A Randomized Phase II Study of Pembrolizumab, an anti-PD (programmed cell death)-1 Antibody, in Combination with Carboplatin Compared to Carboplatin Alone in Breast Cancer Patients with Chest Wall Disease

IND NUMBER: 132879

UCSF Protocol number: CC #157521
Version number: 9.0
Version Date: March 31, 2025
TBCRC Protocol number: 044

Study Drug: Pembrolizumab

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** Note: The HCRN discontinued providing central trial management services for this study, effective March 31, 2025.*

Revision History

Version 9.0	03/31/25
Version 8.0	06/21/22
Version 7.0	03/27/21
Version 6.0	10/22/20
Version 5.0	03/27/19
Version 4.0	09/20/18
Version 3.0	01/24/18
Version 2.0	09/14/17
Version 1.4	10/03/16
Version 1.3	08/10/16
Version 1.2	07/08/16
Version 1.1	02/05/16
Version 1.0	12/07/15

PROTOCOL SIGNATURE PAGE

Protocol No.: 157521 **Version Date:** 03/31/2025

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Keep a copy for your files.

PROTOCOL SIGNATURE PAGE – PARTICIPATING SITES

Protocol No.: 157521 **Version Date:** 03/31/2025

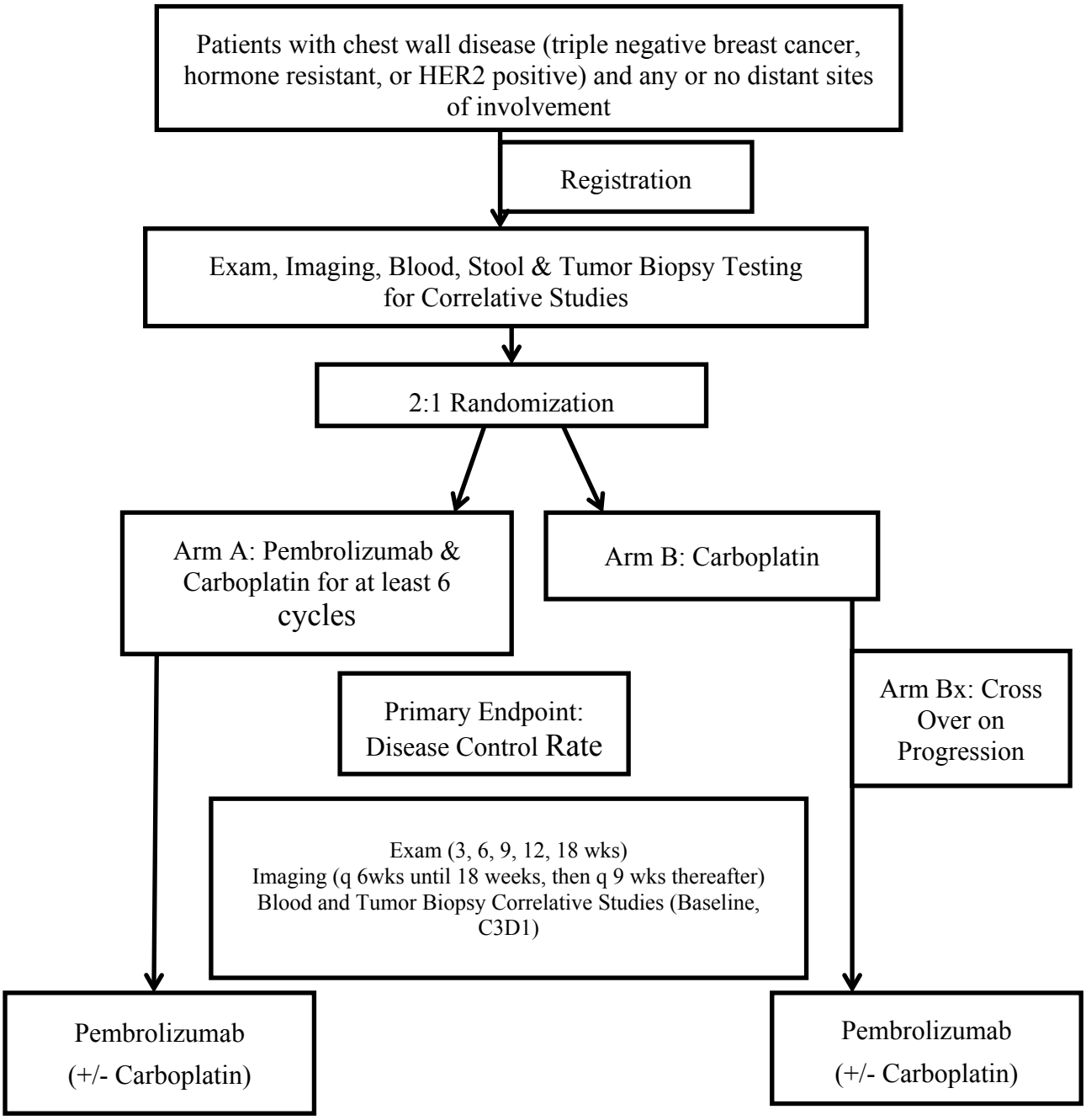
Participating Site(s)

Principal Investigator Name: **Institution Name:** **Address:** **Telephone:** **E-mail:**	**Principal Investigator Name:** **Institution Name:** **Address:** **Telephone:** **E-mail:**

I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.

