IIT-2017-NeoPACT

Neoadjuvant Phase II Study of Pembrolizumab And Carboplatin Plus Docetaxel in Triple Negative Breast Cancer

NCT03639948

Document date: 13 January 2023

THE UNIVERSITY OF KANSAS
CANCER CENTER

Investigator Initiated Trial

Neoadjuvant Phase II Study of Pembrolizumab And Carboplatin plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)

SPONSOR - INVESTIGATOR
Priyanka Sharma, MD
Associate Professor of Medicine
University of Kansas Medical Center
2330 Shawnee Mission Parkway, Suite 210, MS 5003
Westwood, KS 66205
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

Protocol Number:	**IIT-2017-NeoPACT**
Study Drug(s):	Pembrolizumab Carboplatin Docetaxel
IND / IDE Number:	Exempt
IND / IDE Holder Name:	N/A
Initial Version:	Original Protocol Version 1.1 dated 10 July 2018
Amendments	Version 2.0 dated 27 February 2019 Version 3.0 dated 05 April 2019 Version 4.0 dated 09 November 2020 Version 5.0 dated 13 January 2023

LIST OF COLLABORATORS

Priyanka Sharma, M.D. (Principal Investigator)

[redacted]

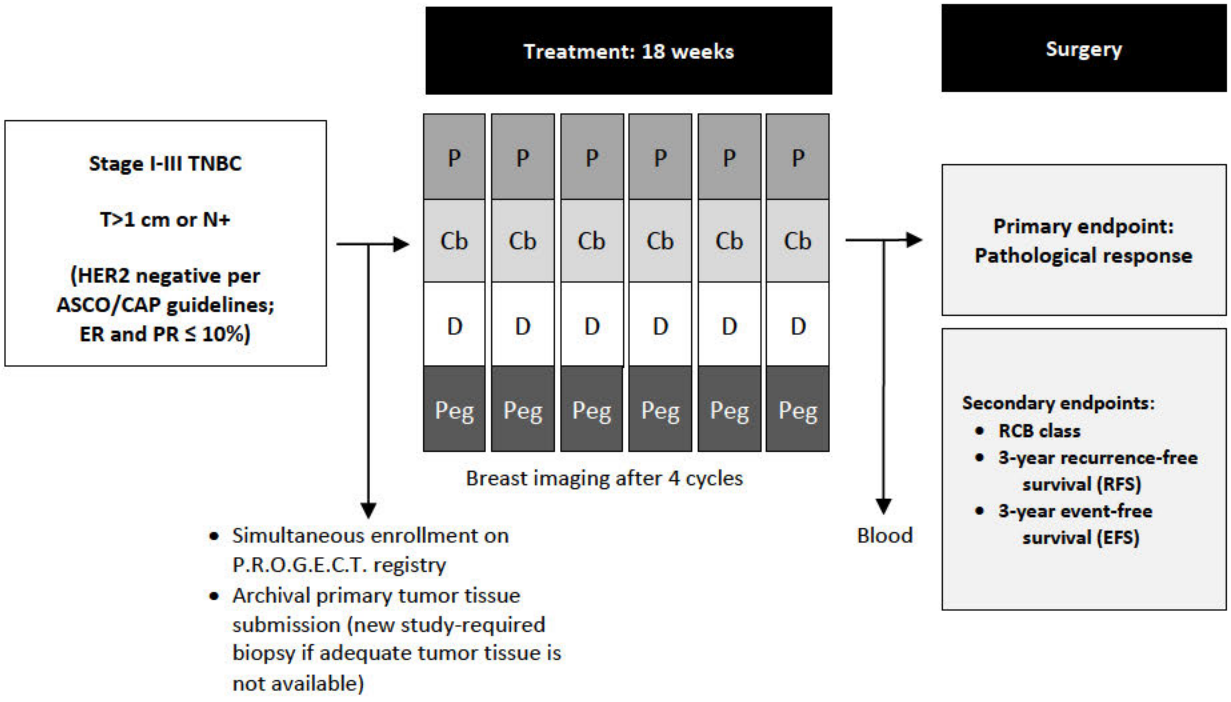
1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

A	Anthracycline
AC	Doxorubicin plus cyclophosphamide regimen
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BA/BE	Bioavailability/Bioequivalence
BCS	Breast conservation surgery
BID	Twice daily
BRCF	Biospecimen Repository Core Facility
BUN	Blood urea nitrogen
C	Cyclophosphamide
CAP	College of American Pathologists
Cb	Carboplatin
CBC	Complete blood count
CbD	Carboplatin plus Docetaxel regimen
CMP	Comprehensive metabolic panel
CRF	Case report form
CTCAE	Common Toxicity Criteria for Adverse Events
CVAP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone regimen
DCIS	Ductal carcinoma in situ
ddAC	Dose dense Doxorubicin + Cyclophosphamide
DNA	Deoxyribonucleic Acid
ECG	Electrocardiography
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
DSMC	Data and Safety Monitoring Committee
ER	Estrogen receptor
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FNA	Fine needle aspiration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HER2	Human epidermal growth factor receptor 2
HR	Homologous recombination
IgG	Immunoglobulin G
IND	Investigational new drug
IRB	Institutional review board
IULN	Institutional Upper Limit of Normal
IV	Intravenous
LFT	Liver function tests
LVEF	Left ventricular ejection fraction
MRD	Minimal residual disease
MRI	Magnetic resonance imaging

MUGA	Multi gated acquisition scan
N+	Lymph node positive
NCI	National Cancer Institute
pCR	Pathological complete response
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death protein ligand 1
PI	Principal Investigator
PO	Per os/by mouth/orally
PR	Progesterone receptor
RBC	Red blood cells
RCB	Residual cancer burden
SAE	Serious adverse event
SC	Subcutaneous
SGOT	Serum glutamic oxaloacetic transaminase
SPGT	Serum glutamic pyruvic transaminase
T	Tumor size
Ta	Taxanes
TNBC	Triple-negative breast cancer
US	Ultrasound
USP	United States Pharmacopeia

3 SCHEMATIC OF STUDY DESIGN



P — Pembrolizumab 200 mg every 21 days

Cb — Carboplatin AUC 6 every 21 days

D — Docetaxel 75 mg/m^2 every 21 days

Peg — Pegfilgrastim (or its biosimilar equivalent) 6 mg every 21 days

4 PROTOCOL SUMMARY

Title	Neoadjuvant Phase II Study of Pembrolizumab And Carboplatin plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)
Protocol Number	IIT-2017-NeoPACT
Phase	Phase II
Methodology	Single arm
Study Duration	66 months
Study Center(s)	[redacted]
Objectives	**Primary Objective**: To determine pathological complete response rate with neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC. *Hypothesis*: Addition of Pembrolizumab to CbD will lead to improvement in pCR rates compared to historical control in patients with stage I-III TNBC.
Number of Participants	120 patients, accrued over 30 months.
Diagnosis and Main Inclusion Criteria	Newly diagnosed stage I (T>1cm or N+), II or III TNBC who have not undergone definitive breast surgery and have not received any systemic chemotherapy.
Study Product(s), Dose, Route, Regimen	Carboplatin (AUC 6, IV) and Docetaxel (75 mg/m2, IV) plus Pembrolizumab (200 mg, IV) every 21 days x 6 cycles. Pegfilgrastim or its biosimilar equivalent (6 mg) SC Day 2 of each cycle.
Duration of Administration	18 weeks
Reference Therapy	Carboplatin (AUC 6, IV) and Docetaxel (75mg/m2, IV) every 21 days x 6 cycles.
Interim Monitoring	None
Statistical Methodology For Primary Endpoint	The pCR rate will be estimated and 95% exact binomial confidence bounds will be calculated.
Correlative Studies OR SAMPLE BANKING FOR FUTURE RESEARCH	Yes
Stopping Rules	No

5 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

5.1 Background Information

5.1.1 Triple Negative Breast Cancer

Breast cancer is the most commonly diagnosed malignancy and second leading cause of cancer mortality in American women. The lifetime risk of developing breast cancer is 12.2%, and the lifetime risk of breast cancer death is 3.3% [1]. Triple negative breast cancer (TNBC) is defined by the lack of expression of estrogen receptor (ER) and progesterone receptor (PR), and absence of ERBB2 (HER2) overexpression and/or gene amplification. TNBC accounts for 15% of all breast cancer and is associated with poor long-term outcomes compared to other breast cancer subtypes [2-4]. Systemic neoadjuvant chemotherapy is recommended for all TNBC patients with stage I (T>1cm)-III disease [5]. Due to the lack of specific therapeutic targets, chemotherapy remains the mainstay of systemic treatment in the adjuvant setting. However, despite receiving standard anthracycline-based adjuvant chemotherapy, a significant proportion (approximately 30-40%) of patients with early stage TNBC develop metastatic disease and succumb to the cancer [6-8]. To improve outcomes for this subtype, we not only need novel targeted agents, but also need to identify predictors of response/resistance to standard chemotherapy.

5.1.2 Neoadjuvant Chemotherapy

Neoadjuvant (primary) chemotherapy refers to induction chemotherapy given before local treatment, such as surgery or radiation [9]. The biologic rationale for the use of neoadjuvant therapy in breast cancer is based on several key observations. Animal models have demonstrated that the removal of a primary tumor may increase the rate of growth of micrometastases. Fisher suggested that this accelerated growth which is controlled by serum growth factors, could be prevented by systemic chemotherapy before tumor resection [10]. Goldie and Coldman have proposed that the number of tumor cells is proportional to the number of chemoresistant clones, and therefore, neoadjuvant chemotherapy would be effective in maximizing future drug response [11].

Clinically, neoadjuvant chemotherapy has a number of potential advantages. Decreasing the size of the primary tumor may effectively downstage a mass to make breast preservation more likely, and may improve local control [9]. Chemotherapy may also decrease the intensity and morbidity of irradiation required to treat the breast or chest wall. Additionally, it allows for immediate objective assessment of chemotherapy response which offers prognostic information, as well as guides alterations in therapy. Finally and most importantly, neoadjuvant chemotherapy allows for rapid early assessment of new treatment approaches and to study the relationship of biologic markers and treatment response.

In the landmark phase III randomized study (National Surgical and Adjuvant Breast Project [NSABP] B-18), it was demonstrated that in patients with stage I and II disease, neoadjuvant chemotherapy was equivalent to adjuvant chemotherapy in terms of disease free survival, distant disease free survival and overall survival, however, a higher percentage of breast conservation surgeries (67% vs. 59%) was possible with neoadjuvant chemotherapy [12]. For breast cancer, neoadjuvant chemotherapy was initially used in patients only with locally advanced or inoperable disease, but now is considered for patients who are candidates for adjuvant chemotherapy.

It has been demonstrated that degree of tumor response and extent of residual disease after neoadjuvant chemotherapy are associated with relapse and long-term survival [13,14]. Prospective trials have demonstrated that patients who achieve a pathological complete response (pCR) of the primary

tumor with neoadjuvant chemotherapy have significantly improved disease free and overall survival when compared with patients who do not have a pCR [13-18]. Due to its value as a surrogate for survival, response to neoadjuvant chemotherapy is being used as a primary endpoint in studies that examine the efficacy of new drugs and novel drug combinations [19].

5.1.3 DNA Damaging Therapy in Triple Negative Breast Cancer

Sporadic and germline *BRCA* mutation-associated triple negative breast cancers (TNBC) share several pathological and molecular similarities. These similarities have led to the exploration of DNA damaging agents like platinum compounds in the general population of patients with TNBC. Growing evidence suggests that platinum compounds may be active in a significantly larger number of TNBC patients beyond germline *BRCA* mutation carriers [20,21]. Currently, anthracyclines (A), cyclophosphamide (C) and taxanes (Ta) form the backbone of systemic chemotherapy for stage I-III TNBC (www.nccn.org). Recent studies demonstrate that addition of neoadjuvant carboplatin (Cb) to A/C/Ta-based chemotherapy improves pCR in patients with stage I-III TNBC (pCR improvement from 41% to 54% with addition of Cb) [22-24]. However, this improvement in pCR rate comes at the cost of increase in toxicity (dose reductions/omissions needed in 40-50% of patients) and also increases the financial cost of chemotherapy [23,24]. Furthermore, anthracyclines and cyclophosphamide, although very active for treatment of breast cancer, have well-known small but serious long term risks (secondary leukemia and myelodysplastic syndrome, cardiomyopathy, premature menopause), and development of effective chemotherapy regimens that are devoid of long term side effects is desirable.

Furthermore, although anthracycline agents induce double-strand breaks, repair of these lesions appears to require non-homologous end joining, an error-prone double strand break repair pathway that does not require BRCA1, and preclinical data suggests that anthracyclines do not exhibit selective toxicity in BRCA1-deficient cells [25-27]. Conversely, repair of platinum-induced interstrand crosslinks invokes BRCA1-mediated homologous recombination, and there is abundant clinical and in vitro evidence that BRCA1-deficient cells are hypersensitive to platinum agents [25,27-29].

5.1.4 Neoadjuvant Carboplatin plus Docetaxel

Taxanes are an integral part of chemotherapy regimens for breast cancer treatment and appear to contribute particularly among patients with early stage TNBC [30,31]. Several in vitro studies have demonstrated synergy between platinum compounds and taxanes in TNBC cell lines [32]. Efficacy of anthracycline-devoid neoadjuvant platinum/taxane chemotherapy combination in sporadic and *BRCA*-associated TNBC has not been well studied. We recently reported encouraging pCR rates with a non-anthracycline carboplatin plus docetaxel (CbD) neoadjuvant chemotherapy regimen in 190 stage I-III TNBC patients [33]. This CbD regimen yielded an overall pCR rate of 55% in unselected TNBC, with pCR rates of 59% and 56% for *BRCA*-associated and wild type TNBCs, respectively, indicating response among TNBC regardless of germline *BRCA* status (Table 1).

