. We will assume a Beta(1,2) prior, which is prior information equivalent to one DLT observed in three treated subjects. Early termination for toxicity will be considered based on a posterior probability above 75% that the toxicity rate exceeds 30%. A formal dose-limiting toxicity (DLT) evaluation (assessed on day 21) will be done after the first 13 subjects for the interim safety analysis have completed treatment with combination of nivolumab and chemotherapy. If no more than 5 of the first 13 subjects have DLT (clinically significant, pre-specified AEs), enrollment will continue (posterior probability that toxicity rate exceeds 30% is 72%). If six or more of the first 13 have DLT, consideration would be given to modifying the dose of chemotherapy given in combination with nivolumab (posterior probability that toxicity rate exceeds 30% is 87%).

b) Invasive recurrence-free interval (IRFI) will be evaluated using Kaplan-Meier analysis. IRFI will be assessed as the time from study entry until diagnosis of the first invasive local, regional, or distant breast cancer recurrence during the 24 months after study entry.

Analytic plan for exploratory/correlative objectives:

The association between biomarkers and best overall response (responder versus non-responder primary) will be described by response rate in subgroups, and assessed using the mid-p adjustment to Fisher's exact test. The association between biomarkers and response will be described by graphical summaries and assessed using a two-sample t-test with transformation as needed.

7.3 Subject Population(s) for Analysis

Intent-to-Treat Population (ITT)

The ITT population will include all participants who are enrolled onto the study. The ITT population will be the primary population for evaluating all efficacy endpoints and participant characteristics.

All-Treated Population (AT)

The AT population will include all participants who receive at least one dose of study treatment (i.e. nivolumab), with treatment assignments designated according to actual study treatment received. The AT population will be the primary population for evaluating treatment administration/compliance, safety, and efficacy.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the Investigator's Brochure (IB), etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm)

SERIOUS ADVERSE EVENTS

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

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

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

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

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

The following hospitalizations are not considered SAEs in BMS clinical studies:

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

ADVERSE EVENTS

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

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

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

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

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

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

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected following the subject's written consent to participate in the study to establish a baseline status for the subjects.

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

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

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

Laboratory Test Abnormalities

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

The following laboratory abnormalities should be documented and reported appropriately:

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

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

8.2 Recording of Adverse Events

At each contact with the subject, the Investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the Study Sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, Section 8.1)

Events should be reported using the NYU CTO Medical Events Form. Please email all SAEs to NYUPCCsafety@nyumc.org, Dr. Maryann Kwa, the NYULMC PCC regulatory specialist, and the Medical Monitor Dr. Elaine Shum within 24 hours of learning of the SAE.

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

8.3.1 Investigator Reporting: Notifying the Study Sponsor

Since multiple sites will be participating, the following describes events that must be reported to the study sponsor (NYU Langone Health PCC) and the study sponsor reports to BMS in an expedited fashion.

Initial Report: within 24 hours:
The following events must be reported to the study sponsor (NYULH PCC) by email within 24 hours of awareness of the event using the NYU CTO Medical Events Form:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

The investigator shall maintain a copy of the Medical Events Form on file at the study site. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Report to: NYUPCCsafetyreports@nyulangone.org

AND

Maryann Kwa, MD
Assistant Professor of Medicine
NYU Perlmutter Cancer Center
160 East 34th Street, Fourth Floor
New York, NY 10016
Tel: (212) 731-6364
Email: maryann.kwa@nyulangone.org

Events of Clinical Interest (any medical event that is deemed significant via Principal Investigator's expertise, but does not apply to SAE categories) will be reported within 2-5 days, or as per study Sponsor specifications.

Follow-up report:
As a follow-up to the initial report, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.
- **Withdrawal of IRB approval**

An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If the BMS safety address is not included in the protocol document (eg, multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.

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

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

- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.

- The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.

  - Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

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

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

1. MedWatch or, CIOMS or
2. BMS Pregnancy Surveillance Form or,
3. Approved site SAE form

* *Note*: Reporting requirements will vary by product. Please check with your ISR Lead for applicable reporting timeframe.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

8.3.2 Pregnancy

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

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

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

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

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

Chemotherapy with docetaxel, paclitaxel, doxorubicin, cyclophosphamide, trastuzumab, or pertuzumab is considered Non-IP as it represents routine or standard of care treatment for the respective patient population.