Principal Investigator	**Site**
Printed Name	Institution Name
Signature	Date

TRIAL SCHEMA



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LIST OF ABBREVIATIONS

AE adverse event
Alk phos alkaline phosphatase
ALT alanine transaminase
ANC absolute neutrophil count
ASCO American Society for Clinical Oncology
AST aspartate transaminase
AUC area under the curve
BSA body surface area
BUN blood urea nitrogen
CHR Committee on Human Research (UCSF IRB)
CR complete response
CRA Clinical Research Associate
CRC Clinical Research Coordinator
CRF case report form
CT computerized tomography
CTC Common Terminology Criteria
CTCs circulating tumor cells
CXR chest x-ray
Dbil direct bilirubin
DFS disease-free survival
DLT dose limiting toxicity
ECI event of clinical interest
ECOG Eastern Cooperative Group
ER/PR Estrogen Receptor/Progesterone Receptor
FDA Food and Drug Administration
GRF Glomerular Filtration Rate
HER2 Human epidermal growth factor receptor 2
HGB hemoglobin
IND investigational new drug application
IEC Independent Ethics Committee
IRB Institutional Review Board
IV Intravenous
LDH lactate dehydrogenase
MDR multi-drug resistance
MK-3475 pembrolizumab
MRI Magnetic Resonance Imaging
MTD maximum tolerated dose
MYC oncogene often over expressed in triple negative and hormone resistant breast cancer
NCI National Cancer Institute
OS Overall Survival
PI Principal Investigator
PD progressive disease
PD-1 Programmed cell death 1
PD-L1 Programmed Death Ligand 1
PD-L2 Programmed Death Ligand 2

PFS Progression Free Survival
PR partial response
PRC UCSF Protocol Review Committee
RBC red blood cell
RR response rate
SAE serious adverse event
SD stable disease
Tbil total bilirubin
TIM-3 immune checkpoint receptor
TNBC triple negative breast cancer
ULN upper limit of normal
WBC white blood cell

1.0 TRIAL SUMMARY TABLE

Abbreviated Title	Pembrolizumab and Carboplatin vs. Carboplatin Alone in Breast Cancer Patients with Chest Wall Disease
Trial Phase	Multi-center phase II consortium
Clinical Indication	Breast Cancer with Chest Wall Disease
Trial Type	Randomized Phase II; 2:1 randomization
Type of Control	Carboplatin (Arm B) Cross-over allowed to pembrolizumab alone on progression (Arm Bx)
Route of Administration	IV administration of Pembrolizumab and/or Carboplatin
Trial Blinding	No blinding
Treatment Groups	Arm A: Pembrolizumab and carboplatin for at least 6 cycles followed by pembrolizumab maintenance treatment (Arm Ax) in patients with stable or responding disease Arm B: Carboplatin alone until documented disease progression followed by cross-over to pembrolizumab alone (Arm Bx) (+/- carboplatin)
Number of trial subjects	84 (56 in Arm A, 28 in Arm B) An additional 9 patients (6 in the pembrolizumab/carboplatin arm and 3 in the carboplatin alone arm) may be accrued for subject replacement to offset an approximate drop out rate of 10%.
Estimated Enrollment Period	18 months
Estimated Duration of Trial	24 months
Duration of Participation	36 months

2.0 TRIAL DESIGN

2.1 Trial Summary

This is a phase II multicenter study including breast cancer patients with chest wall disease that is hormone resistant (ER positive/PR positive/HER2 negative breast cancer with progressive disease on 2 prior lines of hormonal therapy) or triple negative (ER negative/PR negative/HER2 negative, TNBC). We will also allow accrual of patients with HER2+ disease whose chest wall disease has progressed on all approved/feasible HER2 targeted therapies. Patients with HER2+ disease may continue trastuzumab during study therapy. Eighty-four patients will be enrolled at Translational Breast Cancer Research Consortium (TBCRC) sites and will be randomized 2:1 to receive treatment with pembrolizumab and carboplatin (n=56, Arm A) or carboplatin alone (n=28, Arm B) until documented disease progression. Patients randomized to Arm B may cross-over following progression to pembrolizumab with or without carboplatin at investigator's discretion (Arm Bx). Patients may have received any number of prior lines of chemotherapy. Patients in Arm A will be treated with pembrolizumab 200 mg IV and carboplatin AUC 5 IV every 3 weeks for at least 6 cycles followed by maintenance pembrolizumab 200 mg IV every 3 weeks if stable or responding disease (Arm Ax). Patients in Arm B will be treated with carboplatin AUC 5 IV every 3 weeks until progression, whereupon they may cross-over to pembrolizumab 200 mg IV every 3 weeks with or without carboplatin at investigator's discretion (Arm Bx). Patients with prior thrombocytopenia or carboplatin exposure will be treated with carboplatin AUC 4 IV every 3 weeks on both Arm A and B. An interim analysis for futility will be performed after 18 patients are enrolled into Arm B to allow early stopping of that trial arm for lack of efficacy. The primary endpoint is to compare disease control rates at 18 weeks of treatment. This study is powered to detect a 20% difference in disease control rates between arms with a hazard ratio of 0.52 (2 sided logrank test, $\alpha = 0.10$ and $\beta = 0.20$). Secondary endpoints include disease control rates by irRECIST, progression free survival, toxicity, and overall response rate. Exploratory endpoints (to be explored in a companion translational study) include changes in tumor PD-L1 (programmed death ligand 1) gene expression, tumor and peripheral blood immune composition and cytokine expression, plasma tumor DNA, circulating tumor cells, and tumor MYC oncogene expression using tumor biopsy and peripheral blood testing before and after treatment; correlations with these markers and disease control rate will be assessed. Altogether, this study promises to improve our understanding of pembrolizumab for the treatment of breast cancer with chest wall disease.

3.0 BACKGROUND & RATIONALE

3.1 Background

The programmed cell death 1 (PD-1) pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. Pembrolizumab, MK-3475, is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection (1).

Merck is studying pembrolizumab for various oncology indications. Pembrolizumab was recently approved for the treatment of metastatic melanoma in September, 2014. In this study, we will evaluate the combination of pembrolizumab and carboplatin vs. carboplatin alone followed by pembrolizumab alone on disease progression for the treatment of breast cancer patients with chest wall disease.

3.1.1 Pharmaceutical and Therapeutic Background

The importance of intact functions of immune surveillance in controlling outgrowth of neoplastic transformations has been known for decades (2). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells / FoxP3+ regulatory T cells (T regs) correlates with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal, and pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma (3, 4).