Table 1: Response rates among TNBC patients treated with neoadjuvant carboplatin and docetaxel

	All patients (n=190)	*BRCA1/2* wild type (n=133)	*BRCA1/2* mutation carriers (n=27)
Pathological Complete Response; n (%)	100 (55%)	75 (56%)	16 (59%)
		p=0.83	
Residual Cancer Burden 0/1; n (%)	125 (68%)	92 (69%)	19 (70%)
		p=1.0	

The chemotherapy regimen of carboplatin/docetaxel is well tolerated, and is routinely used for HER2 positive and metastatic breast cancer, with well-known safety profile [5,34]. In our neoadjuvant experience, most common Grade 3/4 toxicities with carboplatin/docetaxel were neutropenia (4%), anemia (6%), thrombocytopenia (6%), and diarrhea (6%). Thus, we have recently demonstrated in an observational cohort that the pCR achieved with carboplatin/docetaxel chemotherapy is comparable to the pCR noted with addition of carboplatin to AC/paclitaxel chemotherapy, with a more favorable profile, supporting further studies built on the CbD backbone.

5.1.5 PD-1 Immune Checkpoint Targeting

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [35]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes and favorable prognosis in various malignancies [36,37]. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 is an immunoglobulin (Ig) superfamily member that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [38,39].

Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2, leading to the dephosphorylation of effector molecules which are involved in the CD3 T-cell signaling cascade [39-42]. Thus PD-1 activation by its ligands results in inhibited T-cell activation. Although PD-L1 is absent from normal breast tissue, it is expressed in approximately half of breast cancers, where it activates PD-1 and allows tumor cells to evade detection by the immune system [43]. Furthermore, PD-L1 expression is found at higher rates in TNBC than in non-TNBC. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in TNBC.

Preliminary data in breast cancer show encouraging efficacy of PD-1 inhibitors in both metastatic and early stage TNBC. The PD-L1 inhibitor avelumab has been investigated in breast cancer unselected for PD-L1 status and subtype, in the phase Ib solid tumor JAVELIN study. The overall response rate in this study was 4.8% (with 1 complete response and 7 partial responses), and an overall response rate of 8.6% in TNBC patients (n=58) [44]. Atezolizumab, an anti-PD-L1 monoclonal antibody, was evaluated in a phase I study that included 54 patients with metastatic TNBC. In this study, the overall response rate was 19% (including 2 complete responses and 2 partial responses) [45]. Data on 112 metastatic TNBC patients treated with single-agent atezolizumab were recently presented at the 2017 American Association for Cancer Research Annual Meeting [46]. This study reported an overall response rate of 10%, which was influenced by extent of prior treatment for metastatic disease (overall response rate was 26% among patients with no prior line of therapy). The median duration of response in all response-evaluable patients was encouraging, at 21.1 months. Pembrolizumab, a monoclonal anti-PD-L1 antibody, was also evaluated in KEYNOTE-012, which enrolled multiple tumor types, including 32 patients with metastatic TNBC and tumor PD-L1 positivity. The overall response rate was 18.5%, including 1 complete

response and 4 partial responses [47]. Additionally, the 6-month PFS rate was 24.4%, and at the time of publication, the median duration of response had not been reached. In the ongoing KEYNOTE-086 trial, patients with PD-L1-positive metastatic disease who had not received prior systemic treatment for metastatic disease had an overall response rate of 23.1% (4% complete response) with Pembrolizumab monotherapy [48]. Several ongoing clinical trials are evaluating PD-1 and PD-L1 inhibitors in combination with cytotoxic chemotherapy for metastatic TNBC (NCT02425891, NCT02393794, NCT02628132, NCT02648477, NCT02499367). PD-1/PD-L1 inhibitors are also being evaluated in early stage TNBC in the neoadjuvant setting. In the I-SPY 2 trial, addition of Pembrolizumab to standard neoadjuvant therapy increased the rate of pathologic complete response (pCR) rate in TNBC approximately threefold [49]. Based on these encouraging findings, several ongoing clinical trials are evaluating PD-1/PD-L1 antibodies in combination with various schedules of neoadjuvant chemotherapy in TNBC (NCT03036488, NCT02620280, NCT03281954, NCT03197935, NCT02883062).

5.1.6 Surgery after Neoadjuvant Treatment

Approximately one-third of patients thought to be in complete remission on clinical grounds after neoadjuvant chemotherapy still have residual disease at the time of pathologic examination. Therefore, pathologic examination following surgical excision of the suspected area of involvement is the best indicator of response [12]. Appropriate selection of patients for breast conserving surgery (BCS) following neoadjuvant chemotherapy is important. Absolute contraindications for BCS include extensive, residual, or multifocal tumor, or positive resection margins, while a relative contraindication is predicted poor cosmetic outcome [50].

5.2 Study Agent(s) / Treatment(s)

5.2.1 Carboplatin (Paraplatin)

Please refer to carboplatin package insert for full prescribing information.

Carboplatin is a platinum analog that covalently binds to DNA, producing crosslinks leading to inhibition of DNA synthesis. It is a cell cycle non-specific chemotherapeutic agent. Single agent carboplatin is active in patients with previously untreated metastatic breast cancer, producing response rates of 20-35% [51-55]. Combination regimens of carboplatin with other chemotherapy agents (taxanes, gemcitabine) are also active for treatment of advanced breast cancer [56-58]. Platinum compounds are considered to be especially active for TNBC. Recent studies demonstrate that addition of neoadjuvant carboplatin to A/C/Ta-based chemotherapy improves pCR in patients with stage I-III TNBC [24,59].

5.2.2 Docetaxel (Taxotere)

Please refer to docetaxel package insert for full prescribing information.

Docetaxel is an anti-microtubule taxane agent. Randomized phase III trials have confirmed the anti-tumor activity of docetaxel in breast cancer in neoadjuvant, adjuvant and metastatic settings [60-69]. Addition of docetaxel to anthracycline-based chemotherapy in the neoadjuvant setting has universally been associated with improved outcome in all studies (superior complete clinical and pathologic response rate in all, and improved survival in the Aberdeen study). One of the largest neoadjuvant studies, NSABP B-27, investigated neoadjuvant doxorubicin/cyclophosphamide +/- docetaxel in patients with early breast cancer (T>3 cm or lymph node positive). Addition of neoadjuvant docetaxel to doxorubicin and cyclophosphamide was associated with superior clinical response rate and pCR (pCR of

27% vs. 13%). The Aberdeen Breast Study investigated the use of neoadjuvant docetaxel in large or locally advanced breast cancer after treatment with induction cyclophosphamide, doxorubicin, vincristine, prednisolone (CVAP) [64]. Patients who were responsive to induction CVAP and subsequently treated with sequential docetaxel achieved a 94% clinical and 34% pathologic response rate versus a 66% clinical and 16% pathologic response rate in patients who received four additional cycles of CVAP therapy. Overall survival at 5 years was also superior in the docetaxel arm.

5.2.3 Pembrolizumab (Keytruda)

Please refer to the Pembrolizumab package insert for full prescribing information.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, Pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (Pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

5.2.3.1 Preclinical efficacy in breast cancer

Several preclinical studies have demonstrated activity of monoclonal antibodies targeting PD-1 or PD-L1 in breast cancer cell lines, including TNBC lines [70,71]. In xenograft models, anti-PD-1 antibodies demonstrated activity when combined with other agents targeting cytotoxic T-cells [71]. Preclinical studies in mouse models show that antibody-mediated blockage of PD-1/PD-L1 interaction enhances infiltration of tumor-specific T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities [72].

5.2.3.2 Pharmacodynamics

[redacted] (Merck, internal data).

[redacted] (Merck, internal data).

5.2.3.3 Nonclinical pharmacokinetics and metabolism

[redacted] (Merck, internal data).

[redacted] (Merck, internal data).

[redacted]

[redacted] (Merck, internal data).

5.2.3.4 Clinical pharmacology

[redacted] (Merck, internal data).

[redacted]

[redacted] (Merck, internal data).

[redacted] (Merck, internal data).

[redacted] (Merck, internal data).

5.2.3.5 Clinical efficacy

Clinical efficacy in TNBC

Preliminary data in breast cancer show encouraging efficacy of Pembrolizumab in TNBC. The phase Ib clinical trial KEYNOTE-012 included 32 patients with metastatic PD-L1 positive TNBC. The ORR among these patients was 18.5%, including one complete response and four partial responses [47]. Additionally, the 6-month PFS was 24.4%, and the median duration of response had not been reached at time of publication. A phase II, two-part, multi-site, open-label trial (KEYNOTE-086) is evaluating Pembrolizumab 200 mg IV every 3 weeks in metastatic TNBC. Part 1 of this study includes two cohorts (A and B), results of which were recently reported. In Cohort A, metastatic TNBC patients who had received at least 1 line of systemic treatment for metastatic disease (including an anthracycline and a taxane in neo/adjuvant or metastatic setting), an ORR of 5% (irrespective of PD-L1 expression) was noted with Pembrolizumab monotherapy [73]. In Cohort B, subjects with PD-L1-positive mTNBC who had not received any prior systemic treatment for metastatic disease, ORR was 23.1% (4% had complete response), and the estimated 6-month PFS was 29% [48]. Recently presented data from I-SPY 2 demonstrated that addition of Pembrolizumab to neoadjuvant paclitaxel plus doxorubicin and cyclophosphamide increased the estimated pCR rate in patients with TNBC from 20% to 60% [49].

5.2.3.6 Clinical safety

As of March 2017, over 14,000 patients with hematologic malignancies and solid tumors have received Pembrolizumab monotherapy or combination therapy in clinical trials. Pembrolizumab has been granted approval in a number of markets and indications (melanoma, NSCLC, HNSCC, cHL, UC, gastric and gastroesophageal junction adenocarcinoma, and MSI-H tumors) and has an established safety profile as outlined in the Company Core Data Sheet. Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications, [redacted] Furthermore, the frequency of immune-related reactions is low, and these events are readily managed in the clinical setting.

Merck's Reference Safety Dataset consisted of [redacted]

[redacted]

[redacted] (Merck, internal data).

Table 2: Merck's Reference Safety Dataset, percentage of subjects with adverse events of special interest, by maximum toxicity grade

[redacted]	[redacted]											
	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]Merck, internal data).

[redacted](Merck, internal data).

5.3 Rationale for the Study

Sporadic and germline BRCA mutation associated TNBC share several pathological and molecular similarities. These similarities have led to the exploration of DNA damaging agents like platinum compounds in the general population of patients with TNBC. Evaluation of anthracycline-free platinum-based neoadjuvant chemotherapy has been an area of intense exploration in TNBC, as a way of increasing pCR while limiting anthracycline-induced toxicity. We recently reported a pCR rate of 55% resulting from a non-anthracycline carboplatin plus docetaxel regimen in a cohort of 190 early stage TNBC patients [33]. [redacted](Sharma et al, unpublished data). Furthermore, 83% of patients completed all six cycles of therapy. Thus a combination of neoadjuvant carboplatin and docetaxel is associated with a high rate of pCR and a favorable safety profile in TNBC patients, and should be further investigated as a neoadjuvant chemotherapy backbone in clinical trials.

Cancer cells have been shown to evade detection and destruction by the immune system through inhibiting T cell activity. The immune checkpoint inhibitor PD-1 is activated by its ligand, PD-L1, on the cell surface, whereupon it initiates a signaling cascade resulting in decreased T cell proliferation and survival. TNBC tumors in particular have high rates of PD-L1 expression compared to non-TNBC. Interference with PD-1 ligand binding may restore T cell activity and re-sensitize the immune system to destroy the cancer cells. The PD-1 antibody Pembrolizumab is FDA-approved in several solid tumor types, and has shown promising results in phase I/II clinical trials for TNBC. Concurrent use of neoadjuvant cytotoxic chemotherapy may further increase the efficacy of Pembrolizumab by enhancing antigen exposure. To this end, several ongoing trials are evaluating Pembrolizumab in combination with anthracycline-based therapy; however, the efficacy of neoadjuvant platinum/taxane anthracycline free combination has not been evaluated in TNBC. Thus, a phase II study to further estimate the rate of pCR associated with neoadjuvant carboplatin and docetaxel plus Pembrolizumab x 6 cycles in stage I-III TNBC is proposed.

Lung cancer KEYNOTE-021 study has shown safety of combining Pembrolizumab at a dose of 200 mg every three weeks with carboplatin and pemetrexed [74]. Safety of Pembrolizumab with carboplatin plus paclitaxel chemotherapy backbone is established in solid tumors including breast cancer [49], and a large ongoing randomized phase III trial (KEYNOTE-522) is assessing addition of Pembrolizumab to carboplatin

plus paclitaxel combination in TNBC. Pembrolizumab can be safely combined with docetaxel at 75 mg/m^2 every three weeks (NCT02331251). Ongoing phase II studies in solid tumors are combining Pembrolizumab 200 mg flat-dose every 21 days with docetaxel at a dose of 75 mg/m^2 [75]. Thus, a phase II study of the combination of Pembrolizumab with carboplatin plus docetaxel at the proposed doses is feasible.

5.3.1 Justification for dose

Use of Pembrolizumab at a fixed dose of 200 mg every 21 days is supported by clinical trials in various solid tumors, which demonstrated near-maximal efficacy and an acceptable safety profile at this dose [76,77]. Phase I/II clinical trials in breast cancer have employed 200 mg Pembrolizumab both as monotherapy and in combination with cytotoxic chemotherapy. Based on the totality of data generated in the pembrolizumab development program, 200 mg every 3 weeks is the appropriate dose of Pembrolizumab for adults across all indications and regardless of tumor type (Merck, internal data). This dose level is FDA-approved in combination with chemotherapy for lung cancer (KEYNOTE-021 study).