- Docetaxel injection can cause fetal harm when administered to a pregnant woman. Female subjects /female partners of male subjects should not become pregnant during treatment with docetaxel. Females must not breast-feed while being treated with docetaxel. Males being treated with docetaxel are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because docetaxel may alter male fertility. Use of highly effective contraception during treatment is recommended. This drug is classified as FDA Category D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- Paclitaxel can cause fetal harm when administered to a pregnant woman. Female subjects /female partners of male subjects should not become pregnant during treatment with paclitaxel. Females must not breast-feed while being treated with paclitaxel. Males being treated with paclitaxel, are advised not to father a child during treatment and to seek advice on conservation of sperm prior to treatment because paclitaxel may impair fertility. Use of highly effective contraception during treatment is recommended. This drug is classified as FDA Category D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- Doxorubicin can cause fetal harm when administered to a pregnant woman. Female subjects /female partners of male subjects should not become pregnant during treatment with doxorubicin. Females must not breast-feed while being treated with doxorubicin. Doxorubicin may cause infertility in males and females. Use of highly effective contraception during treatment and for 6 months after treatment is recommended. This drug is classified as FDA Category D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- Cyclophosphamide can cause fetal harm when administered to pregnant women. Female subjects /female partners of male subjects should not become pregnant during treatment with cyclophosphamide. Females must not breast-feed while being treated with cyclophosphamide. Male and female reproductive function and fertility may be impaired in patients being treated with cyclophosphamide. Use of highly effective contraception during treatment and for up to 1 year after treatment is recommended. This drug is classified as FDA Category D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- Trastuzumab can cause fetal harm when administered to pregnant women. Female subjects /female partners of male subjects should not become pregnant during treatment with trastuzumab. There is no information regarding the presence of trastuzumab in human milk, the effects on the breastfed infant, or the effects on milk production. Developmental and health benefits of breastfeeding along with the mother's clinical need for treatment and any potential adverse effects on the breastfed child from treatment or from the underlying maternal condition will be considered by the treating physician. This consideration will also take into account the trastuzumab wash out period of 7 months. Use of highly effective contraception during treatment and for up to 7 months after treatment is recommended. This drug is classified as FDA Category D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- Pertuzumab can cause fetal harm when administered to pregnant women. Female subjects /female partners of male subjects should not become pregnant during treatment with pertuzumab. There is no information regarding the presence of pertuzumab in human milk, the effects on the breastfed infant, or the effects on milk production. Developmental and health benefits of breastfeeding along with the mother's clinical need for treatment and any potential adverse effects on the breastfed child from treatment or from the underlying maternal condition will be considered by the treating physician. This consideration will also take into account the pertuzumab wash out period of 7 months. Use of highly effective contraception during treatment and for up to 7 months after treatment is recommended. This drug is classified as FDA

Category D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

8.3.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

8.3.4 Other Safety Considerations

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

8.3.5 Investigator Reporting: Notifying the IRB

Federal regulations require timely reporting by Investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their local IRB of record. The NYULMC IRB address is:

NYU School of Medicine IRB
One Park Avenue, 6th Floor
New York, NY 10016

Report Promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the Investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable Investigator Brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the Principal Investigator or Sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:

The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***

- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the Investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Investigator's study file.

8.3.6 Sponsor Reporting: Notifying the FDA

The Study Sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*

  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*

  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of Section 8.3. The contact information for submitting IND safety reports is noted below:
NYU Langone Health Contacts:

NYUPCCsafetyreports@nyulangone.org

AND

Maryann Kwa, MD
NYU Perlmutter Cancer Center

160 East 34th Street
New York, NY 10016
Tel: (212) 731-6364
Email: maryann.kwa@nyulangone.org

8.3.7 Sponsor Reporting: Notifying Participating Investigators

For multi-center trials, it is the responsibility of the Study Sponsor to notify all participating Investigators of any adverse event that meets the FDA 15-day reporting requirement criteria. The same materials and timeline used to report to the FDA are used for notifying participating Investigators.

8.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan detailed below. Serious adverse events are evaluated regularly by the principal investigator in conjugation with the research team, the DSMC is notified of serious adverse events via email initially, reviewed offline by the designated medical monitor, and presented at the next DSMC monthly meeting. The Data Safety and Monitoring Committee (DSMC) will review the study at least quarterly. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.4.1 Data Safety Monitoring Committee (DSMC)

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the NYU Perlmutter Cancer Center. The DSMC operates based on the National Cancer Institute approved Charter. It is an existing multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted at the NYU Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYU Perlmutter Cancer Center (Benjamin Neel, MD, PhD).