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 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (5, 6). The structure of murine PD-1 has been resolved (7). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains two tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T cell signaling cascade (6, 8-10). The mechanism by which PD-1 down modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (11, 12). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B cells, T regs, and natural killer cells (13, 14). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells, as well as subsets of macrophages and dendritic cells (15). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types including nonhematopoietic tissues most notably on vascular endothelium; whereas PD-L2 is only detectably-expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues (12). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor

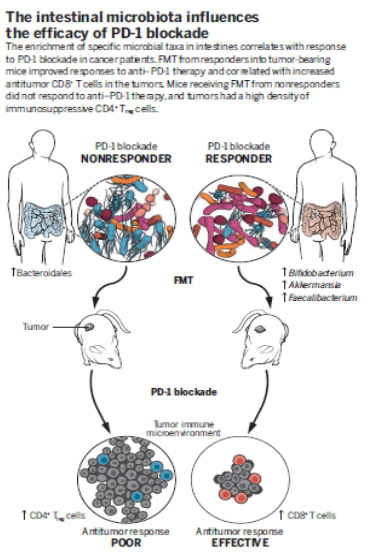
prognosis and survival in various cancer types, including renal cell carcinoma (16), pancreatic carcinoma (17), hepatocellular carcinoma (18), and ovarian carcinoma (19). Furthermore, PD-1 has been suggested to regulate tumor-specific T cell expansion in subjects with melanoma (20). The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Therapeutic studies in mouse models show that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 and anti-mouse PD-L1 have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T cell function in vivo (17, 21-25). In addition, the combination of gemcitabine and anti-PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors (17). In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models.

Immuno-modulatory agents recently showed promising efficacy in multiple cancer types. Two recent Phase III studies of Ipilimumab (IPI), an anti-CTL4 mAb, showed significant prolongation of overall survival in subjects with melanoma (26, 27). Recent data with anti-PD-1 antibodies have validated PD-1 as an attractive target for clinical intervention (28-30). Importantly, responses have been of long duration as pembrolizumab is generally well tolerated. Based on these data and considerations, the anti-PD-1 antibody, MK-3475, appears to be an attractive candidate for continued clinical development in cancer.

3.1.2 Microbiome Studies Background

Recent data show the host gut microbiome influences response to immune checkpoint inhibition (84-86). Preclinical data support manipulation of the microbiome via fecal microbial transplant (FMT) or oral supplementation with beneficent organisms to enhance immunotherapy response and abrogate tumor growth as well as modulate toxicity. While the specific taxa reported to date vary across studies, a convergent mechanism is postulated to underpin these observations (and may be separately targetable) (87).



Phase I clinical studies testing these hypotheses in human cancers are underway. However, these microbial differences are relatively modest and little is known about the microbiome in association with breast cancer treatment. The TBCRC infrastructure, focus on correlative science and collaborative nature makes it uniquely suitable for synchronization of

microbiome correlatives across immuno-oncology breast cancer studies. A standardized approach spanning multiple studies optimizes scientific discovery potential by minimizing variation due to methodologic differences in sample collection, storage, preparation and analysis, and maximizing cohort size, statistical power, potential synergy with other omics, functional studies, blood and histopathology analyses. Having a single laboratory perform DNA extraction, library prep and sequencing with batched samples minimizes variability and batch effects. With this approach, several current challenges in microbiome research including small sample size and lack of standardization across all phases of investigation including sample collection and storage, and sample preparation can be minimized, while exploration of optimal analytic platforms is maximized.

3.1.3 Preclinical and Clinical Trial Data

Preclinical and clinical data from Merck is as follows (1).

Preclinical Data

Pembrolizumab binds to human and Cynomolgus monkey PD-1 with comparable affinity and blocks the binding of human and Cynomolgus monkey PD-1 to PD-L1 and PD-L2 with comparable potency. Pembrolizumab does not cross-react with dog, rat, or mouse PD-1. Pembrolizumab does not bind immunoglobulin superfamily members cluster of differentiation 28 (CD28), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or inducible T-cell costimulator (ICOS).

Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the half-maximal effective concentration (EC_{50}) has been approximately 0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFN□), and levels of other cytokines were found to be modulated by pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells. In the in vitro peripheral blood mononuclear cell (PMBC) and whole blood cytokine release assays, the cytokine levels induced by pembrolizumab were low and comparable to those induced by trastuzumab. Pembrolizumab does not induce antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

Using antimurine PD-1 surrogate antibodies, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased complete tumor regression rates in vivo (1). Studies also revealed that immunosuppressive doses of dexamethasone included in combination with agents used in standard-of-care treatment for NSCLC do not reduce the anti-tumor efficacy of an anti-murine PD-1 surrogate antibody.

The pharmacokinetics (PK) of pembrolizumab were evaluated in a non-Good Laboratory Practices (GLP) single dose PK study and two GLP repeat-dose toxicokinetic (TK) studies (1 month and 6 month) in Cynomolgus monkeys. Pembrolizumab stability as a modified IgG4 molecule was evaluated in vivo in mice.

After single-dose IV administration at 0.3, 3, or 30 mg/kg in cynomolgus monkeys, decline of serum concentration followed multiphase kinetics. Anti-drug antibodies (ADAs) were detected in most of the treated animals. Clearance (CL) and terminal half-life ($t_{1/2}$) appeared to be dose-dependent in the dose range tested with $t_{1/2}$ varying from 4 to 10 days.

In the 1-month repeat-dose (once weekly) GLP toxicity study at 6, 40, or 200 mg/kg in Cynomolgus monkeys, ADAs were detected in most of the low-dose (6 mg/kg) treated animals. The systemic exposure over the 7-day dosing interval (AUC0-7 days) was sex-independent and increased with increasing dose. The mean $t_{½}$ values in individual animals ranged from 15.7 to 22.3 days) across the doses (1).