5.4 Study Risk / Benefit Ratio

The potential benefit of this study is judged to outweigh risk; therefore, the risk/benefit ratio is in favor of benefit.

5.4.1 Study Known Potential Risks

The research in this study poses greater than minimal risk with some potential prospect for direct benefit to the participant . The study is likely to yield generalizable knowledge about the treatment of triple negative breast cancer.

5.4.2 Study Known Potential Benefits

Potential benefits include the possibility of increased pathological response rates (compared to historical standard-of-care chemotherapy) for participants enrolling in this study. In addition, the study will yield information that may benefit future subjects by advancing knowledge regarding treatment of TNBC.

6 INVESTIGATIONAL NEW DRUG (IND)

This study treatment meets the requirements for IND exemption; FDA confirmation has been obtained and is on file for this study.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 OBJECTIVE(S)

7.1.1 Primary Objective

To determine the pathological complete response (pCR) rates with a neoadjuvant chemotherapy regimen of carboplatin and docetaxel (CbD) plus Pembrolizumab in patients with stage I-III TNBC.

7.1.2 Secondary Objective(s)

1. To evaluate minimal residual disease (MRD) rate (residual cancer burden score of 0/1) with a neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.
2. To determine 3-year recurrence-free survival with a neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.
3. To determine 3-year event-free survival with a neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.
4. To evaluate toxicity of neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.

7.1.3 Exploratory Objective(s)

1. To evaluate markers of DNA repair deficiency and/or tumor genomic instability as biomarkers of response to treatment.
2. To evaluate immune therapy response biomarkers (e.g. PD-L1 expression, gene expression signatures).
3. To evaluate overall survival with a neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.

7.2 ENDPOINTS AND MEASURE(S)

7.2.1 Primary Endpoint

Rate of pathological complete response (pCR) in breast and axilla after neoadjuvant CbD plus Pembrolizumab.

Primary Endpoint Timeframe
Time of definitive breast surgery.

Primary Endpoint Measure(s):
Percentage of participants with pathological response in breast and axilla, as evidenced by absence of invasive disease in breast and axillary lymph nodes (ypT0/Tis ypN0) determined by histopathological examination.

7.2.2 Secondary Endpoint(s)

1. Rates of minimal residual disease (MRD) after neoadjuvant CbD plus Pembrolizumab.

   Secondary Endpoint Timeframe(s):
   Time of definitive surgery.

Secondary Endpoint Measure(s):
Residual cancer burden (RCB) score of 0/1. Residual cancer burden score for each patient is calculated using surgical pathology parameters using an online tool (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3).

2. 3-year recurrence-free survival (RFS)

   Secondary Endpoint Timeframe(s):
   Recurrence-free survival (RFS) is defined as the time from diagnosis to first recurrence (invasive ipsilateral breast, invasive local/regional, or distant), or to death as a result of any cause [78].

   Secondary Endpoint Measure(s):
   Recurrence-free survival (RFS) as defined above.

3. 3-year event-free survival (EFS)

   Secondary Endpoint Timeframe(s):
   Event-free survival (EFS) is defined as the time from diagnosis to first recurrence (invasive ipsilateral breast, invasive local/regional, or distant), to second non-breast primary malignancy of any type, or to death from breast cancer or death from study treatment-related toxicity.

   Secondary Endpoint Measure(s):
   Event-free survival (EFS) as defined above.

4. Toxicity

   Secondary Endpoint Timeframe(s):
   Start of study treatment (cycle 1 day 1) until 30 days after last dose of study treatment.

   Secondary Endpoint Measure(s):
   Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03.

7.2.3 Exploratory Endpoint(s)

1. To evaluate markers of DNA repair deficiency and/or tumor genomic instability as biomarkers of pathological response to treatment .
2. To evaluate immune therapy response markers (e.g. PD-L1 expression, gene expression signatures) as biomarkers of pathological response to treatment.
3. To evaluate overall survival (defined as time from diagnosis to death as a result of any cause) with a neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.

8 STUDY ENROLLMENT AND WITHDRAWAL

8.1 Participant Inclusion Criteria

Participants must meet **all** of the inclusion criteria listed below to participate in this study.

1. Ability of participant to understand this study, and participant willingness to sign a written informed consent for this trial.
2. Female subjects age 18-70 years.
3. Histologically confirmed stage I (T>1cm or cN+), II or III TNBC.
    a. The invasive tumor must be hormone receptor-poor, defined as both estrogen receptor (ER) and progesterone receptor (PR) staining present in ≤10% of invasive cancer cells by IHC.
    b. HER2 negativity will be based on current ASCO-CAP guidelines for HER2 testing [79].
4. No previous definitive ipsilateral breast surgery for the current breast cancer.
5. No previous chemotherapy, endocrine therapy, or radiation therapy with therapeutic intent for this cancer.
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix A) [80]. Evaluation of performance status is to be performed within 10 days prior to the start of study treatment.
7. Have adequate organ function as defined below:
    a. Hematological:
        i. Absolute neutrophil count ≥ 1,500/uL
        ii. Platelets ≥ 100,000/uL
        iii. Leukocytes ≥ 3,000/uL
        iv. Hemoglobin ≥ 9.0 g/dL or ≥ 5.6 mmol/L (criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within last 2 weeks)
    b. Renal:
        i. Creatinine ≤ 1.5 mg/dL and/or creatinine clearance ≥ 60 mL/min
    c. Hepatic:
        i. Total bilirubin ≤ 1.5x IULN, OR direct bilirubin ≤ IULN for participants with total bilirubin levels > 1.5x IULN
        ii. AST(SGOT) and ALT(SPGT) ≤ 2x IULN
    d. Coagulation:
        i. International normalized ratio (INR) of coagulation OR prothrombin time (PT) OR activated partial thromboplastin time (aPTT) ≤ 1.5x IULN, unless patient is receiving anticoagulant therapy. If patient is receiving anticoagulant therapy, PT or aPTT is within therapeutic range of intended use of anticoagulants.
    e. Serum albumin ≥ 3.0 g/dL
8. Pretreatment lab values must be performed within 10 days of treatment initiation, and other baseline studies performed within 30 days prior to registration.
9. Subjects should have breast and axillary imaging with breast MRI (preferred) or breast and axillary ultrasound within 30 days prior to treatment initiation.
10. Subjects with clinically/radiologically abnormal axillary lymph nodes should have pathological confirmation of the disease with image-guided biopsy/fine needle aspiration.
11. Subjects must already be enrolled in P.R.O.G.E.C.T. observational registry (HSC #12614). This inclusion criteria is only applicable to patients enrolling at University of Kansas Cancer Center and its affiliates.

12. Have provided archival breast tumor tissue sample, which should include a formalin-fixed paraffin-embedded (FFPE) block or 12 unstained slides (ten 5-micron uncharged slides and two 5-micron charged slides) from primary breast tumor and/or axillary lymph node. If adequate archival breast tumor specimen is not available, a newly obtained core biopsy of breast tumor should be performed for submission of tumor specimen (details are provided in section 12.1).
13. Staging to rule out metastatic disease is suggested for subjects with clinical stage III disease.
14. Subjects with bilateral disease are eligible if they meet other eligibility criteria.
15. Neuropathy: no baseline neuropathy grade >2.
16. Cardiac function:
    a. Subjects should have LVEF ≥ 50% by echocardiogram or MUGA scan performed within 30 days prior to treatment initiation.
    b. Subjects with congestive heart failure are not eligible, nor are subjects with myocardial infarction, unstable angina pectoris, an arterial thrombotic event, stroke or transient ischemia attack within the past 12 months, uncontrolled hypertension (systolic BP > 160 or diastolic BP > 90), uncontrolled or symptomatic arrhythmia, or grade 2 or greater peripheral vascular disease.
17. A female participant is eligible to participate if she is not pregnant (see Appendix B, Contraceptive Guidance and Pregnancy Testing), not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix B, OR
    b. A WOCBP who agrees to follow the contraceptive guidelines in Appendix B during the treatment period and for at least 120 days after the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treated physician immediately (see section 16.2.5, Reporting of Pregnancy and Lactation).

8.2 Participant Exclusion Criteria

Participants meeting **any** of the exclusion criteria listed below at screening will be excluded from study participation.

1. Current or anticipated use of other investigational agents while participating in this study.
2. Subject has received chemotherapy, radiotherapy, or surgery for the treatment of breast cancer.
3. Subject has metastatic disease.
4. Subject has inflammatory breast cancer.
5. Subjects with concomitant or previous malignancies within the last 5 years are excluded from the study.
    a. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. ductal carcinoma in situ (DCIS), carcinoma in situ of the cervix) that have undergone potential curative therapy are not excluded.
6. History of allergic reactions attributed to compounds of similar chemical or biologic composition to carboplatin, docetaxel, or other agents used in this study.

7. Has severe hypersensitivity (≥ grade 3) to Pembrolizumab or any of its excipients.
8. Subject has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).
9. If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
10. Subject has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
11. Subject is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
12. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of Pembrolizumab.
13. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
14. Has a history of (non-infectious) pneumonitis that required steroids, or has current pneumonitis.
15. Has an active infection requiring systemic therapy.
16. Has a known history of Human Immunodeficiency Virus (HIV).
17. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as detectable HCV RNA) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
19. Subject has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
20. Subject is pregnant or breast feeding, or expecting to conceive within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment. There is a potential for congenital abnormalities and for this regimen to harm breastfeeding infants (if applicable).
21. Subject is a WOCBP who has had a positive urine pregnancy test within 24 hours prior to initiation of study treatment (see Appendix B, Contraceptive Guidance and Pregnancy Testing, for definition of WOCBP). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

a. Note: In the event that 24 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

22. Ejection fraction < 50% on ECHO or MUGA.

8.3 Participant Withdrawal Or Termination

8.3.1 Reasons For Withdrawal Or Termination

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- Participant or participant's legally acceptable representative requests to discontinue study treatment;
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment;
- Unacceptable adverse experiences;
- Medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, places the participant at unnecessary risk from continued administration of study treatment;
- Confirmed positive serum pregnancy test (pregnancy to be reported along the same timelines as a serious adverse event; see Section 16.2.5, Reporting of Pregnancy);
- Recurrent grade 2 pneumonitis
- Noncompliance with study treatment or procedure requirements;
- Treating physician judges continuation on the study would not be in the participant's best interest;
- Administrative reasons;
- Lost to follow-up

A participant must be discontinued from study treatment and further monitoring in the study for the following reason (no further data collection will be done):

- Participant withdraws consent.

8.3.2 Participant Replacement

Participants who do not complete the study treatment due to toxicity or other reasons will not be replaced.

9 MEASUREMENT OF EFFECT

9.1 Solid Tumor

9.1.1 Antitumor Effect

Definitions
Evaluable for toxicity: Any eligible participant who receives treatment on this protocol will be evaluable for toxicity. Each subject will be assessed for the development of toxicity according to the Schedule of Events table (Table 6). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03 [81]. Dose modifications for chemotherapy in event of toxicity (see Section 11.1.4, Dose Adjustments/Modifications/Delays) are applicable only if the toxicity is deemed "treatment-related." This is in accordance with standard clinical practice. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Response Criteria
Pathological complete response (pCR): Absence of invasive disease in breast and axillary lymph nodes at the time of pathology review, with the exception of ductal carcinoma in situ (DCIS) in breast (ypT0/Tis ypN0).
Residual cancer burden (RCB) 0/1: Residual cancer burden (RCB) score is used to determine minimal residual disease (MRD). RCB will be calculated by study personnel utilizing surgical pathology parameters using a free online tool (*http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3*)

Recurrence-Free Survival
Recurrence-free survival (RFS), is defined as the time from diagnosis to first recurrence (invasive ipsilateral breast, invasive local, /regional, or distant), or to death as a result of any cause [78]. Recurrence will be determined by the treating physician using clinical, radiological, and/or pathological methods. Participants who are lost to follow-up will be censored on the date they were last known to be alive and without recurrence. Patients who withdraw consent will be censored on the date of consent withdrawal.

Event-Free Survival
Event-free survival (EFS) is defined as the time from diagnosis to first recurrence (invasive ipsilateral breast, invasive local/regional, or distant), to second non-breast primary malignancy, or to death from breast cancer or death from study treatment-related toxicity. Recurrence will be determined by the treating physician using clinical, radiological, and/or pathological methods. Participants who are lost to follow-up will be censored on the date they were last known to be alive and without recurrence or second primary malignancy. Patients who withdraw consent will be censored on the date of consent withdrawal.

10 STUDY AGENT

10.1 Study Agent(s) / Therapy / Device And "Control" Description

10.1.1 Acquisition / How Supplied

Carboplatin, docetaxel, and pegfilgrastim (or its biosimilar equivalent) are commercially available.

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

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

10.1.2 Formulation, Appearance, and Packaging

10.1.2.1 Carboplatin

Other names for the drug(s): Paraplatin

Classification - type of agent: Alkylating agent/platinum coordination compound

Mode of action: Covalently binds to DNA, producing cross-links which lead to inhibition of DNA synthesis.

Preparation: Carboplatin injection is a premixed aqueous solution of 10 mg/mL carboplatin. Carboplatin injection, 10 mg/mL, can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride Injection (NS), USP.

Storage and Stability: Unopened vials of carboplatin injection, 10 mg/mL, are stable to the date indicated on the package when stored at 25°C (77°F), excursions permitted from 15°C-30°C (59°F - 86°F) [see USP Controlled Room Temperature]. Protect from light. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin aqueous solutions be discarded 8 hours after dilution.

Nursing implications: Incompatible with amphotericin B cholesteryl sulfate complex. Use appropriate precautions for handling and disposal (hazardous).