Per the NYU Institutional Data Safety and Monitoring Plan, this phase II trial will be monitored by the DSMC quarterly (from the date the first subject is enrolled), at protocol-specified interim time points, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 3 months. DSMC summary reports are available to facilitate the review and monitoring of this study. These reports include the following: subject listings and summary reports that describe study enrollment and accrual, eligibility, demographic characteristics, dose modifications, adverse experiences, subject's death and additional external published data if applicable to the study. Cumulative toxicities, SAEs, and AEs are reviewed, to identify possible adverse events with elevated frequency that is unexpected. Once a recommendation is made if further action is required, the Investigator's must respond within 10 business days of receipt of DSMC letter.

9 Data Handling and Record Keeping

9.1 Confidentiality

The NYU Perlmutter Cancer Center Clinical Trials Office (CTO) together with the PI will oversee the data management of this trial. TrialMaster, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff

will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 4-6 weeks for data entry accuracy.

Source documentation should be consistent with data entered into any electronic medical record or Trial master. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Concurrent medications
3. Treatment records
4. Adverse events

The study team will maintain clinical and laboratory data in a designed manner to ensure patient confidentiality. All study personnel have passed human subject protection courses. If applicable, tissue samples sent to collaborators outside of NYU will only be labeled with an assigned protocol-patient identification number without patient identifiers. Systems used for electronic data capture are compliant with FDA regulations in 21 CFR Part 11 and applicable local regulatory agency guidelines. All documents are kept in strictly confidential files and are only made accessible for review of sponsors, monitors and authorized representatives of regulatory agencies as described in the informed consent document.

9.2 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.4 Records Retention

It is the Investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if

required by an agreement with the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan detailed below, subsite monitoring follows parameters detailed in Appendix 1. The Investigator will also ensure that the monitor, other compliance or quality assurance reviewer is given access to all the above noted study-related documents. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform NYU PCC CTO and BMS of any audit requests by health authorities, and will provide BMS with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, quarterly

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

In addition, the quality assurance unit will monitor this trial every 4-6 weeks, this includes real-time review of all eCRFs to ensure completeness and to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines. Additionally, a first subject audit is to be conducted within four weeks of enrollment.

10.2 Auditing and Inspecting

The Investigator will permit study-related monitoring, audits, and inspections by the IRB/Ethics Committee (EC), the Sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) or independent Ethics Committee (EC) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of this study. The Investigator should provide a list of IRB/EC members and their affiliate to the Sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB/EC for the study. The formal consent of a subject, using the IRB/EC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This investigator-initiated trial is supported by Bristol-Myers Squibb, Inc. Subjects will not be paid for their participation in this research study.

12.2 Conflict of Interest

Any Investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the Study Sponsor prior to participation in this study. All NYULH investigators will follow the applicable University conflict of interest policies.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the Study Sponsor. Any Investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study.

The study PI holds the primary responsibility for publication of the results of the study. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation. All draft publications must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission.

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16 Appendices

Appendix 1: Guidelines for Sub-site Institutions in Multi-Center Studies

1. Multi-site Communication

The Clinical Trials Office (CTO) at NYU Permutter Cancer Center (PCC) provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CTO office will coordinate regularly scheduled conference calls with affiliate sites.

2. Regulatory Documents

Prior to Site Initiation:

Regulatory documents may be sent to: PCC-QAU@nyulangone.org

3. Central Registration Procedures: Sub-site Institution Research Participant Registration Process

All sub-site Institutions must register subjects with the coordinating center (NYULH) prior to any administration of study drug/intervention/local institution registration. Please see instructions below:

Enrollment at additional sites can begin once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYU Langone Health Perlmutter Cancer Center (PCC) Clinical Trials Office. Once, all required documents are provided to NYU Clinical Trials Office an activation notification will be sent to the PI and research coordinator of that site. Central registration for this study will take place at NYU Langone Health PCC Quality Assurance Unit (PCC-QAU@nyulangone.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYU Langone Health PCC Quality Assurance Unit and forward a copy of the signed consent to NYU Langone Health PCC Clinical Trials Office within 24 hours.

1. Within 24 hours of obtaining consent (excluding holidays and weekends), the sub-site Institution CRN and/or CRC is required to submit the following documents via email (PCC-QAU@nyulangone.org), with a request to register the patient "pending eligibility" to the NYULH's Clinical Trials Office, Quality Assurance Unit.. The documents will be reviewed for accurateness, and subsequently the patient will be registered.

2. Registration will occur once the Senior Research Nurse for Quality Assurance conducts a central review of the submitted materials. Once eligibility is verified, a unique subject study number will be issued within 24 hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYU Langone Health PCC CTO will return a signed eligibility confirmation worksheet email with the subject's unique study number.