In the 6-month repeat-dose (every other week) GLP toxicity study at 6, 40, or 200 mg/kg in Cynomolgus monkeys, ADAs were detected in most of the low-dose (6 mg/kg) treated animals. The systemic exposure to pembrolizumab was independent of sex and was approximately dose-proportional across all doses. The mean $t_{1/2}$ values in individual ADA-negative animals ranged from 21 to 22 days across doses.

IgG4 wild type molecule can undergo in vivo molecular rearrangement called Fab-arm (or half molecule) exchange by swapping their half molecule with other IgG4 half molecules, thereby generating bispecific or hybrid antibodies. Pembrolizumab is a hinge mutated IgG4 (S228P), which prevents in vivo half-molecule swap (formation of hybrid). An in vivo mice experiment has demonstrated that pembrolizumab did not form hybrid antibody with another wild type IgG4 molecule.

The potential for systemic toxicity of pembrolizumab was assessed in a 1-month repeat-dose toxicity study with a 4-month recovery in cynomolgus monkeys and in a 6-month repeat dose toxicity study with a 4-month recovery period in cynomolgus monkeys. In the 1-month toxicity study, cynomolgus monkeys were administered an IV dose of 6, 40, or 200 mg/kg once weekly for a total of five doses. Four monkeys/sex/group were euthanized during Week 5. The remaining two monkeys/sex/group were euthanized during Week 23, after a four-month post-dose period. In this study, pembrolizumab was well tolerated in monkeys with the systemic exposure (AUC) up to approximately 170,000 µg/day/mL over the course of the study. There was no test article-related mortality, and test article-related changes were limited to an increased incidence of inguinal swelling, and increased splenic weights in males receiving 200 mg/kg. Both of these findings were not considered adverse and there was no histopathologic correlation. Splenic weights were normal at the post-dose necropsy. Anti-pembrolizumab antibodies were detected in 7 out of 8 animals in the 6 mg/kg dose group and 1 animal out of 8 in the 40 mg/kg dose group, and were associated with an apparent increase in clearance of pembrolizumab. The presence of anti-drug antibodies (ADA) in monkeys in the low-dose group and in one monkey in the mid-dose group did not impact the pharmacodynamic response because sufficient target engagement was demonstrated for the duration of the study (with the exception of 1 low-dose

monkey). Additionally, anti-pembrolizumab antibodies were not detected in any monkeys in the high-dose group, suggesting that potential toxicity has been evaluated at the highest exposure levels in the study. Based on the lack of adverse test article-related findings in this study, no observed adverse effect level (NOAEL) was ≥200 mg/kg (1).

In the 6-month toxicity study, the potential for systemic toxicity was assessed in cynomolgus monkeys administered an IV dose of 6, 40, or 200 mg/kg once every other week for approximately 6 months (a total of 12 doses) followed by a 4-month treatment free period. Three animals/sex/group were designated for interim necropsy at the end of the 6-month dosing phase (3 days after receiving the last dose in Study Week 23); and the remaining monkeys were designated for final necropsy following the 4-month treatment-free period. Pembrolizumab was well tolerated at all dose levels. There were no test article-related antemortem findings, electrocardiographic or ophthalmic findings, changes at injection sites, gross observations or organ weight changes at the interim or final necropsy. Because there were no test article-related histomorphologic findings at interim necropsy, histomorphologic evaluation of tissues collected at final necropsy was not conducted. The presence of ADA was observed in 5 out of 10 animals at 6 mg/kg/dose during the dosing phase, which correlated with an apparent increased rate of elimination of pembrolizumab in these animals. No anti-pembrolizumab antibodies were detected at 40 or 200 mg/kg/dose during the dosing phase, and no pembrolizumab serum concentration profiles in these two groups suggested an effect of ADA on pembrolizumab elimination rate. During the treatment-free period, anti-MK-3475 antibodies were detected in two animals at 6 mg/kg/dose, which already had ADA present during the dosing phase, and in two additional animals (one at 6 mg/kg/dose and one at 200 mg/kg/dose), which were ADA negative during the dosing phase. The detection of anti-pembrolizumab antibodies had a minimal effect on the mean group systemic exposure to pembrolizumab during the study and did not impact the evaluation of potential toxicity of pembrolizumab for the duration of the 6-month study because there were no test article-related effects on any of the parameters examined and as no monkey in the mid- and high-dose groups developed ADA during the dosing phase. In conclusion, pembrolizumab administered once every other week over a 6-month duration to cynomolgus monkeys was well tolerated and the NOAEL was ≥200 mg/kg/dose (the highest dose tested).

In addition, tissue cross-reactivity studies using monkey and human specimens were conducted to evaluate the potential cross reactivity of pembrolizumab with cryosections of cynomolgus monkey tissues and normal human tissues. Results demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. The off-target staining (cytoplasmic and stromal) that occurred in many tissues of both species was considered spurious binding inherent to the experimental conditions of the in vitro tissue cross-reactivity studies with no *in vivo* toxicological significance (1).

Clinical Data

Eight ongoing, Merck-sponsored clinical trials: P001, P002, P011, P012, P013, P021, P023, and P028 are evaluating pembrolizumab (1). Subjects received 1 of 6 different pembrolizumab dose regimens, either as monotherapy (P001, P002, P011, P012, P013, P028) or as combination

therapy (P021, P023). P011 is a combination therapy trial in which pembrolizumab monotherapy was compared with pembrolizumab in combination with cisplatin/pemetrexed and carboplatin/paclitaxel.

P001 is an open-label, Phase I, first-in-human (FIH) study of IV pembrolizumab in subjects with progressive locally advanced or metastatic carcinomas, especially melanoma or NSCLC (non small cell lung cancer). Part A of the study involved dose escalation that used a traditional 3+3 design. Cohorts of 3 to 6 subjects were enrolled sequentially at escalating doses of 1, 3, or 10 mg/kg administered Q2W. Once the dose escalation was completed, additional subjects were enrolled into Parts A1 and A2 to further characterize the PK and pharmacodynamics of pembrolizumab.