10.1.2.2 Docetaxel

Other names for the drug(s): Taxotere

Classification - type of agent: Anti-microtubule agent

Mode of action: Induces apoptosis via bcl-2 phosphorylation, binds to tubulin and inhibits microtubule depolymerization, has antiangiogenic properties.

Preparation: Docetaxel for injection concentrate is diluted to 10 mg/mL in 13% ethanol in water for injection. The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours. This initial dilution (10 mg/mL) is further diluted into 250 mL of 0.9% sodium chloride or 5% dextrose solution to produce a final concentration of 0.3 to 0.74

mg/mL. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL is not exceeded.

Storage and Stability: The initial diluted solution (10 mg/mL) may be stored either in the refrigerator or at room temperature for a maximum of 8 hours. Final infusion solution, if stored between 2° and 25°C (36°F - 77°F) is stable for 4 hours; fully prepared infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 4 hours (including the 1 hour IV administration).

Nursing implications: Incompatible with amphotericin B, doxorubicin liposome, methylprednisolone sodium succinate, nalbuphine; compatibility with ceftriaxone is variable (consult detailed reference). Administer anti-emetics, advise regarding alopecia, monitor for hypersensitivity reactions, evaluate LFTs, evaluate for sites of infiltration, peripheral neuropathy, and monitor for fluid retention.

10.1.2.3 Pembrolizumab

Other names for the drug(s): [redacted]Keytruda

Classification - type of agent: PD-1 humanized monoclonal antibody

Mode of action: Blocks PD-1 activation to reverse checkpoint inhibition of endogenous immune reaction

Formulation: [redacted]

Appearance and Packaging: T[redacted]

Preparation: [redacted]

Storage and Stability: [redacted]

[redacted]

Nursing implications: [redacted]

10.1.3 Agent Known Potential Side Effects

10.1.3.1 Carboplatin

- Alopecia
- Hypomagnesemia, hypokalemia, hyponatremia, hypocalcemia
- Nausea, vomiting, stomatitis
- Myelosuppression (dose-related and dose-limiting); thrombocytopenia (37% to 80%); leukopenia (27% to 38%)
- Increase in alkaline phosphatase and AST (usually mild and reversible)
- Hearing loss at high tones
- BUN and/or creatinine increase
- Peripheral neuropathy

10.1.3.2 Docetaxel

- Neutropenia is the dose-limiting hematologic toxicity
- During organogenesis, docetaxel is embryotoxic and fetotoxic
- Fluid retention, possibly severe; requires appropriate steroid pre-medication
- Hypersensitivity reactions can occur within minutes following administration and subjects should be appropriately pre-medicated
- Neurotoxicity (paresthesias, dysethesias, pain)
- Alopecia
- Nausea/vomiting/diarrhea
- Transaminase or bilirubin elevation

10.1.3.3 Pembrolizumab

- Fatigue, headache, dizziness
- Cough, dyspnea
- Diarrhea, abdominal pain
- Pruritis, rash, vitiligo, skin peeling
- Arthralgia, myalgia, back pain
- Hypothyroidism, hyperthyroidism
- Pyrexia
- Pneumonitis
- Infusion reactions
- Gastrointestinal inflammation/colitis

- Neuritis, neuropathy
- Myositis
- Pancreatitis
- Uveitis
- Hepatitis
- Hypophysitis
- Renitis
- Endocarditis
- Thyroiditis
- Adrenal insufficiency
- Type 1 diabetes mellitus
- Granulomatosis
- Graft versus host disease
- Hyponatremia
- Arthritis

10.1.4 Concomitant, Precautionary, Prohibited Medications, Foods And Treatments

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

10.1.4.1 Acceptable concomitant medications

All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

<u>Antiemetics</u>
Use of antiemetics is allowed.

<u>Fertility preservation</u>
Use of goserelin for fertility preservation is allowed.

<u>Anticoagulants</u>
Anticoagulants or other anti-aggregation agents may be administered at the discretion of the investigator. Subjects on anticoagulation with warfarin should be carefully monitored and have PT/INR checked every week.

Contraceptives

Highly effective contraception should be maintained throughout the study and for 120 days after study drug discontinuation. Hormone contraceptives are not allowed for this study. Allowed contraceptive methods are described in Appendix B, Contraceptive Guidance and Pregnancy Testing.

10.1.4.2 Prohibited concomitant medications and treatments

Participants are prohibited from receiving the following therapies during the Screening and Treatment phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Pembrolizumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or for use as a pre-medication for chemotherapeutic agents.
  Note: Inhaled steroids are allowed for management of asthma.
  Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contrast dye) is permitted.

Additionally, use of erythropoietin-stimulating agents is not allowed.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

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

10.1.4.3 Rescue medications and supportive care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 11.1.4.3.1, [Table 4]. Where appropriate, these guidelines include the use of oral or IV treatment with

corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to Pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Section 11.1.4, Dose Adjustments/Modifications/Delays for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

10.1.5 Return And Retention Of Study Agent

Study drug will be obtained from commercial supply and handled according to institutional drug handling procedures. Upon completion or termination of the study, all unused and/or partially used Pembrolizumab will be destroyed at the site per institutional policy.

11 TREATMENT PLAN

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy will consist of carboplatin, docetaxel, Pembrolizumab, and supporting medications, and will be given for 6 cycles of 21 days each. Following neoadjuvant chemotherapy, participants will undergo definitive breast surgery. Adjuvant chemotherapy and radiation therapy will be administered at the discretion of the treating physician.

In general chemotherapy pre-medications and at-home supportive medications to prevent anticipated side effects are to follow institutional guidelines. Appendix D describes the suggested pre-medication use during treatment.

Table 3: Study drug treatment summary

Agent	Dose	Route	Schedule	Cycle Length
Carboplatin[a]	AUC 6	IV over 30 min	Day 1	21 days[b] x 6
Docetaxel	75 mg/m^2	IV over 60 min	Day 1	
Pembrolizumab	200 mg	IV over 30 min	Day 1	
Pegfilgrastim (or its biosimilar equivalent)	6 mg	SC	Day 2	

[a] The SWOG (Southwest Oncology Group) guidelines must be followed for carboplatin dose calculation: 1) Use of Modified Cockcroft-Gault formula for calculating renal function, 2) Calculating Modified Cockcroft-Gault with serum creatinine set to 0.8 mg/dL if actual serum creatinine < 0.8 mg/dL, 3) Maximum GFR is 125 mL/min, 4) Limiting weight to 140% of ideal body weight for calculation of creatinine clearance, 5) Maximum carboplatin dose to be given is 900 mg.

[b] +/- one day

Growth factor support: Erythropoietin growth factor support for fatigue/anemia is not allowed. Packed RBC transfusion is allowed at the discretion of the treating physician. Pegfilgrastim (or its biosimilar equivalent) growth factor support as described above is included in the treatment plan.

Surgery

After completion of neoadjuvant therapy, subjects will proceed with definitive surgery (appropriate surgery type to be determined by surgeon). Surgery should take place between 3-10 weeks after the last chemotherapy cycle.

All subjects with pretreatment lymph node positive disease and positive sentinel lymph node will undergo complete axillary lymph node dissection and/or axillary radiation. Histopathological examination of the surgical specimen will be done to determine the extent of residual disease. Pathological complete response (pCR) will be defined as no evidence of disease in the breast and axilla at the time of pathology review, except for DCIS.

Adjuvant therapy

Adjuvant chemotherapy: as per recommendations of treating physician.

Adjuvant radiation therapy: As per recommendations of the treating physician. In general adjuvant radiation is recommended for patients who undergo breast-conserving surgery, have tumors > 5 cm, have skin or chest wall involvement, or have pathologically positive lymph node(s) after neoadjuvant chemotherapy.

Duration of follow-up

After completion of all local and systemic treatment for breast cancer (surgery, chemotherapy, or radiation, whichever comes last), all subjects will be followed approximately every 6 months until 3 years post-diagnosis. Information to be collected includes but is not limited to new anti-cancer therapy, disease progression, and death.

11.1 Dosing And Administration

11.1.1 Administration

Trial treatment will be administered on the given cycle day(s) after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Table 6). All trial treatments will be administered on outpatient basis.

Carboplatin

Carboplatin AUC 6 will be given on day 1 of each cycle of 21 days (±1 day), for 6 cycles. The SWOG (Southwest Oncology Group) guidelines must be followed for carboplatin dose calculation, below. Dosing calculations should be based on actual body weight, with the exception of point #4 below.

1) Use of Modified Cockcroft-Gault formula for calculating renal function
2) Calculating Modified Cockcroft-Gault with serum creatinine set to 0.8 mg/dL if actual serum creatinine < 0.8 mg/dL
3) Maximum GFR is 125 mL/min
4) Limiting weight to 140% of ideal body weight for calculation of creatinine clearance
5) Maximum carboplatin dose to be given is 900 mg.

Carboplatin will be administered as a 30-minute (± 5 minutes) IV infusion, using a volumetric pump with a 0.2-1.2 um in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Other considerations: Dose rounding per institutional guidelines. Pre-medications per institutional guidelines.

Docetaxel

Docetaxel 75 mg/m^2 will be given on day 1 of each cycle of 21 days (±1 day), for 6 cycles. Dosing calculations should be based on actual body weight. If the participant's body weight differs more than 10% from the weight used to calculate the dose of docetaxel, the dose will be recalculated using current body weight.

Docetaxel will be administered as a 60-minute (± 10 minutes) IV infusion, using a volumetric pump with a 0.2-1.2 um in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Other considerations: Dose rounding per institutional guidelines. Pre-medications per institutional guidelines.

Pembrolizumab

Pembrolizumab 200 mg will be given on day 1 of each cycle of 21 days (±1 day), for 6 cycles.

Pembrolizumab will be administered as a 30-minute IV infusion, using a volumetric pump with a 0.2-1.2 um in-line filter at the protocol-specified dose. Every effort will be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window a -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Pegfilgrastim (or its biosimilar equivalent)

Pegfilgrastim (or its biosimilar equivalent) 6 mg will be given on day 2 of each cycle of 21 days, for 6 cycles.

Pegfilgrastim (or its biosimilar equivalent)will be administered subcutaneously at the protocol-specified dose.

11.1.2 Duration Of Therapy

In the absence of treatment delays due to adverse events, all subjects will receive 6 cycles of neoadjuvant chemotherapy with carboplatin, docetaxel, and Pembrolizumab given every 21 days. The total duration of this treatment should not exceed 22 weeks.

Treatment may be stopped at any time during the schedule if any of the following occur:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Death
- Subject's decision to withdraw from the study
- General or specific changes in the subject's condition which render the subject unacceptable for further treatment in the judgment of the investigator.

11.1.3 Study Agent Accountability Procedures / Participant Compliance

Study drugs are administered by clinical staff, and thus study drug accountability/patient compliance is not required.

11.1.4 Dose Adjustments/Modifications/Delays

Any eligible participant who receives treatment on this protocol will be evaluable for toxicity. Each participant will be assessed for the development of toxicity according to the Schedule of Events table. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03 [81]. The document may be viewed on the Cancer Therapy Evaluation Program (CTEP) website at this URL:

[redacted]

Dose adjustments should be made according to the system showing the greatest degree of toxicity. Dose modifications for therapy in event of toxicity are applicable only if the toxicity is deemed "treatment-related." This is in accordance with standard clinical practice. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

11.1.4.1 CARBOPLATIN AND DOCETAXEL

Carboplatin dose levels:

Level 0 = AUC 6
Level -1 = AUC 5
Level -2 = AUC 4

Docetaxel dose levels:

Level 0 = 75 mg/m^2
Level -1 = 60 mg/m^2
Level -2 = 50 mg/m^2

There are no dose reductions below level -2 for carboplatin or docetaxel. If dose reduction below level -2 is required, discontinue the respective drug.

11.1.4.1.1 Hematologic toxicities

Toxicity[a]	Treatment Modifications

ANC[a] < 1000/uL (day 1 of cycle)	Delay docetaxel and carboplatin until ANC ≥1,000/uL. If counts recover to ≥ 1,000/uL in ≤ 1 week, resume at current dose. If docetaxel and carboplatin are delayed for 2 consecutive weeks for ANC < 1000/uL, reduce docetaxel and carboplatin by one dose level for all subsequent cycles. If docetaxel and carboplatin are delayed for 3 consecutive weeks for ANC < 1000/uL, discontinue docetaxel and carboplatin.
ANC < 100/uL or febrile neutropenia[a] (at any time)	Reduce docetaxel and carboplatin by one dose level for all subsequent cycles.
Platelets < 50,000/uL (day 1 of cycle)	Hold docetaxel and carboplatin until platelets ≥ 75,000/uL, then resume docetaxel and carboplatin with one dose level reduction for both drugs for all subsequent doses. If docetaxel and carboplatin are held for 3 consecutive weeks for platelets < 75,000/uL, discontinue treatment.
Platelets ≥ 50,000/uL and < 75,000/uL (day 1 of cycle)	Hold both docetaxel and carboplatin until platelets ≥ 75,000/uL and resume docetaxel at previous dose and carboplatin with one dose level reduction for all subsequent doses. If docetaxel and carboplatin are held for 3 consecutive weeks for platelets < 75,000/uL, discontinue treatment.

[a] There will be no dose modifications for grade 1-4 anemia. If the ANC is < 1,000/uL or platelet count is < 50,000/uL when drawn more than 24 h prior to the scheduled treatment, CBC should be re-checked on the day of treatment to see if the blood counts have recovered sufficiently to allow the schedule treatment to be given.

[b] Febrile neutropenia: a single temperature ≥ 38.3˚C or a sustained temperature of ≥ 38˚C for more than an hour in presence of ANC < 1,000/uL.

If carboplatin and docetaxel are delayed for > 4 weeks for any reason, discontinue study treatment.