3. The subject will not be identified by name. This is the point, at which, the patient is considered accrued on study. Protocol treatment should begin within designated timeframe; issues that would cause treatment delays should be discussed with the overall PI, Dr. Kwa. All screen failures/ineligible subjects, as well as subject's who withdraw consent prior to initiation of protocol therapy must be submitted to the CTO in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

4. Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYU Langone PCC Clinical Trials Office and to their IRB as per site institutional policy.

5. Please email all SAEs to NYUPCCsafetyreports@nyulangone.org, Dr. Kwa, and the NYU Langone Health QA Unit (PCC-QAU@nyulangone.org) .

4. Protocol Deviation/Subject Waiver Request for Sub-sites

The sub-site MUST submit a prospective deviation request to the NYULH lead PI and NYU DSMC for review and submission. Approvals must be obtained from all entities prior to implementation at the Sub-site. If a prospective protocol deviation request is submitted for review (from a sub-site), the PI/site memo(s), NYU DSMC approval(s) and correspondence and NYU IRB eligibility deviation approval letter(s) should be forwarded to the sub-site for documentation. The sub-site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation and registering/enrolling the subject via NYULH Central Registration. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described.

5. Guidelines for Monitoring

An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the external site.

Monitoring visits are done remotely unless otherwise specified, via remote EMR access. If not possible, secure email exchange will be utilized. The quality assurance specialist will confirm an upcoming monitoring visit with a sub-site Investigator and staff. If remote EMR access is not available, then the sub-site Coordinator will ensure that all source documents for subjects are de-identified and labeled only with the subject ID number(s), and emails all requested documents to the quality assurance specialist by the specified visit date. All documents are reviewed and a monitoring report is submitted within 5 business days from the date of the visit. Any outstanding documents will be listed in the report as a high- priority request for the next monitoring visit. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database. Continued non-compliance and failure to submit documentation will result in the suspension of subject enrollment at the site, until the documents have been received.

1. External sites will be monitored by the QA Specialist on both a regulatory level, as well as a clinical data/source documentation review level.
2. Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated QA Specialist via secure email for all subjects enrolled at external sites. Timelines for submission procedures will be defined on a case-by-case basis.
3. The QA Specialist will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The QA Specialist will issue queries when/if necessary.
4. The external site research staff will respond to queries within the designated time frame (response times vary based on trial risk). If queries remain outstanding, the QA Specialist will send a delinquent query reminder for the outstanding items.
5. The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:

- Informed consent procedures
- Eligibility criteria
- Protocol specific treatment compliance
- Protocol specific toxicity/outcome documentation/compliance
- Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
- Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc.).

- Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
- Pharmacy accountability records
- Adherence to the CRF submission timeframes to NYULH (within the protocol specified timeframes)

6. External site remote monitoring reports will be sent to the lead PI, NYULH DSMC, and sub-sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall site performance. These reports will be generated by the QA Specialist and reviewed with the QA Manager prior to dissemination.

6. Dose Level Determinations

The Sponsor-Investigator/Statistician will review enrollment for each dose level cohort during the regularly scheduled conference call with the sub-sites.

The dose level for newly enrolled subjects will be determined by the study statistician upon notification that a subject has signed informed consent to participate in the study. The assigned dose level for any subject to begin study treatment will be communicated to the affiliate site along with the determination by Central Registration that the subject is eligible for enrollment in the study.

If a Dose Limiting Toxicity (DLT) is identified in a subject, the affiliate site must notify the Sponsor-Investigator via email at the study specific email address within 1 business day of identification. The lead site will communicate that a DLT has been experienced within 1 business day.

7. Confidentiality

Each external site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g. 04-10). All sites will be required to enter their data in the designated electronic data capture Clinical Trial Management System used for all cancer-related clinical research at NYULH. All users must login with their own application username and password. Users off campus must first access the NYULMC Portal with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.
Except when required by law, study information shared with persons and organizations outside of NYULH must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.

If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

8. Data Reporting Plan

NYULH is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, NYULH encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

NYULH's policies that pertain to patient data sharing conform to NYU IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the NYU IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the NYULMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

9. Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. A designated electronic data capture system will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into the system via customized case report forms for the study. The research staff will generate reports from the designated electronic data capture system to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

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

Appendix 3: Management Algorithms for Investigational Agent, Nivolumab

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

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

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

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended. The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