In Parts B and D, subjects with metastatic melanoma were enrolled to assess the safety and antitumor activity of pembrolizumab. Additionally, Part B explored 3 different dose regimens in subjects with metastatic melanoma: 10 mg/kg Q2W, 10 mg/kg Q3W, and 2 mg/kg Q3W.

In Part C, subjects with NSCLC (with prior systemic therapy) were enrolled at 10 mg/kg Q3W to assess the tolerability, safety, and antitumor activity of pembrolizumab in NSCLC. In Part F, subjects with NSCLC in Cohort F-1 (without prior systemic therapy) and Cohort F-2 (with prior systemic therapy), whose tumors expressed PD-L1, were enrolled at 10 mg/kg Q2W and 10 mg/kg Q3W to characterize the tolerability, safety, and antitumor activity of pembrolizumab. A small cohort of previously treated subjects with NSCLC and at least 2 lines of systemic therapy, whose tumors did not express PD-L1, were enrolled and treated at a dose of 10 mg/kg Q2W in Cohort F-2. In Cohort F-3, previously treated subjects with NSCLC whose tumors express PD-L1 were enrolled at 2 mg/kg Q3W to better characterize the efficacy, safety, and antitumor activity of pembrolizumab.

Each of the 2 disease specific cohorts (melanoma and NSCLC) were enrolled to confirm tolerability and evaluate tumor response to pembrolizumab. P002 is a partially blinded, randomized, Phase II study designed to evaluate 2 doses of pembrolizumab versus a chemotherapy control arm in subjects with IPI-refractory metastatic melanoma. Subjects were randomized in a 1:1:1 ratio to receive pembrolizumab 2 mg/kg Q3W or pembrolizumab 10 mg/kg Q3W, or chemotherapy (according to current clinical practice) for the treatment of melanoma. Subjects assigned to the control chemotherapy arm could cross over to the experimental pembrolizumab arm once progression was confirmed (approximately ≥ Week 12).

P006 is a multicenter, worldwide, randomized, controlled, open-label, 3-arm pivotal Phase III study of 2 dosing regimens of IV pembrolizumab versus IV ipilimumab in subjects with unresectable or metastatic melanoma who had not received prior ipilimumab treatment. Subjects were randomized in a 1:1:1 ratio to receive pembrolizumab at 10 mg/kg Q2W, 10 mg/kg Q3W, or ipilimumab at 3 mg/kg Q3W for a total of 4 doses.

P010 is a multicenter, worldwide, randomized, adaptively designed Phase II/III trial of IV pembrolizumab at 2 dosing schedules versus docetaxel in subjects with NSCLC with PD-L1 positive tumors, who have experienced disease progression after platinum-containing systemic

therapy. Subjects were randomized in a 1:1:1 ratio to receive pembrolizumab 10 mg/kg Q3W, 2 mg/kg Q3W, or docetaxel 75 mg/m2 Q3W.

P011 is an open-label, nonrandomized, multicenter Phase I study of pembrolizumab monotherapy in Japanese subjects with advanced solid tumors and in combination with cisplatin/pemetrexed and carboplatin/paclitaxel in subjects with advanced NSCLC in Japan. In Part A (monotherapy, 3+3 design), subjects with advanced solid tumors received escalating doses of pembrolizumab 2 mg/kg Q2W (dose level 1) or 10 mg/kg Q2W (dose level 2). In Part B (combination, 3+6 design), subjects with advanced NSCLC receive pembrolizumab 10 mg/kg Q3W in combination with either cisplatin/pemetrexed (Cohort 1) or carboplatin/paclitaxel (Cohort 2) are to be enrolled.

P012 is a multicenter, nonrandomized, multi-cohort Phase Ib trial of pembrolizumab in subjects with PD-L1 positive advanced solid tumors. All subjects receive pembrolizumab 10 mg/kg Q2W. Cohort A enrolled subjects with TNBC; Cohorts B and B2 enrolled subjects with squamous cell carcinoma of the head and neck; Cohort C enrolled subjects with urothelial tract cancer of the renal pelvis, ureter, bladder, or urethra; and Cohort D enrolled subjects with adenocarcinoma of the stomach or gastroesophageal junction.

P013 is an open-label, multicenter trial of pembrolizumab in subjects with hematologic malignancies. All subjects receive pembrolizumab at 10 mg/kg Q2W. Cohort 1 is enrolling subjects with intermediate-1, intermediate-2, or high-risk myelodysplastic syndrome who have failed at least 4 cycles of hypomethylating agent treatment. Cohort 2 is enrolling subjects with relapsed/refractory multiple myeloma. Cohort 3 is enrolling subjects with relapsed/refractory Hodgkin lymphoma who are ineligible for or refused a stem cell transplant and whose disease has relapsed after treatment with or failed to respond to brentuximab vedotin. Cohort 4a is enrolling subjects with relapsed/refractory mediastinal large B cell lymphoma who are ineligible for or refused a stem cell transplant, and Cohort 4b is enrolling subjects with any other positive PD-L1 positive relapsed/refractory non-Hodgkin lymphoma who are ineligible for or refused a stem cell transplant.

P021 is a multicenter, open-label Phase I/II study of IV pembrolizumab at 2 dosing schedules in combination with chemotherapy or immunotherapy in subjects with locally advanced or metastatic NSCLC. The study is composed of 2 parts.