11.1.4.1.2 Non-hematologic toxicities

Peripheral neuropathy	Grade 1: Continue treatment Grade 2: Decrease the dose of docetaxel by one dose level for all subsequent doses. The dose of carboplatin is not reduced. Grade 3: Hold docetaxel and carboplatin. When neuropathy improves to ≤ grade 2, resume treatment with one dose level reduction of both docetaxel and carboplatin. If grade 3 peripheral neuropathy does not improve within 3 weeks, discontinue docetaxel and carboplatin. For grade 3 neuropathy that has recurred after recovery to ≤ grade 2, discontinue docetaxel and carboplatin. Grade 4: Discontinue docetaxel and carboplatin
Hypersensitivity reactions	See below for management.
Fluid retention	There are no dose reductions for fluid retention (see below for management).
Hepatic dysfunction (day 1 LFTs)	See below for dose reductions chart. Patients with total bilirubin > 1.5x IULN should not receive docetaxel. Patients with AST and/or ALT > 1.5x IULN concomitant with alkaline phosphatase > 2.5x IULN should not receive docetaxel.
Other non-hematologic toxicities	For any other grade 3 or 4 toxicity (with the exception of fatigue, nausea or vomiting), delay docetaxel and carboplatin until toxicity improves to ≤ grade 2. When treatment is resumed, reduce the doses of docetaxel and carboplatin by one dose level. If toxicity does not improve to ≤ grade 2 within 3 weeks, discontinue docetaxel and carboplatin and proceed to surgery when feasible.

If carboplatin and docetaxel are delayed for > 4 weeks for any reason, discontinue study treatment.

11.1.4.1.3 Hypersensitivity reactions:

During docetaxel infusion

Grade 1: Continue docetaxel infusion. Consider decreasing the rate of infusion. Consider more intensive pre-medication prior to subsequent doses.

Grade 2: Interrupt docetaxel infusion. Manage reaction according to institutional procedures. Resume docetaxel when reaction has completely resolved. Consider more intensive pre-medication prior to subsequent doses.

Grade 3: Stop docetaxel infusion. Manage reaction according to institutional procedures. Do not resume docetaxel infusion that day and delay carboplatin dose that was to be administered that day. It is up to the treating physician to decide whether to attempt re-treatment with docetaxel the following cycle with more intensive pre-medication or to discontinue docetaxel.

Grade 4: Stop docetaxel infusion. Manage reaction according to institutional procedures. Discontinue docetaxel. Carboplatin and Pembrolizumab can be continued per the discretion of the treating physician.

During carboplatin infusion

Grade 1 or 2: Stop carboplatin infusion. Manage reaction according to institutional procedures. Do not resume carboplatin infusion that day. It is up to the treating physician to decide whether to re-attempt carboplatin infusion with next cycle (with or without desensitization) or to discontinue carboplatin and continue treatment with docetaxel only.

Grade 3 or 4: Stop carboplatin infusion. Manage reaction according to institutional procedures. Discontinue carboplatin. Docetaxel and Pembrolizumab can be continued per the discretion of the treating physician.

11.1.4.1.4 Management of edema/fluid retention related to docetaxel:

No dose reduction is required. Subjects developing new onset edema, progression of existing edema, or another sign of fluid retention (e.g. pound weight gain) can be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below:

- Hydrochlorothiazide/Triamterene one capsule 25/37.5 mg PO up to three times per day per the discretion of the treating physician
- Furosemide 40 mg PO daily if edema progresses despite hydrochlorothiazide/triamterene therapy. Potassium supplementation should be given as needed.
- If after a two week trial, furosemide 40 mg PO daily is ineffective, the patient may be treated with furosemide 20 mg PO daily plus metolazone 2.5 mg PO daily, with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the subject, the overall tumor response, and the medical judgment of the investigator will determine if it is in the subject's best interest to continue or discontinue treatment.

11.1.4.1.5 Hepatic dysfunction

Dose modifications are based on day 1 liver function tests:

Liver Function Tests	Dose Modification
Total bilirubin > 1.5x IULN concomitant with alkaline phosphatase > 2.5x IULN	Do NOT administer docetaxel. If not resolved in one week, subject should be removed from protocol treatment.
AST/ALT >2.5x IULN but ≤ 5x IULN AND Alkaline phosphatase > IULN but ≤ 2.5x IULN	Docetaxel dose reduced by 20%.
AST/ALT >1.5x IULN and ≤ 5x IULN AND Alkaline phosphatase > 2.5x IULN but ≤5x IULN	Docetaxel dose reduced by 20%.

AST/ALT > 5x IULN AND/OR Alkaline phosphatase > 5x IULN	Do NOT administer docetaxel. If not resolved in one week, subject should be removed from protocol treatment.

If docetaxel is delayed for > 4 consecutive weeks for any reason, discontinue docetaxel.

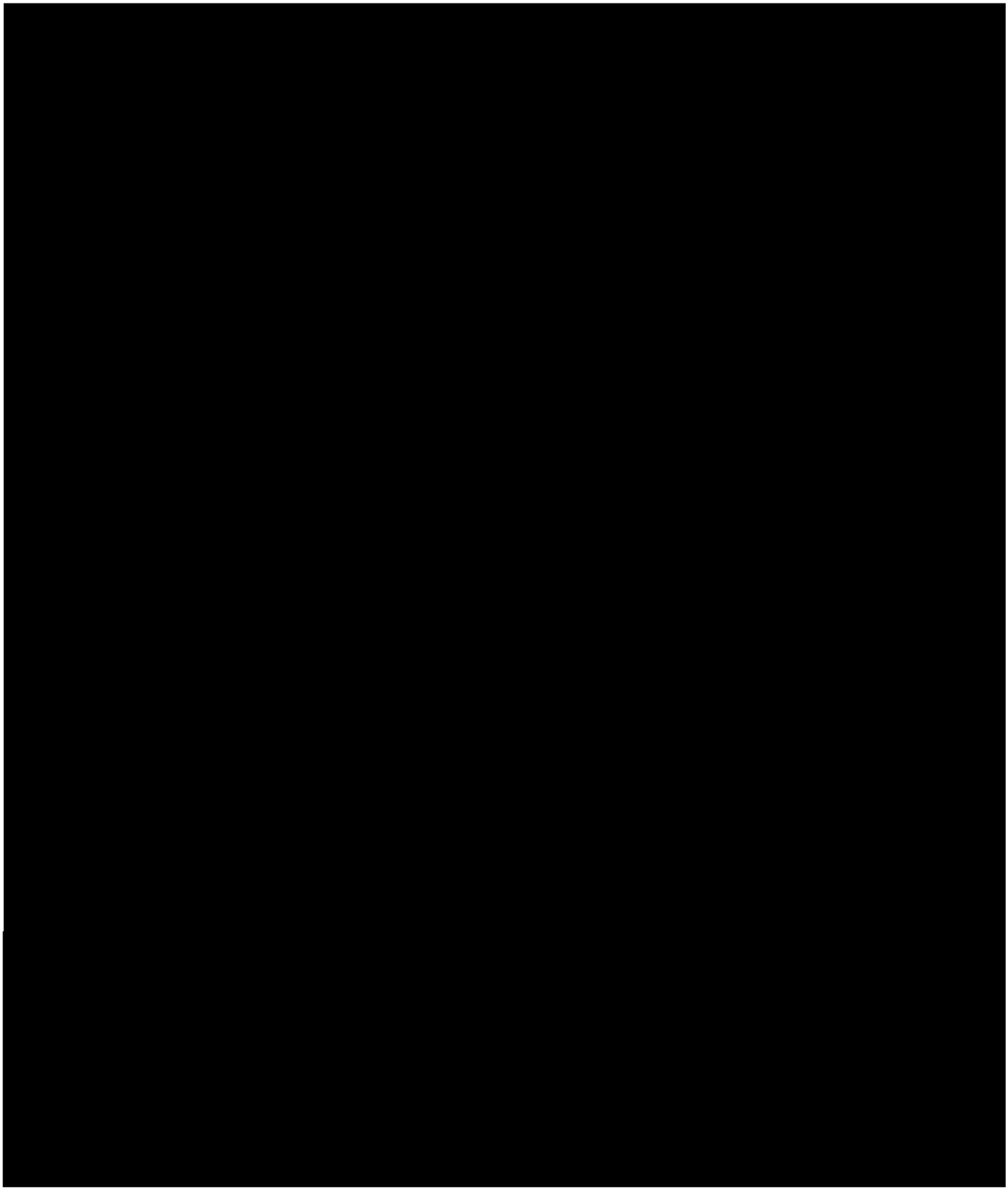
11.1.4.2 PEMBROLIZUMAB

Pembrolizumab dose levels:

Level 0 = 200 mg

There are no dose reductions for Pembrolizumab.

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

11.1.5 Concomitant, Precautionary, Prohibited Medications, Foods And Treatments

See Section 10.1.4, “Concomitant, Precautionary, Prohibited Medications, Foods And Treatments” for a list and discussion of acceptable and unpermitted medications.

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

12 STUDY PROCEDURES AND SCHEDULE

12.1 DESCRIPTIVE SCHEDULE OF EVENTS

12.1.1 Screening/Enrollment/Baseline

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. If the tests required at screening were performed as part of standard of care prior to signing consent for this study, the results from those tests are allowed in this study if the tests were completed within the timeframe listed below.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated.

SCREENING

Informed Consent
Consent must be documented by the participant's dated signature or by the participant'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 will be given to the participant before participation in the trial.
The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative will be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant's dated signature or by the participant'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 IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

Medical history
Complete medical, surgical and oncology history, as well as history of infections, are obtained at screening. Medical history will include all active conditions, and any conditions diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

Disease details and treatments
Prior and current details regarding disease status will be collected.

Demographics
Demographic profile will include date of birth, gender, race, ethnicity, and zip code.

Review participant eligibility criteria
Review of eligibility criteria to ensure participant qualification for study entry.

Previous and concomitant medications (performed within 10 days prior to start of study treatment)
All prior medications taken by the participant within 4 weeks before starting the study are to be recorded. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. Concomitant medications (including prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids) taken by the participant during the study are to be recorded up until 30-days after last study dose. If a reportable adverse event (see section with title *Adverse Events*) occurs within 30-days after last study dose, recording of concomitant medications should continue until resolution of the adverse event.

Physical exam (performed within 10 days prior to start of study treatment)
Exam will include vital signs, height (to be measured at screening/baseline only), and assessment of all major body systems.
Note: Vital signs include temperature, pulse, respiration rate, blood pressure, and weight.

Performance status (evaluated within 10 days prior to start of study treatment)
Performance status based on ECOG criteria (Zubrod scale) will be evaluated prior to study entry. Specific criteria for assessing performance status can be found in Appendix A.

Hematology (collected within 10 days prior to start of study treatment)
Hematology testing will include hemoglobin, hematocrit, platelets, red blood cells, leukocyte total and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), absolute neutrophil count, and absolute lymphocyte count.

Serum chemistries (collected within 10 days prior to start of study treatment)
Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, lactate dehydrogenase (LDH), BUN, uric acid, creatinine or GFR (creatinine clearance to be evaluated if creatinine >1.5x IULN), electrolytes (sodium, potassium, phosphorus, magnesium, calcium, chloride, bicarbonate), glucose, total bilirubin (direct bilirubin to be evaluated if total bilirubin is elevated > 1.5x IULN), and total protein.

Additional laboratory tests (collected within 30 days prior to start of study treatment)
International normalized ratio (INR) of coagulation OR prothrombin time (PT) OR activated partial thromboplastin time (aPTT), total thriiodothyronine (T3), free tyroxine (T4), thyroid stimulating hormone (TSH), ACTH, and AM cortisol.

Pregnancy test for WOCBP (performed within 24 h prior to start of study treatment)
Urine pregnancy test to be performed for all participants who qualify as WOCBP (see Appendix B). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β-human chorionic gonadotropin, β-hCG) will be required.

> Note: In the event that 24 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

Tumor assessment
All patients must have breast and axillary ultrasound or breast MRI (preferred unless MRI is contraindicated, e.g. presence of metal hardware in body, or if unable to be performed) within 30 days prior to treatment initiation, for accurate assessment of breast and axillary disease. Subjects with clinically or radiologically abnormal axillary lymph node(s) should have pathological documentation of the nodal involvement (fine needle aspiration or core needle biopsy).

Cardiac function evaluation
MUGA or echocardiogram will be performed for all patients within 30 days prior to treatment initiation.

Primary tumor tissue submission

Formalin-fixed paraffin-embedded (FFPE) block or 12 unstained slides (ten 5-micron uncharged slides and two 5-micron charged slides) from primary breast tumor and/or axillary lymph node will be collected for all patients prior to start of study treatment.

If adequate archival breast tumor specimen is not available, a newly obtained image-guided core biopsy of breast tumor should be performed for submission of tumor specimen. The use of imaging to facilitate biopsies will be decided by members of the radiology team and may include ultrasound or MRI.
Sites are requested to follow the below standard instructions for preparation of FFPE block:

- Obtain four 16-gauge or 14-gauge core needle biopsy specimens.
- Place the fresh tissue in formalin. Do not exceed 24 hours fixation time.
- Fixed tissue must be paraffin embedded within 24 hours.
- Cut one H&E (hematoxylin and Eosin) stained section from the representative paraffin-embedded tissue block.
- Fixed tissue block and the H&E slide should be sent for storage to BRCF (see section 13.4)

12.1.2 Procedures During Treatment

PRIOR TO EACH TREATMENT CYCLE #2-6:

Concomitant medications (collected within 48 hours prior to each treatment cycle)
Any new medications, discontinued medications, or dose alterations will be reviewed.

History and physical exam (collected within 48 hours prior to each treatment cycle)
History and physical exam will be performed as clinically indicated. Vital signs to be collected are temperature, pulse, respiratory rate, weight, and blood pressure. Toxicity evaluation will be included.