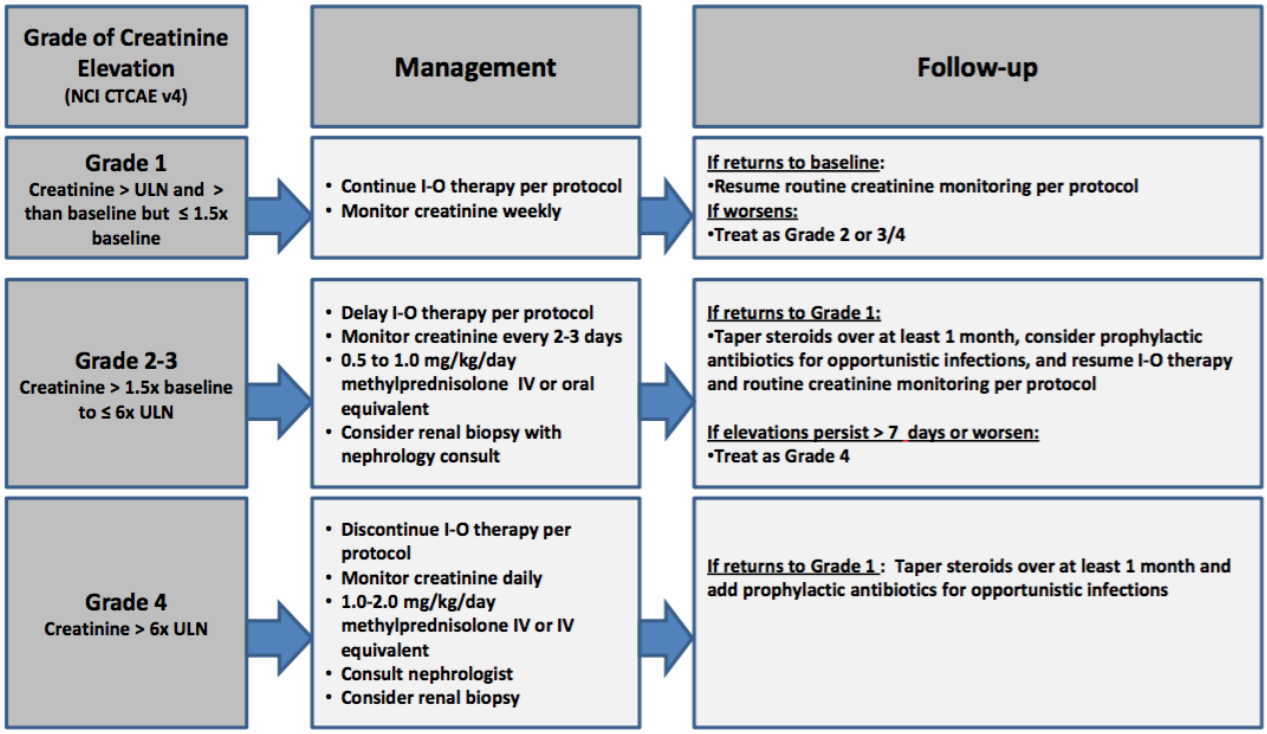
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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

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

Renal Adverse Event Management Algorithm

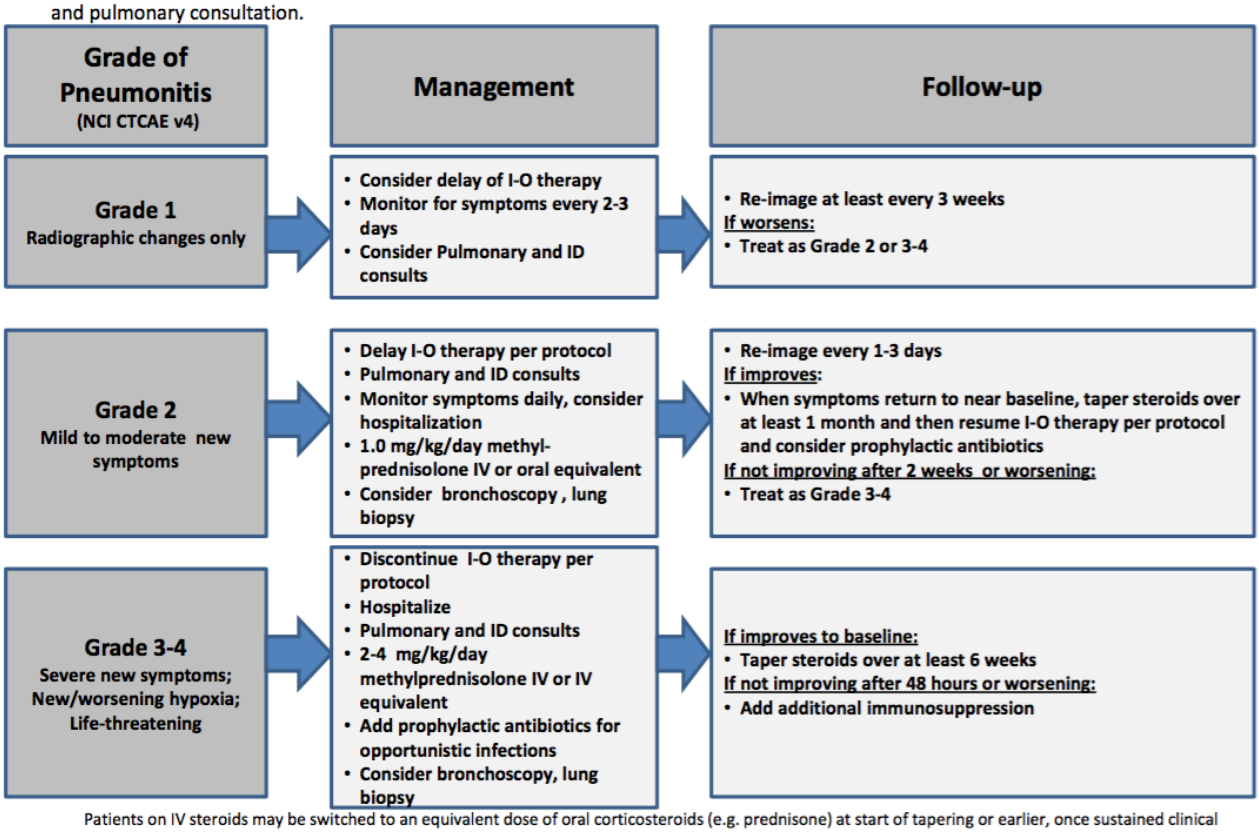
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