The objective of Part 1 is to determine the recommended Phase II dose (RP2D) for pembrolizumab in combination with different chemotherapy and/or immunotherapy regimens:

• Cohort A – 1:1 randomization to carboplatin and paclitaxel plus either pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg
• Cohort B – 1:1 randomization to carboplatin, paclitaxel, and bevacizumab plus either pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg
• Cohort C – 1:1 randomization to carboplatin and pemetrexed plus either pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg
• Cohort D – ipilimumab plus pembrolizumab
• Cohort E – erlotinib plus pembrolizumab

• Cohort F – gefitinib plus pembrolizumab

The objective of Part 2 is to evaluate the antitumor activity of pembrolizumab in combination with chemotherapy or immunotherapy. Part 2 includes a randomized comparison of chemotherapy ± pembrolizumab based on the doses defined in Part 1, as well as a cohort expanding the ipilimumab cohort from Part 1:

• Cohort G – 1:1 randomization to carboplatin and pemetrexed with or without pembrolizumab 200 mg
• Cohort H – ipilimumab (RP2D from Part 1 Cohort D) plus pembrolizumab, followed by pembrolizumab monotherapy

P022 is a multicenter, worldwide, Phase I/II 3-part trial of IV pembrolizumab in combination with oral dabrafenib and/or trametinib in subjects with advanced or metastatic melanoma. Part 1 is a non-randomized, multi-site, open-label portion of the study using a traditional 3+3 design to evaluate safety, tolerability, and dosing of pembrolizumab (MK) in combination with dabrafenib (D) and trametinib (T) in BRAF mutation-positive (V600 E or K) melanoma subjects. Additionally in Part 1, dosing of pembrolizumab in combination with trametinib only (MK+T) will be explored in BRAF mutation-negative (without V600 E or K) melanoma subjects, to evaluate safety, tolerability, and efficacy of MK+T in Part 2 in this population. Part 2 is a non-randomized, multisite, open-label portion of the study using an expansion cohort to further evaluate safety and confirm dose of MK+D+T. Also in Part 2, an expansion cohort will be used to further evaluate safety and preliminary efficacy in the MK+T combination. Part 3 is a randomized (1:1), active-controlled, multi-site, 2-arm study of the confirmed dose of the triplet combination (MK+D+T) versus placebo (PBO) in combination with D+T (PBO+D+T).

P023 is an open-label, Phase I, multicenter, trial of pembrolizumab in combination with lenalidomide (Len) and dexamethasone (Dex) or pembrolizumab and Len in subjects with relapsed/refractory multiple myeloma who have failed at least 2 lines of prior therapy, including a proteasome inhibitor (e.g., bortezomib or carfilzomib) and an immunomodulary derivative (thalidomide, pomalidomide, lenalidomide). The trial uses a modified 3+3 design for dose determination, followed by dose confirmation and expansion, a further evaluation of safety, and a preliminary assessment of efficacy. During dose determination, cohorts of approximately 3 to 6 subjects are enrolled and receive pembrolizumab 2 mg/kg or 1 mg/kg IV Q2W in each 28-day cycle, in combination with Dex 40 mg QW and/or Len 25 mg or 10 mg on Days 1 to 21. After a preliminary MTD/maximum administered dose (MAD) is identified, additional subjects are enrolled at a fixed dose of pembrolizumab 200 mg or 100 mg in combination with Len/Dex to confirm the MTD/MAD.

P024 is a multicenter, international, randomized, open-label trial of IV pembrolizumab monotherapy vs. the choice of multiple, standard-of-care, platinum-based chemotherapies in subjects previously untreated for their Stage IV, PD-L1 strong, NSCLC. All subjects are randomized in a 1:1 ratio to receive pembrolizumab at 200 mg IV Q3W or 1 of the 5 following platinum doublets:

• pemetrexed at 500 mg/m2 Q3W and carboplatin AUC 5-6 day 1 Q3W for 4 to 6 cycles followed by optional pemetrexed 500 mg/m2 Q3W

• pemetrexed 500 mg/m2 Q3W and cisplatin 75 mg/m2 day 1 Q3W for 4 to 6 cycles followed by optional pemetrexed 500 mg/m2 Q3W
• gemcitabine 1250 mg/m2 days 1 and 8 and cisplatin 75 mg/m2 day 1 Q3W for 4 to 6 cycles
• gemcitabine 1250 mg/m2 days 1 and 8 and carboplatin AUC 5-6 day 1 Q3W for 4 to 6 cycles
• paclitaxel 200 mg/m2 Q3W and carboplatin AUC 5-6 day 1 Q3W for 4 to 6 cycles followed by optional pemetrexed maintenance

P025 is an open-label, non-randomized, multicenter Phase Ib study of pembrolizumab in Japanese subjects with positive PD-L1 advanced NSCLC in Japan. All subjects received pembrolizumab at 10 mg/kg Q3W.

P028 is an open-label, non-randomized, multicenter, multicohort Phase Ib trial of pembrolizumab in subjects with PD-L1 positive advanced solid tumors. Subjects are enrolled into 1 of the following 20 solid tumor cohorts: A1 Colon or Rectal Adenocarcinoma; A2 Anal Canal Squamous Cell Carcinoma; A3 Pancreas Adenocarcinoma; A4 Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction); A5 Biliary Tract Adenocarcinoma (Gallbladder and Biliary Tree but excluding Ampulla of Vater Cancers); A6 Carcinoid Tumors; A7 Neuroendocrine Carcinomas (well or moderately differentiated Pancreatic Neuroendocrine Tumor); B1 ER Positive HER2 Negative Breast Cancer; B2 Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma; B3 Endometrial Carcinoma; B4 Cervical Squamous Cell Cancer; B5 Vulvar Squamous Cell Carcinoma; C1 Small Cell Lung Cancer; C2 Mesothelioma (Malignant Pleural Carcinoma; D3 Nasopharyngeal Carcinoma; E1 Glioblastoma Multiforme E2 Leiomyosarcoma; or E3 Prostate Adenocarcinoma. All subjects receive pembrolizumab P029 is a multicenter, open-label, 3-part Phase I/II trial of IV pembrolizumab in combination with subcutaneous Pegylated Interferon Alfa-2b (PEG-IFN) or IV ipilimumab in subjects with advanced or metastatic melanoma or renal cell carcinoma. Part 1A, the Phase I portion of the trial, will define the preliminary MTD or MAD of pembrolizumab + PEG-IFN (Group A) and pembrolizumab + ipilimumab (Group B), and confirm the tolerability of these treatment doublets.