Performance status (collected within 48 hours prior to cycle treatment)
ECOG performance status will be evaluated prior to each treatment cycle. Specific criteria for assessing performance status can be found in Appendix A.

Hematology (collected within 48 hours prior to each treatment cycle)
Hematology testing will include hemoglobin, hematocrit, platelets, red blood cells, leukocyte total and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), absolute neutrophil count, and absolute lymphocyte count.

Serum chemistries (collected within 48 hours prior to each treatment cycle)
Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, lactate dehydrogenase, carbon dioxide, BUN, uric acid, creatinine or GFR (creatinine clearance to be evaluated if creatinine >1.5x IULN), electrolytes (sodium, potassium, phosphorus, magnesium, calcium, chloride, bicarbonate), glucose, total bilirubin (direct bilirubin to be evaluated if total bilirubin is elevated > 1.5x IULN), and total protein.

Pregnancy test for WOCBP (performed within 24 h prior to cycle treatment)
Urine pregnancy test to be performed for all participants who qualify as WOCBP (see Appendix B). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β-human chorionic gonadotropin, β-hCG) will be required.

> Note: In the event that 24 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

EACH TREATMENT CYCLE (every 21 ± 1 days)

Chemotherapy and growth factor support
Carboplatin, docetaxel and Pembrolizumab on day 1 of each cycle.
Pegfilgrastim (or its biosimilar equivalent) on day 2 (+ 2 days) of each cycle.

CYCLE #4, DAY 1

Additional laboratory tests
Total thriiodothyronine (T3), free tyroxine (T4), and thyroid stimulating hormone (TSH) will be evaluated on Day 1 of cycle #4.

PRIOR TO CYCLE #5:

Tumor re-assessment (performed +/- 14 days prior to start of cycle #5)
All patients must have a repeat breast and axillary ultrasound or breast MRI (preferred unless MRI is contraindicated, e.g. presence of metal hardware in body, or unable to be performed) prior to study treatment cycle #5, for preliminary assessment of response.

AFTER CYCLE #6:

Correlative blood specimen (collected 21 ±7 days after cycle #6)
A blood specimen for correlative studies (see Section 13, Correlative Studies) will be drawn after the last cycle of chemotherapy and before surgery. Collection of this specimen is required for all participants who received at least one dose of study treatment. These blood draws do not need to be duplicated if already done under P.R.O.G.E.C.T. protocol.

Safety follow-up visit (30 +21/-7 days after day 1 of cycle #6)
Adverse events and concomitant medications will be reviewed at the mandatory safety follow-up visit. The safety follow-up visit should be conducted approximately 30 days after the last dose of Pembrolizumab or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the safety follow-up visit should be recorded. Participants with an AE of grade >1 will be followed until the resolution of the AE to grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of Pembrolizumab treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

Thyroid function laboratory tests (at safety follow-up visit, 30 +21/-7 days after day 1 of cycle #6)
Total thriiodothyronine (T3), free tyroxine (T4), and thyroid stimulating hormone (TSH) will be evaluated at the safety follow-up visit.

Pregnancy test for WOCBP (approximately 120 days after day 1 of cycle #6)
Urine pregnancy test to be performed approximately 120 days after the last dose of Pembrolizumab for all participants who qualify as WOCBP (see Appendix B). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β-human chorionic gonadotropin, β-hCG) will be required.

Surgery (between 3 and 10 weeks after cycle #6)
After completion of study treatment cycle #6, subjects will proceed to either mastectomy or lumpectomy.

12.1.3 Post-Treatment Follow-Up Visit(s)

After completion of all local and systemic treatment for breast cancer (surgery, chemotherapy, or radiation, whichever comes last), all subjects will be followed approximately every 6 months until 3 years post-diagnosis. Information to be collected includes but is not limited to new anti-cancer therapy, disease progression, and death.

12.2 SCHEDULE OF EVENTS TABLE

The Schedule of Events table below summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail in Section 12.1.2, Procedures During Treatment. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.
Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
Each treatment cycle is 21 days (+/- 1 day).

Table 6: SCHEDULE OF EVENTS

REQUIRED PROCEDURES	Eligibility screening and Baseline		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Definitive breast surgery	Safety follow-up	Survival follow-up[l]
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	3-10 weeks after last cycle	30 days after last dose of Pembrolizumab	
Scheduling window, unless specified:	*Day -30 to 1*	*Day -10 to 1*	*~~+/- 1 day~~*	*+ 2 days*	*+/- 1 day*	*+ 2 days*	*+/- 1 day*	*+ 2 days*	*+/- 1 day*	*+ 2 days*	*+/- 1 day*	*+ 2 days*	*+/- 1 day*	*+ 2 days*		*- 7/+ 21 days*	
STUDY TREATMENT																	
Carboplatin			X		X		X		X		X		X				
Docetaxel			X		X		X		X		X		X				
Pembrolizumab			X		X		X		X		X		X				
Pegfilgrastim (or its biosimilar equivalent)				X		X		X		X		X		X			
EXAMS, TESTS, AND PROCEDURES																	
Informed consent	X																
Medical history	X																
Disease details and treatments	X																
Demographics	X																
Review eligibility criteria	X																
Review medications		X			X[a]		X[a]		X[a]		X[a]		X[a]			X	
Physical exam and vital signs[b]		X			X[a]		X[a]		X[a]		X[a]		X[a]			X	
ECOG performance status		X			X[a]		X[a]		X[a]		X[a]		X[a]			X	
Tumor assessment (MRI or US)[c]	X										X[d]						
Cardiac function (echocardiogram or MUGA)	X																

REQUIRED PROCEDURES	Eligibility screening and Baseline		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Definitive breast surgery	Safety follow-up	Survival follow-up[l]
			D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	3-10 weeks after last cycle	30 days after last dose of Pembrolizumab	
Scheduling window, unless specified:	*Day -30 to 1*	*Day -10 to 1*	*~~+/- 1 day~~*	*+ 2 days*	*+/- 1 day*	*+ 2 days*	*+/- 1 day*	*+ 2 days*	*+/- 1 day*	*+ 2 days*	*+/- 1 day*	*+ 2 days*	*+/- 1 day*	*+ 2 days*		*- 7/+ 21 days*	
Primary tumor submission[e]	X																
LABORATORY TESTS																	
Hematology		X			X[a]		X[a]		X[a]		X[a]		X[a]				
Serum chemistries including magnesium, phosphorus, LDH[f]		X			X[a]		X[a]		X[a]		X[a]		X[a]				
INR/PT/aPTT[g]		X															
Total T3, free T4, TSH	X								X							X	
ACTH and AM cortisol	X																
Pregnancy test – urine ± serum[h]			X[i]		X[i]		X[i]		X[i]		X[i]		X[i]			X[j]	
CORRELATIVE RESEARCH																	
Correlative blood specimen (required)			X[m]												X[k]		X[m, n]

[a] Performed within 48 h prior to day 1 of the cycle.

[b] Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be collected at the initial physical exam only.

[c] MRI preferred. US allowed if MRI contraindicated or unable to be performed.

[d] Tumor re-assessment to be performed ± 14 days prior to start of cycle #5.

[e] Tumor tissue submission (see section 13.1 for more details).

[f] Full list includes: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, LDH, BUN, uric acid, creatinine or GFR, sodium, potassium, phosphorus, magnesium, calcium, chloride, bicarbonate, glucose, bilirubin, and total protein.

[g] INR/PT/aPTT should be tested at baseline and monitored closely for subjects on anticoagulation therapy.
[h] For WOCBP only. Serum β-hCG required if urine test is positive or cannot be confirmed as negative.
[i] Performed within 24 h prior to day 1 of the cycle.
[j] Performed approximately 120 days after last dose of Pembrolizumab.
[k] Drawn 21 ± 7 days after day 1 of cycle #6, prior to breast surgery.
[l] After completion of all local and systemic treatment for breast cancer (surgery, chemotherapy, or radiation, whichever comes last), to be performed approximately every 6 months until 3 years post-diagnosis.
[m] These blood draws do not need to be duplicated if already done under P.R.O.G.E.C.T. protocol.
[n] At the end of all definitive curative breast cancer treatment (14-180 days after surgery, radiation, and chemotherapy, whichever treatment comes last).

13 CORRELATIVE STUDIES

Correlative blood specimen collection is to be performed day 1 cyle 1 and 21 ± 7 days after the last chemotherapy cycle, and prior to surgery. Specimen will be collected from all patients who undergo at least one dose of study treatment.

[redacted]

13.1 Sample Collection Instructions

[redacted]

13.2 Sample Preparation, Handling, And Storage

[redacted]

[redacted]

13.4 Sample Banking

Blood and tumor samples
After collection by clinic nurse, phlebotomist, qualified technician, or physician and preparation by laboratory personnel, the samples will be labeled with the study number, participant's de-identified study number, and collection date and delivered for storage for future research to:

The University of Kansas Cancer Center
Biospecimen Repository Core Facility (BRCF)
G001 Wahl Hall West
Mailstop 1027
3901 Rainbow Boulevard
Kansas City, KS 66160
[redacted]
http://www.kumc.edu/school-of-medicine/biospecimen.html

under the direction of:

[redacted]

[redacted]

14 STATISTICAL CONSIDERATIONS

Endpoints

Primary endpoint is pathologic complete response (pCR) in breast and axilla, which is defined as no evidence of disease in the breast and axillary lymph nodes at the time of pathology review, except for DCIS in the breast and isolated tumor cells in the axillary lymph nodes.

Secondary endpoints:

Assessment of minimal residual disease (MRD), which is defined as residual cancer burden (RCB) score of 0/1. Residual cancer burden score will be calculated utilizing surgical pathology parameters by a study personnel by using a free online tool (*http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3*)

Recurrence-free survival (RFS), is defined as the time from diagnosis to first recurrence (invasive ipsilateral breast, invasive local/regional, or distant), or to death as a result of any cause [78].

14.1 Statistical Hypotheses

Primary study objective: To determine the pathological complete response (pCR) rates with a neoadjuvant chemotherapy regimen of carboplatin and docetaxel (CbD) plus Pembrolizumab in patients with stage I-III TNBC.

Hypothesis: Addition of Pembrolizumab to CbD will lead to improvement in pCR rates over known historical control (improvement from 50% → 65%).

Secondary study objectives:

1. To evaluate minimal residual disease (MRD) rate (residual cancer burden score of 0/1) with a neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.

   Hypothesis: Addition of Pembrolizumab to CbD will lead to improvement in MRD rates over known historical control (improvement from 65% → 78%).

2. To determine 3-year recurrence-free survival with a neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.

   Hypothesis: Addition of Pembrolizumab to CbD will lead to improvement in 3-year recurrence-free survival over known historical control (improvement from 75% → 86%).

3. To determine 3-year event-free survival with a neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.

   Hypothesis: Addition of Pembrolizumab to CbD will lead to improvement in 3-year event-free survival over known historical control (improvement from 75% → 86%).

4. To estimate pathological complete response (pCR) rates in subgroup of patients with node positive and/or T3-T4 disease

   Hypothesis: Addition of Pembrolizumab to CbD will lead to improvement in pCR rates over known historical control (improvement from 40% →60%).

5. To evaluate toxicity of with a neoadjuvant chemotherapy regimen of CbD plus Pembrolizumab in patients with stage I-III TNBC.

14.2 Sample Size Justification

[redacted]

14.3 Accrual Method

[redacted]

Intent-to-treat (ITT) population will include all enrolled and eligible patients and serve as the population for primary and secondary analyses.

Patients with disease progression during protocol therapy will be classified as not having pathological complete response. Patients with death due to disease progression during protocol therapy will also be classified as not having a pathological complete response.

14.4 Description Of Statistical Methods

14.4.1 General Approach

This is a prospective, open-label, single-arm multi-centered study.

- Baseline demographic and clinical characteristics will be summarized overall with means, standard deviations, medians, ranges, frequency counts, and proportions.

  Rates of pCR, MRD, and 3-year recurrence-free, event-free, and overall survival will be summarized as percentages of treated participants. 95% exact binomial confidence bounds will be calculated for pCR, MRD, and survival percentages.

  Survival curves will assessed by the Kaplan-Meier method. Cox regression model will be used for univariate and multivariate analysis of factors associated with risk of recurrence/event/death.

- According to sample size calculations, the Type I error rate for the primary objective is $\alpha = 0.05$.

14.4.2 Analysis Of Primary Objective

Rate of pathological complete response will be calculated, and 95% exact binomial confidence bounds will be calculated.

14.4.3 Analysis Of Secondary Objective(s)

The MRD rate will be estimated and 95% exact binomial confidence bounds will be calculated.

Recurrence-free survival and event-free survival curves will assessed by the Kaplan-Meier method. The 3-year survival will be reported with the corresponding 95% confidence interval.

14.4.4 Safety Analyses

Safety data will be summarized and reported on all eligible subjects who received at least one dose of a study drug. Frequency of adverse events and serious adverse events will be summarized by type of event and grade of severity (CTCAE v 4.03) [81]. Adverse events that are determined by the investigator to be possibly, probably, or definitely related to study drug(s) will be reported by event type and grade. The percentage of eligible patients who complete all doses of study treatment will be calculated.

14.4.5 Planned Interim Analysis

There is no planned interim analysis for the study.

14.4.6 Exploratory Analysis

[redacted]

15 PARTICIPANT REGISTRATION PROCEDURES

General Guidelines
Institutions will register eligible participants through the KUCC Clinical Research Office central registration process. Registration must occur prior to the initiation of therapy, with treatment assignment (for both randomized and non-randomized studies) provided by KUCC. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

The completed source documentation provided for eligibility verification and registration must be kept in the participant binder for monitoring purposes and documentation of participant eligibility.