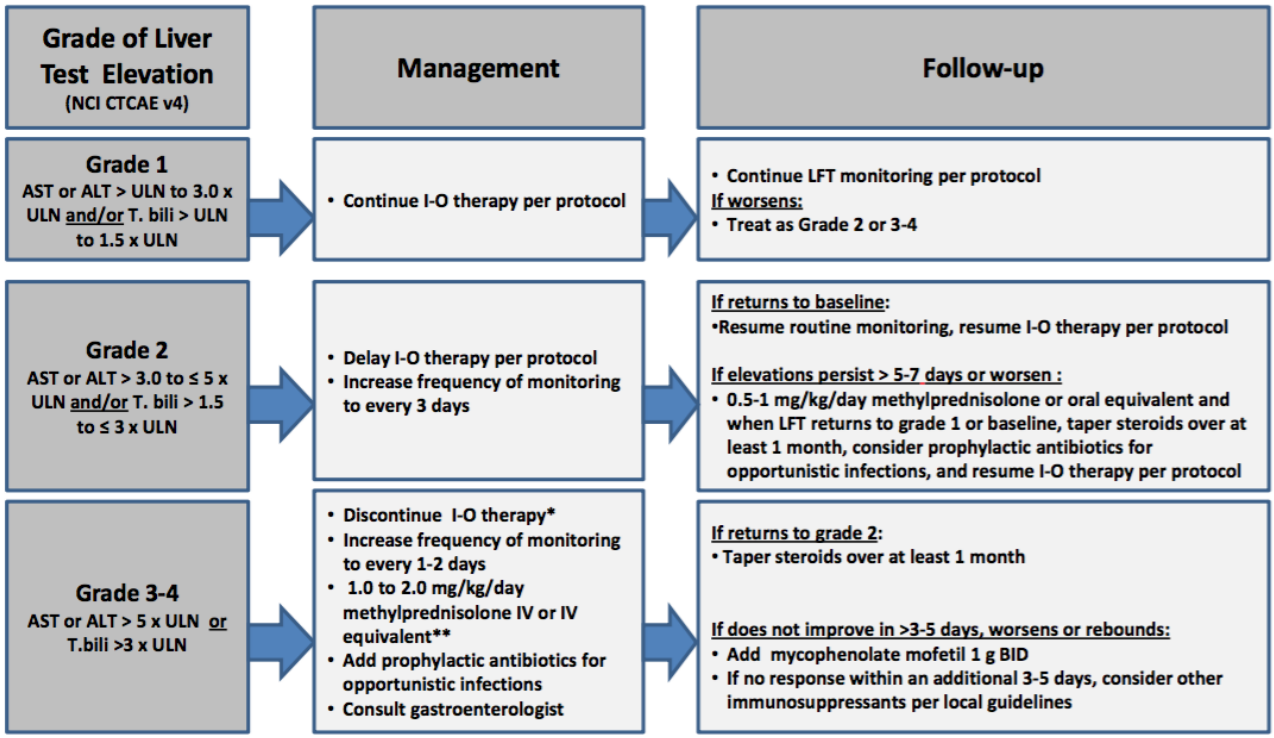
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.