Part 1B is a single-arm expansion cohort designed to better characterize the safety and tolerability, as well as to evaluate preliminary efficacy of the pembrolizumab + ipilimumab combination in melanoma subjects. Part 2, the randomized portion of the trial, will evaluate preliminary clinical efficacy in advanced melanoma at the RP2D for pembrolizumab + PEG-IFN and the Phase II Dose determined in Part 1A and 1B for pembrolizumab + ipilimumab. Evaluation of pembrolizumab monotherapy may also occur during Part 2.

P030 is a multisite, worldwide, expanded access program for subjects with metastatic melanoma who have limited or no treatment options. Subjects must have progressed after prior systemic therapy, including standard-of-care agents which include ipilimumab and a BRAF/MEK inhibitor when indicated. Subjects cannot be eligible for an available pembrolizumab clinical trial or have participated in a pembrolizumab clinical trial. Subjects are evaluated for safety at baseline and before each cycle of treatment with pembrolizumab 2 mg/kg/Q3W. Subjects are treated until progression of disease or until the subject has received up to 2 years of treatment.

P041 is an open-label, nonrandomized, multicenter Phase Ib study to evaluate the safety, tolerability, and antitumor activity of treatment with pembrolizumab 2 mg/kg Q3W in subjects with advanced melanoma in Japan. Treatment with pembrolizumab will continue unless a subject meets the discontinuation criteria such as disease progression (evaluated by modified Response Evaluation Criteria In Solid Tumors [RECIST] 1.1), unacceptable toxicity, or completion of 24 months of treatment with pembrolizumab.
P045 is a randomized, active-controlled, multisite, open-label, Phase III trial to evaluate the efficacy of treatment with pembrolizumab versus paclitaxel, docetaxel, or vinflunine in subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy. Subjects are randomized in a 1:1 ratio to receive pembrolizumab 200 mg Q3W or the Investigators' choice of paclitaxel 175 mg/m2 Q3W, docetaxel 75 mg/m2 Q3W, or vinflunine 320 mg/m2 Q3W. The study also evaluates the safety and tolerability profile of pembrolizumab in subjects with recurrent/progressive metastatic urothelial cancer.

P055 is a multicenter, unblinded, open-label, single-cohort, Phase II trial to determine the safety, tolerability, and antitumor activity of a 200 mg Q3W dose of pembrolizumab in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy. Antitumor activity is also assessed in the subset of subjects for whom a biopsy sample is determined to be PD-L1 positive.

3.1.4 Rationale for the Trial and Selected Subject Population

Pembrolizumab, an anti-PD-1 antibody, has shown efficacy for the treatment of a number of different solid tumors resulting in the first FDA approval for the treatment of advanced melanoma in September 2014. Recent Phase I data suggests single agent efficacy in TNBC expressing PD-L1 (31). The purpose of this study is to investigate the use of pembrolizumab in combination with carboplatin in breast cancer patients with chest wall disease, with associated immunologic and genomic correlative studies to determine mechanism of action.

Up to 30% of patients with breast cancer may experience chest wall recurrence (32). Patients who develop chest wall recurrence after mastectomy or following lumpectomy and radiation with hormone resistant or TN breast cancer have a poor prognosis (33), with almost all developing distant metastases. Even with combined modality treatment with surgery, radiation, and chemotherapy, patients with skin involvement from breast cancer have a high risk of developing distant metastases (34). Chest wall disease has a high morbidity with possible complications including skin ulceration, pain, bleeding, and lymphedema (32). In addition, local disease recurrence is almost always associated with subsequent systemic relapse (35). Therefore, better therapies are needed for treating chest wall disease from breast cancer.

Thus far, anti-PD-1 antibodies have not been specifically investigated for the treatment of chest wall disease in patients with breast cancer. We hypothesize that the anti-PD-1 antibody, pembrolizumab, may be effective in treating chest wall or inflammatory disease in patients who have TN or hormone resistant breast cancer. Extrapolating from the promising outcomes noted in melanoma with pembrolizumab (36), we hypothesize that chest wall and skin involvement with breast cancer will likewise respond to pembrolizumab, as breast cancer, like melanoma, often

involves the skin and subcutaneous tissues. High levels of PD-1 have been associated with a poorer prognosis in patients with breast cancer, so targeting this pathway may be beneficial in improving outcomes (37, 38). *In vitro,* basal type breast cancer cells were noted to have high PD-L1 expression (39) and preliminary data suggest single agent efficacy in TNBC expressing PD-L1 and in some cases of hormone resistant disease (personal communication 8/14, Merck). The basal breast cancer subtype has been found to be associated clinically with higher rates of loco-regional recurrence (40), hence targeting the PD-1 pathway may be beneficial in treating chest wall recurrence in patients with breast cancer. In addition, recent pre-clinical data has shown that nearly 50% of breast cancer tumor specimens may have mutations in PD-1 with a high predominance in TNBC (41, 42). Additionally, lymphovascular invasion with breast cancer is associated with a higher risk of recurrent chest wall disease (43), and PD-1 has been associated with the presence of intense lymphocytic infiltration (44) so a heightened immune response triggered by the anti-PD-1 antibody may be beneficial in treating chest wall disease. A recent study also showed that topical imiquimod, a Toll like receptor agonist, may be beneficial in treating recurrent skin metastases in patients with breast cancer (45), lending further support to the possible benefit of immunotherapy, such as the anti-PD-1 antibody, in the setting of skin and chest wall involvement of breast cancer.

Two recent phase I trials have suggested the efficacy of anti-PD-1/PD-L1 antibodies in TNBC. In a phase Ib study, Nanda et al evaluated pembrolizumab in patients with advanced heavily pretreated triple negative breast cancer whose tumors expressed PD-L1 (31). Of 27 patients enrolled, 1 patient had a complete response, 4 patients had a partial response, and 7 patients had stable disease, for a clinical benefit rate of 44%. The median time to response was 18 weeks. A second phase I study evaluated MPDL3280A (atezolizumab), an anti-PD-L1 monoclonal antibody, in patients with pre-treated metastatic TNBC (46-48). Fifty-four patients with metastatic TNBC that had progressed on several lines of prior chemotherapy were treated with atezolizumab in a phase Ib expansion. Approximately 69% of patients had at least 5% of tumor cells positive for PD-L1 by IHC staining. Twenty-one patients with PD-L1 positive disease were evaluable for efficacy; 2 complete and 2 partial responses were observed. At the time of presentation at the recent American Association of Cancer Research Meeting in April 2015, 3 of 4 responses were ongoing, and the median time to progression had not yet been reached (range 18-56 weeks). For the PD-L1 positive population, the 24 week progression free survival rate was 27%, with a median duration of survival of 40 weeks (range 2-85 weeks).