Issues that would cause treatment delays should be discussed with the Sponsor - Investigator. If a participant does not receive protocol therapy following registration, notify the KU Cancer Center Project Director or designee so that the participant's status can be changed in the CRIS system.

Registration Process for KUCC and Other Participating Centers
The Coordinating Center (KUCC), specifically the Project Director or designee is accessible for registration Monday through Friday from 8:00 AM to 5:00 PM Central Time.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments. **NOTE** – if tests required at screening were performed as part of standard of care prior to signing consent for this study, the results from those tests are allowed in this study IF those tests were performed within the timeframe listed in the section of this protocol.

2. Complete the appropriate baseline demographic information in CRIS and any required registration forms using the eligibility assessment documented in the participant's medical/research record. To be eligible for registration to the study, the participant must meet each inclusion and none of the exclusion criteria listed in this protocol.

3. Send via e-mail the eligibility checklist (checklist to be created from each version of this protocol and maintained by the KU Clinical Project Director and clinical team), supporting eligibility documentation, and all pages of the consent form to the appropriate KU Clinical Project Director.

4. The KU Clinical Project Director or designee will a) validate eligibility and b) register the participant on the study.

5. The KU Project Director or designee will send an email confirmation of the registration to the person initiating the registration within 24 h of validating eligibility.

16 ASSESSMENT OF SAFETY

16.1 Specification Of Safety Parameters

Analyses will be performed for all eligible participants having received at least one dose of study drug. The study will use the CTCAE version 4.03 [81]. The document may be viewed on the Cancer Therapy Evaluation Program (CTEP) website at this URL:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

The investigators in this study will use this document for assessing and reporting of adverse events.

16.1.1 Definition Of Adverse Events (AEs)

Text below in italics is verbatim from "Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies," issued December 2012 by U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. The guidance may be retrieved from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf?source=govdelivery

Adverse Event [21 CFR 312.32(a)]
An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Suspected Adverse Reaction [21 CFR 312.32(a)]
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.

Unexpected [21 CFR 312.32(a)]
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in

the general investigational plan or elsewhere in the current application… "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the Particular drug under investigation.

This definition relies entirely on a listing of the adverse events or suspected adverse reactions in the investigator brochure…as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is unexpected. This means that events not listed for the Particular drug under investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for safety reporting purposes.

Serious [21 CFR 312.32(a)]
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

16.1.2 Relationship To Study Agent

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from study drug administration: The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): participant's response after drug discontinuation (de-challenge) or participants response after study drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.
- Concomitant medication or treatment: The other drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them may be suspected to cause the event in question.

- The pharmacology and pharmacokinetics of the study drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual participant's pharmacodynamics should be considered.

Attribution is the relationship between an adverse event or serious adverse event and the study treatment.

Attribution will be assigned as follows:

Unrelated – The AE is clearly **NOT** related to the study treatment.
Unlikely – The AE is **doubtfully related** to the study treatment.
Possible – The AE **may be related** to the study treatment.
Probable – The AE is **likely related** to the study treatment.
Definite – The AE is **clearly related** to the study treatment.

16.2 Reporting Procedures

16.2.1 Adverse Event Reporting

Information for adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported in the study Case Report Form (CRF) as described in the following sections.

ALL adverse events experienced by participants will be collected and reported after signing consent form as follows:

- Adverse events will be reported from Day 1 of study treatment and/or procedure, throughout the study, and up to and including day 30 after the last dose of study drug and/or last study procedure.

- SERIOUS adverse events that meet the definition(s) of a serious adverse event will be reported from date of screening (if related to the screening procedure(s)), then from Day 1 of study treatment and/or procedure, and up to and including day 30 after the last dose of study drug and/or last study procedure.

Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the Sponsor-investigator.

Study participants should also be instructed to report any new serious post-study event(s) that might reasonably be related to participation in this study.

Medical conditions/diseases, or cancer related symptoms present before starting study treatment are considered adverse events only if they worsen after initiation of study drug.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or require therapy. In this case they will be recorded on the Adverse Events CRF, along with the associated signs, symptoms or diagnosis.

16.2.2 Recording Adverse Events And Documentation In *CRIS*

All **expected** and **unexpected** adverse events and serious adverse events occurring after the participant has initiated study treatment will be reported as described previously in this document, and must be fully recorded in the participant's case record form.

All AEs and SAEs regardless of causality must be entered in the [redacted] Unexpected and expected adverse events must be entered within 5 days and include: new unexpected adverse events; worsening baseline conditions; clinically significant laboratory findings; disease-related signs and symptoms that were not present at baseline, and any event of findings that the Investigator feels is clinically significant.

Documentation must be supported by an entry in the participant's file. A laboratory test abnormality considered clinically significant (e.g., causing the participant to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event). Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

16.2.3 Serious Adverse Event Reporting

For serious adverse events, the clinical research site will follow local IRB policies and procedures.

All SAEs, regardless of causality, must be entered into CRIS within 24 hours. Entering the event into CRIS will send an automatic email to the KUCC Regulatory team and the KUCC DSMC.

Follow-up source documentation is required within 5 days.

Send all supporting documents with a cover sheet to:

KUCC DSMC
[redacted]

16.2.4 Reporting To Merck

16.2.4.1 Serious Adverse Events

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

17 DATA AND SAFETY MONITORING

17.1 DSMC Oversight And Monitoring Plan

The multidisciplinary KUCC Data and Safety Monitoring Committee (DSMC) is charged with overseeing the monitoring of participant safety, conduct and scientific progress of research protocols, and the validity and integrity of the data for clinical trials. The KUCC DSMC has the authority to require amendments, suspend, or terminate any research activities that fall within its jurisdiction, and can institute other appropriate actions as needed to protect subject safety.

The study will be monitored at appropriate intervals, no less than those assigned by the KUCC Protocol Review and Monitoring Committee, to assure compliance to GCP and to assess the data quality and study integrity. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected.

The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The study monitor will have direct access to source data for data verification. Data verification will be conducted by comparing the data entered into the CRFs with source data

17.2 Safety Review And Oversight Requirements

17.2.1 Serious Adverse Event

Serious adverse events that require expedited reporting will be reviewed by the DSMC Chair or designee who will determine if immediate action is required. If determined to be necessary by the DSMC, all participating sites will be notified of the event and any resulting action within one working day of this determination.

17.2.2 Review Of Adverse Event Rates

Once per month, adverse event rates will be monitored by the DSMC Coordinator. If any study site has had 2 or more of the same SAE reported within one month, or more than 6 of the same SAE in 6 months, the DSMC will review summaries of SAEs, and discuss events in detail with the PI. The DSMC chair or designee determines whether further action is required. The DSMC Coordinator ensures that collaborating investigators and IRBs for all participating sites are notified of any resulting action.

17.2.3 Study Safety And Progress

An overall assessment of toxicities as described in the protocol is reviewed at DSMC meetings. This review enables DSMC committee members to assess whether significant risks are occurring that would warrant study suspension/closure or protocol amendment.

The DSMC is an autonomous committee. However, its actions are communicated to other committees engaged in oversight of clinical research at KUCC. The PI is responsible for forwarding all DSMC letters, including those recommending continuation of the study, to the IRB and PRMC. DSMC recommendations for modifications to the trial are forwarded to the Deputy Director of KUCC. The PI is notified of this recommendation, and is expected to alert all collaborating investigators about the DSMC action. At this time the PI may appeal the Committee's decision to the Deputy Director of KUCC or their designee. The Deputy Director of the KUCC or their designee will notify the PI if he/she concurs with the DSMC's recommendation, including suspension or closure.

17.3 Unblinding Rules

None.

18 REGULATORY CONSIDERATIONS

18.1 Protocol Review And Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The sponsor-Investigator will disseminate protocol amendment information to all study team members.
All decisions of the IRB concerning the conduct of the study must be made in writing.

19 ETHICS/PROTECTION OF HUMAN SUBJECTS

19.1 Ethical Standard

Ethics and Good Clinical Practice (GCP)
This study is to be conducted according to the following considerations, which represent good and sound research practice:

1. State laws

2. ICH Consolidated Good Clinical Practice: Guidelines (E6)
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

3. US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

4. *http://www.ecfr.gov/cgi-bin/ECFR?page=browse*

   With attention to the following specific regulations:

   a. Title 21 Part 50 – Protection of Human Subjects
   b. Title 21 Part 56 – Institutional Review Boards
   c. Title 21 Part 312 – Investigational New Drug Application Responsibilities of Sponsors and Investigators

5. Institutional research policies and procedures:

http://policy.ku.edu/research/human-subjects

AND

http://www.kumc.edu/human-research-protection-program/institutional-review-board/policies-and-regulations.html

19.2 Informed Consent Process

Informed Consent
All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

20 DATA HANDLING AND RECORD KEEPING

20.1 Data Collection And Management Responsibilities

Case report forms (CRFs) will be completed for each subject enrolled. All CRFs will be customized to this study, in order to emphasize completeness and accuracy. The medical chart and any other clinical worksheets, procedural reports, etc. will be the source documentation of data captured into the study database. Data entry for each subject (enrolled or screen failure) will be entered in a timely manner. Data entry timelines will be reviewed regularly with notification sent to site if found outstanding.

20.2 Study Records Retention

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records and clinic charts, laboratory and pharmacy records, ECG, signed ICFs, participant diaries and pathology reports. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

20.3 Protocol Deviations

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. All deviations must be entered into CRIS and reported to the DSMC. All deviations must be reported to the IRB according to the local reporting policy.

21 LITERATURE REFERENCES

1. Harris J, Morrow M, Norton L. Malignant tumors of the breast. In: DeVita VJ, Hellman S, Rosenberg S, eds. *Cancer: principles and practice of oncology*. 5th ed. Philadelphia: Lippincott-Raven; 1997:1557-1602.
2. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res.* 2007;13(15 Pt 1):4429-4434.
3. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol.* 2008;26(8):1275-1281.
4. Osborne C, Kannan L, Xie X, Ashfaq R, Bian A, Baylor T. Neoadjuvant chemotherapy for basal-like breast cancer cohort: clinical and pathological outcome [abstract]. *Breast Cancer Res Treat.* 2006;100:S53.
5. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer. 2017; 2.2017:*https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf*. Accessed May 18, 2017.
6. Haffty BG, Yang Q, Reiss M, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. *J Clin Oncol.* 2006;24(36):5652-5657.
7. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clin Cancer Res.* 2004;10(16):5367-5374.
8. Tan DS, Marchio C, Jones RL, et al. Triple negative breast cancer: molecular profiling and prognostic impact in adjuvant anthracycline-treated patients. *Breast Cancer Res Treat.* 2008;111(1):27-44.
9. Bear HD. Indications for neoadjuvant chemotherapy for breast cancer. *Semin Oncol.* 1998;25(2 Suppl 3):3-12.
10. Fisher B, Gunduz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases. *Cancer Res.* 1983;43(4):1488-1492.
11. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep.* 1979;63(11-12):1727-1733.
12. Fisher B, Mamounas EP. Preoperative chemotherapy: a model for studying the biology and therapy of primary breast cancer. *J Clin Oncol.* 1995;13(3):537-540.
13. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol.* 1998;16(8):2672-2685.
14. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol.* 1999;17(2):460-469.
15. Green M, Hortobagyi GN. Neoadjuvant chemotherapy for operable breast cancer. *Oncology (Williston Park).* 2002;16(7):871-884, 889; discussion 889-890, 892-874, 897-878.
16. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol.* 2001;19(22):4224-4237.
17. Valero V, Buzdar AU, McNeese M, Singletary E, Hortobagyi GN. Primary chemotherapy in the treatment of breast cancer: the University of Texas M. D. Anderson Cancer Center experience. *Clin Breast Cancer.* 2002;3 Suppl 2:S63-68.
18. Wang J, Buchholz TA, Middleton LP, et al. Assessment of histologic features and expression of biomarkers in predicting pathologic response to anthracycline-based neoadjuvant chemotherapy in patients with breast carcinoma. *Cancer.* 2002;94(12):3107-3114.
19. Cortazar P, Zhang L, Untch M, et al. Meta-analysis results from the collaborative trials in neoadjuvant breast cancer (CTNeoBC) [abstract]. *Cancer Res.* 2012;72(24 Suppl):Abstract nr P1-14-20.
20. Isakoff SJ, Mayer EL, Taina T, et al. Impact of BRCA1/2 mutation status in TBCRC009: a multicenter phase II study of cisplatin or carboplatin for metastatic triple negative breast cancer. *Cancer Research.* 2012;72(24 Suppl):Abstract nr PD09-03.
21. Telli ML. Insight or confusion: survival after response-guided neoadjuvant chemotherapy in breast cancer. *J Clin Oncol.* 2013;31(29):3613-3615.
22. Rugo HS, Olopade O, DeMichele A, et al. Veliparib/carboplatin plus standard neoadjuvant therapy for high-risk breast cancer: first efficacy results from the I-SPY2 trial. *Cancer Res.* 2013;73(24 Suppl):Abstract nr S5-02.

23. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol.* 2015;33(1):13-21.
24. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol.* 2014;15(7):747-756.
25. Rottenberg S, Nygren AO, Pajic M, et al. Selective induction of chemotherapy resistance of mammary tumors in a conditional mouse model for hereditary breast cancer. *Proc Natl Acad Sci U S A.* 2007;104(29):12117-12122.
26. Schonn I, Hennesen J, Dartsch DC. Ku70 and Rad51 vary in their importance for the repair of doxorubicin- versus etoposide-induced DNA damage. *Apoptosis.* 2011;16(4):359-369.
27. Tassone P, Tagliaferri P, Perricelli A, et al. BRCA1 expression modulates chemosensitivity of BRCA1-defective HCC1937 human breast cancer cells. *Br J Cancer.* 2003;88(8):1285-1291.
28. Bolton KL, Chenevix-Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA.* 2012;307(4):382-390.
29. Husain A, He G, Venkatraman ES, Spriggs DR. BRCA1 up-regulation is associated with repair-mediated resistance to cis-diamminedichloroplatinum(II). *Cancer Res.* 1998;58(6):1120-1123.
30. Hayes DF, Thor AD, Dressler LG, et al. HER2 and response to paclitaxel in node-positive breast cancer. *N Engl J Med.* 2007;357(15):1496-1506.
31. Jacquin JP, Jones S, Magne N, et al. Docetaxel-containing adjuvant chemotherapy in patients with early stage breast cancer. Consistency of effect independent of nodal and biomarker status: a meta-analysis of 14 randomized clinical trials. *Breast Cancer Res Treat.* 2012;134(3):903-913.
32. Corkery B, Crown J, Clynes M, O'Donovan N. Epidermal growth factor receptor as a potential therapeutic target in triple-negative breast cancer. *Ann Oncol.* 2009;20(5):862-867.
33. Sharma P, Lopez-Tarruella S, Garcia-Saenz JA, et al. Efficacy of neoadjuvant carboplatin plus docetaxel in triple negative breast cancer: combined analysis of two cohorts. *Clin Cancer Res.* 2017;23(3):649-657.
34. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344(11):783-792.
35. Disis ML. Immune regulation of cancer. *J Clin Oncol.* 2010;28(29):4531-4538.
36. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol.* 2005;23(10):2346-2357.
37. Hunder NN, Wallen H, Cao J, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. *N Engl J Med.* 2008;358(25):2698-2703.
38. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol.* 2005;23:515-548.
39. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proc Natl Acad Sci U S A.* 2001;98(24):13866-13871.
40. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol.* 2004;173(2):945-954.
41. Riley JL. PD-1 signaling in primary T cells. *Immunol Rev.* 2009;229(1):114-125.
42. Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett.* 2004;574(1-3):37-41.
43. Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. *Curr Opin Immunol.* 2012;24(2):207-212.
44. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. *Breast Cancer Res Treat.* 2017.
45. Emens LA, Braiteh FS, Cassier P, et al. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer (TNBC) [abstract]. *Cancer Res.* 2015;75(15 Suppl):Abtract nr 2859.

46. Schmid P, Cruz C, Braiteh FS, et al. Atezolizumab in metastatic TNBC (mTNBC): long-term clinical outcomes and biomarker analyses [abstract]. *Cancer Res.* 2017;77(13 Suppl):Abstract nr 2986.
47. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. *J Clin Oncol.* 2016;34(21):2460-2467.
48. Adams S, Loi S, Toppmeyer D, Cescon D, De Laurentiis M, Nanda R. Phase 2 study of pembrolizumab as first-line therapy for PD-L1-positive metastatic triple-negative breast cancer (mTNBC): preliminary data from KEYNOTE-086 cohort B [abstract]. *J Clin Oncol.* 2017;35(15_suppl):1088-1088.
49. Nanda R, Liu M, Yau C, et al. Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): Results from I-SPY 2 [abstract]. 2017 ASCO Annual Meeting; 2017.
50. Brenin DR, Morrow M. Breast-conserving surgery in the neoadjuvant setting. *Semin Oncol.* 1998;25(2 Suppl 3):13-18.
51. Baselga J, Norton L, Masui H, et al. Antitumor effects of doxorubicin in combination with anti-epidermal growth factor receptor monoclonal antibodies. *J Natl Cancer Inst.* 1993;85(16):1327-1333.
52. Carmo-Pereira J, Dittrich C, Keizer J. Phase II trial of carboplatin in carcinoma of the breast. *Ann Oncol.* 1990;1(P3):33.
53. Kolaric K, Vukas D. Carboplatin activity in untreated metastatic breast cancer patients--results of a phase II study. *Cancer Chemother Pharmacol.* 1991;27(5):409-412.
54. Martin M, Diaz-Rubio E, Casado A, et al. Carboplatin: an active drug in metastatic breast cancer. *J Clin Oncol.* 1992;10(3):433-437.
55. O'Brien ME, Talbot DC, Smith IE. Carboplatin in the treatment of advanced breast cancer: a phase II study using a pharmacokinetically guided dose schedule. *J Clin Oncol.* 1993;11(11):2112-2117.
56. Nasr FL, Chahine GY, Kattan JG, et al. Gemcitabine plus carboplatin combination therapy as second-line treatment in patients with relapsed breast cancer. *Clin Breast Cancer.* 2004;5(2):117-122; discussion 123-114.
57. Perez EA. Carboplatin in combination therapy for metastatic breast cancer. *Oncologist.* 2004;9(5):518-527.
58. Perez EA, Suman VJ, Fitch TR, et al. A phase II trial of docetaxel and carboplatin as first-line chemotherapy for metastatic breast cancer: NCCTG study N9932. *Oncology.* 2005;69(2):117-121.
59. Sikov W, Berry D, Perou C, et al. Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/- carboplatin and/or bevacizumab in triple-negative breast cancer: Outcomes from CALGB 40603 (Alliance) [poster]. *Cancer Res.* 2016;76(4 Supplement):Abstract S2-05.
60. Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol.* 2006;24(13):2019-2027.
61. Bonneterre J, Roche H, Monnier A, Serin D, Fargeot P, Guastalla JP. Taxotere versus 5-fluorouracil plus navelbine as second line chemotherapy in patients with metastatic breast cancer - preliminary results [abstract]. *Breast Cancer Res Treat.* 1997;50(1):261.
62. Goldstein L, O'Neill A, Sparano J, et al. E2197: Phase III AT (doxorubicin/docetaxel) vs. AC (doxorubicin/cyclophosphamide) in the adjuvant treatment of node positive and high risk node negative breast cancer [abstract]. *J Clin Oncol.* 2005;23(16_suppl):512.
63. Gradishar WJ. Docetaxel as neoadjuvant chemotherapy in patients with stage III breast cancer. *Oncology (Williston Park).* 1997;11(8 Suppl 8):15-18.
64. Hutcheon AW, Heys SD, Sarkar TK, Aberdeen Breast G. Neoadjuvant docetaxel in locally advanced breast cancer. *Breast Cancer Res Treat.* 2003;79 Suppl 1:S19-24.
65. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol.* 2006;24(34):5381-5387.
66. Malhotra V, Dorr VJ, Lyss AP, et al. Neoadjuvant and adjuvant chemotherapy with doxorubicin and docetaxel in locally advanced breast cancer. *Clin Breast Cancer.* 2004;5(5):377-384.
67. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med.* 2005;352(22):2302-2313.
68. Nabholtz JM, Senn HJ, Bezwoda WR, et al. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. *J Clin Oncol.* 1999;17(5):1413-1424.

69. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. *J Clin Oncol.* 2006;24(36):5664-5671.
70. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med.* 2002;8(8):793-800.
71. Zhang P, Su DM, Liang M, Fu J. Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis. *Mol Immunol.* 2008;45(5):1470-1476.
72. Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res.* 2007;13(7):2151-2157.
73. Adams S, Schmid P, Rugo H, et al. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A [abstract]. *J Clin Oncol.* 2017;35(suppl; abstr 1008).
74. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016;17(11):1497-1508.
75. Seiwert TY, De Souza J, Vokes E, Agrawal N. A phase II study of pembrolizumab and docetaxel for aggressive RAI refractory thyroid carcinomas or salivary gland cancers: the iPRIME study [abstract]. *J Clin Oncol.* 2017;35(15_suppl):TPS6099.
76. Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. *J Immunother Cancer.* 2017;5:43.
77. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med.* 2016;375(19):1823-1833.
78. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol.* 2007;25(15):2127-2132.
79. Wolff AC, Hammond MEH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol.* 2013;31(31):3997-4013.
80. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.
81. National Cancer Institute. Common terminology criteria for adverse events (CTCAE), version 4.03. 2010. *https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf*. Accessed July 10, 2017.

22 APPENDICES

Appendix A: Performance Status

Zubrod Performance Scale (Eastern Cooperative Oncology Group)

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix B: Contraceptive Guidance and Pregnancy Testing

WOMAN OF CHILDBEARING POTENTIAL (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). Women must meet the criteria below to be considered non-WOCBP, regardless of sexual orientation, having undergone tubal ligation, or remaining celibate by choice.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION REQUIREMENTS

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 8 during the protocol-defined time frame in Section 10.1.4.1.

Table 8: Highly effective contraceptive methods that have low user dependency

Highly effective methods that have low user dependency *Failure rate of <1% per year when used consistently and correctly*
• **Non-hormone-releasing intrauterine device (IUD)**
• **Progestogen-only implant**
• **Vasectomized partner**

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

PREGNANCY TESTING

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable, this test should be repeated a maximum of 24 hours before the first dose of study treatment.

Following initiation of treatment, additional pregnancy testing will be performed within 24 hours prior to each treatment cycle (at a minimum of monthly) during the treatment period and at 120 days after the last dose of study treatment. Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix C: Suggested Chemotherapy Pre-medication and Antiemetics

Carboplatin/Taxotere

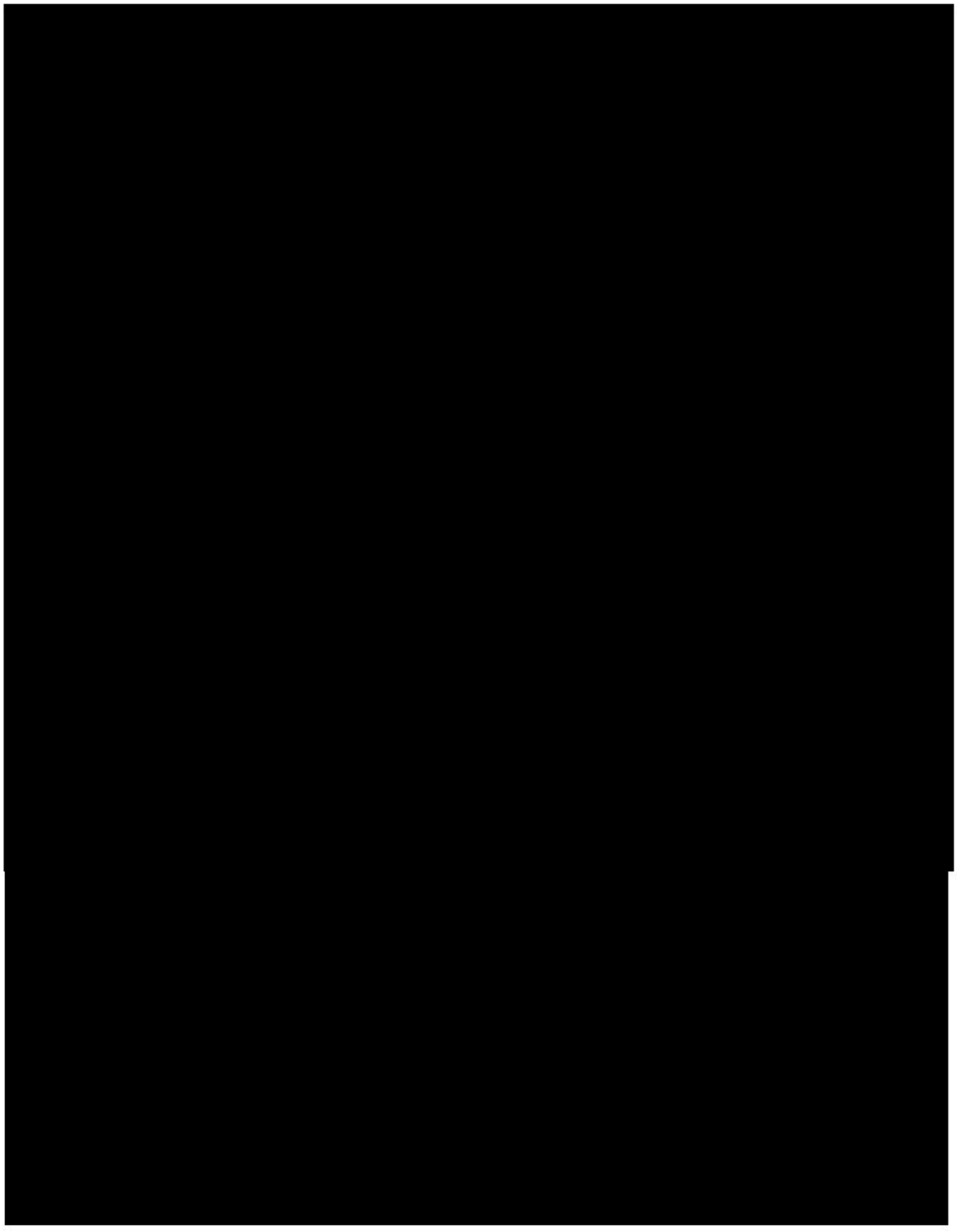
Day 1 of Treatment (cycles 1-6)
LORazepam tablet 0.5-1 mg
Dexamethasone 20 mg in sodium chloride 0.9% (NS) 50 mL IVPB
Palonosetron injection 0.25 mg
Take-Home Medication
Decadron 4-8mg PO BID Day -1, 1, 2
Ondansetron 4 mg PO TID PRN
Prochlorperazine 10 mg PO TID PRN
Ativan 0.5 mg PO TID PRN

*For patients who have uncontrolled nausea after first cycle of carboplatin, consider adding Emend (fosaprepitant dimeglumine) 150 mg or Cinvanti (aprepirant, injectable emulsion) 130 mg to chemotherapy premedication for remaining carboplatin doses. If aprepirant is added, 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with aprepirant.

Appendix D: Specimen Collection, Processing, and Shipping

[redacted]

Appendix E: For Non-KU Sub-Sites Only – Specimen Packing List



Appendix F: Serious Adverse Event Fax Reporting Form