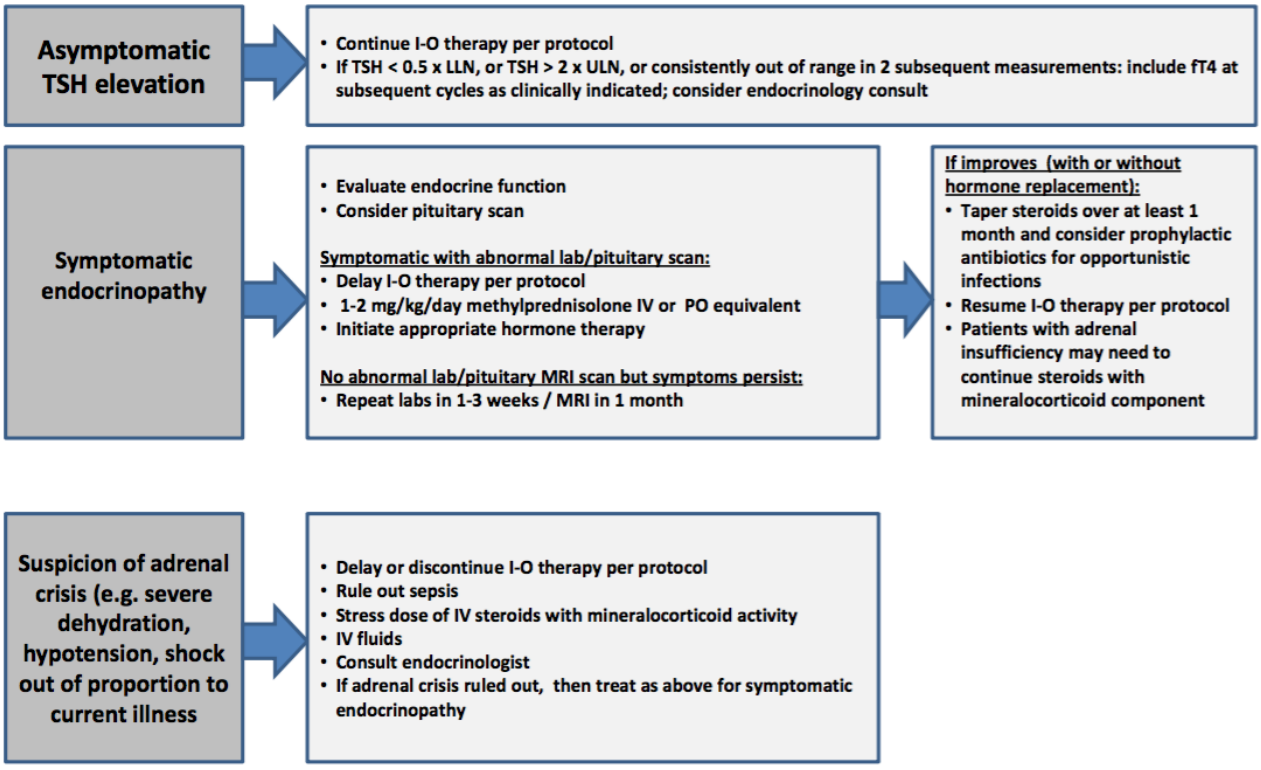
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Endocrinopathy Management Algorithm

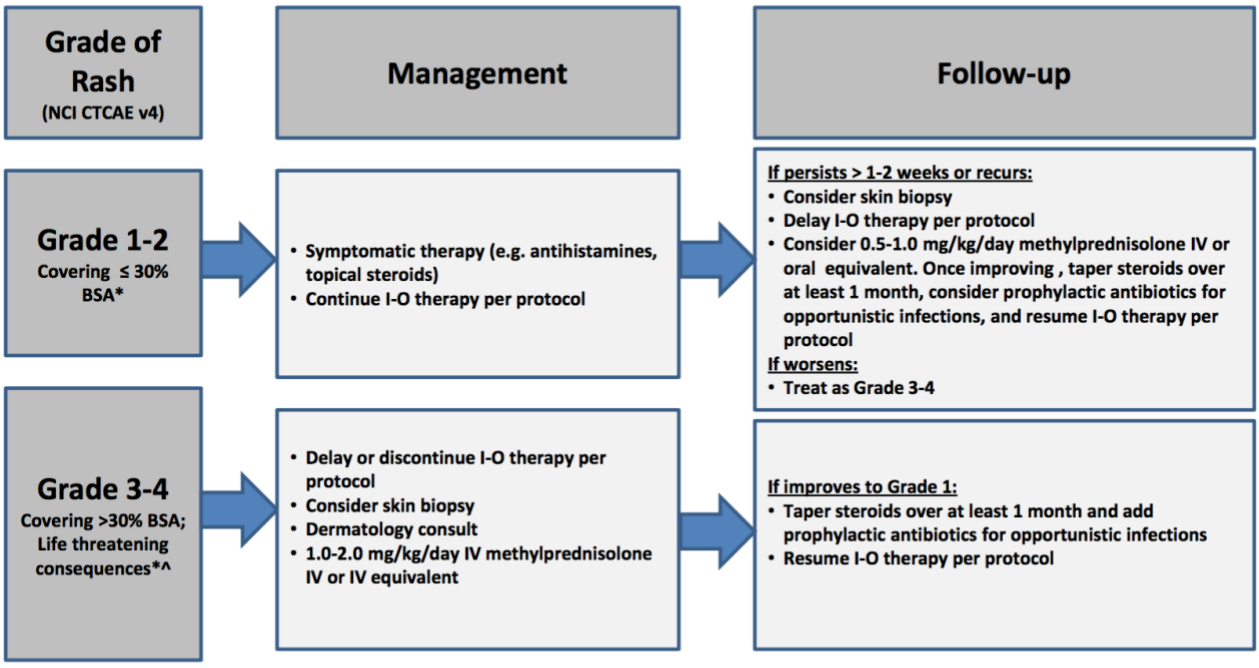
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



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

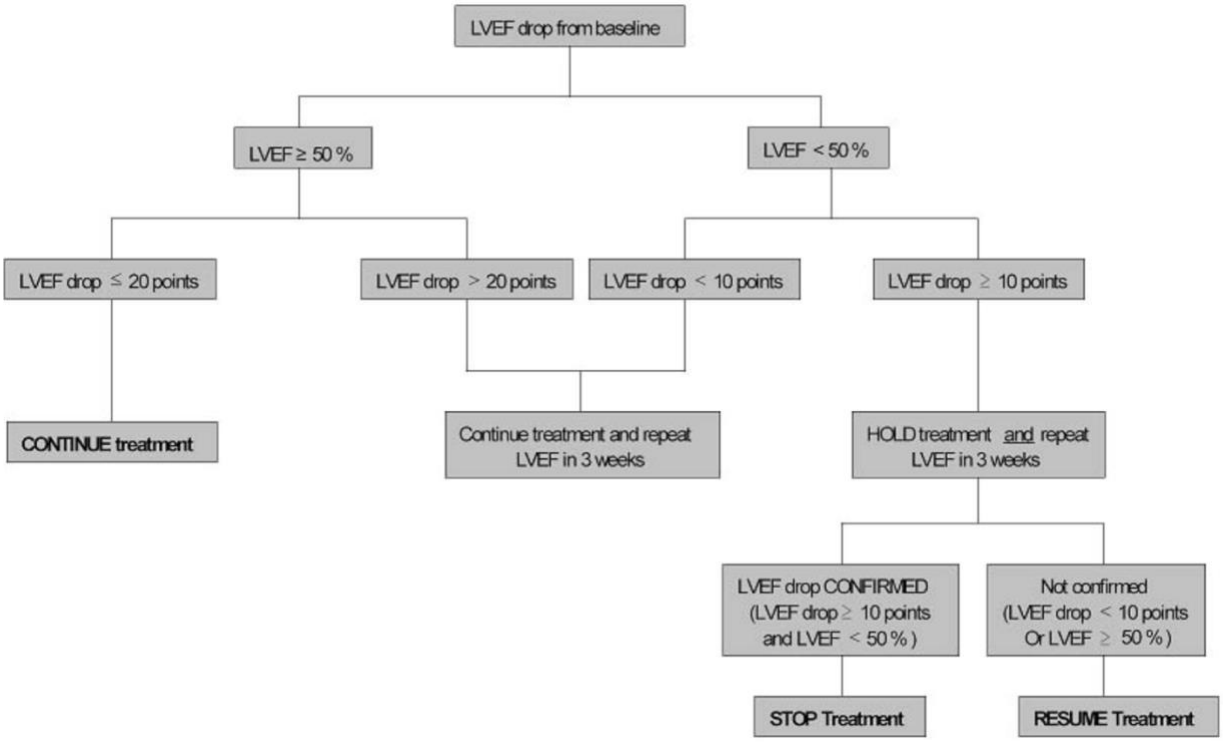
Neurological Adverse Event Management Algorithm

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

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

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

Appendix 4: Asymptomatic Decline in LVEF: Algorithm for Continuation and Discontinuation of Treatment with Trastuzumab, and/or Pertuzumab



Appendix 5:

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