Carboplatin was selected as a chemotherapy partner with pembrolizumab in this trial based on data demonstrating efficacy in both the first and later line settings in the treatment of metastatic breast cancer (49). Response rates range from 10 to 27%, and PFS has been noted to be around 4 months with platinum monotherapy (54-56,57). Platinum agents are also effective in subpopulations of metastatic or recurrent breast cancer with impaired DNA repair mechanisms, including but not limited to those with germline or acquired mutations in BRCA 1 or 2 (50).

In this study, chemotherapy (carboplatin) will be combined with immunotherapy (pembrolizumab). Chemotherapy may facilitate anti-tumor immunity (51) by inducing immunologic cell death leading to adaptive tumor specific immune responses, modulating tumor antigens and immune checkpoint molecules, and facilitating antigen processing (52). Platinum agents may help mediate an immune response through a variety of mechanisms including the

upregulation of mannose-6-phosphate receptors and an increase in perforin-independent permeability to granzyme-B released by cytotoxic T-lymphocytes (53), induction of autophagy allowing for an infiltration of dendritic cells and T cells in a tumor (54), and the induction of immunogenic cell death via calreticulin expression (55). Platinum agents may also decrease regulatory T-cells and decrease myeloid-derived suppressor cells (52). Wu et al studied the immunogenicity of apoptotic ovarian cancer cells obtained from patients with ovarian cancer undergoing treatment with paclitaxel and carboplatin (56). The authors found that apoptotic ovarian cancer cells unleash a strong cytotoxic T cell response with anti-tumor activity in vitro. With chemotherapy treatment, changes occurred in patient peripheral blood specimens; the percentage of regulatory T cells decreased and the proportions of natural killer cells, helper T cells, cytotoxic T lymphocytes, and interferon gamma secreting CD8+ T cells increased, suggesting an anti-tumor immune response from chemotherapy.

Chemotherapy has been combined with immunotherapy in pre-clinical studies. An animal tumor model combined an anti-PD-1 antibody with low dose cyclophosphamide, and a tumor vaccine, and noted antigen-specific immune responses, tumor immune cell infiltration, and regression of tumors in animals (57). Pre-clinical studies in ovarian cancer cells have shown that immune activation may trigger platinum induced apoptosis and restore sensitivity to platinum agents. El-Gazzar et al studied AD5-10, a monoclonal antibody to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and found that this agent re-sensitizes ovarian cancer cells to apoptosis, and that this effect is augmented by carboplatin, due to carboplatin induced triggering of TRAIL receptor expression on ovarian cancer cells (58). In vivo, AD5-10 restored ovarian cancer sensitivity to carboplatin.

Clinical studies have combined chemotherapy and immunotherapy. In patients with advanced ovarian cancer, oregovomab, a monoclonal antibody to CA125, was combined with chemotherapy with carboplatin and paclitaxel in 2 dosing schedules (simultaneous combined therapy or delayed oregovomab therapy)(59). Simultaneous combination therapy with oregovomab and chemotherapy induced more rapid and strong humoral immunity.

Immune checkpoint blockade has also been investigated with chemotherapy. The combination of ipilimumab, a monoclonal antibody to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), an immune checkpoint molecule, with dacarbazine significantly improved survival in patients with metastatic melanoma compared with dacarbazine alone (OS 11.2 months in ipilimumab/dacarbazine cohort vs. 9.1 months for dacarbazine cohort) (60). Recent studies have suggested that the combination of anti-PD-1 immunotherapy and chemotherapy with a platinum agent may be more effective than platinum based chemotherapy alone. Antonio et al studied the combination of nivolumab, an IgG4 PD-1 inhibitor, in combination with platinum doublet chemotherapy in patients with advanced non small cell lung cancer. One year overall survival rates were 59-87%, an improvement from typical one year overall survival rates of approximately 54% with platinum doublet chemotherapy alone (61). The KEYNOTE-021 trial is an ongoing trial evaluating pembrolizumab in combination with carboplatin and paclitaxel or carboplatin and pemetrexed, in patients with advanced non-small cell lung cancer (62). The initial results from this study were presented at the ASCO 2015 meeting. Forty-four patients were treated, with preliminary overall response rates ranging from 30-58%. One patient experienced a grade 3 rash, which was a dose limiting toxicity. Twenty-seven percent of patients

experienced grade 3-4 adverse events which included reversible transaminitis, anemia, rash, and colitis. Overall, the combination of pembrolizumab with chemotherapy including carboplatin was found to be both safe and effective (63). The patients enrolled in this study will have chest wall disease that is triple negative or hormone resistant, supporting the use of carboplatin in the control arm, as well as in combination with pembrolizumab (64, 65).

This study seeks to determine whether pembrolizumab in combination with carboplatin vs. carboplatin alone is effective in breast cancer patients with hormone resistant or triple negative disease who have chest wall disease. In a companion translational study, we will determine the immunologic and genomic basis underlying the mechanism of action. In Arm A, pembrolizumab will be combined with carboplatin, while Arm B will receive carboplatin alone, with cross-over to pembrolizumab on progression (Arm Bx). We hypothesize that the combination of pembrolizumab and carboplatin will have heightened activity in treating chest wall disease compared with carboplatin alone. As patients with systemic sites of disease are eligible, we will also have the opportunity to evaluate the effectiveness of this therapy on distant sites of disease.

Based on these compelling data, we propose to evaluate the combination of pembrolizumab and carboplatin in this study.

3.1.5 Rationale for Dose Selection

Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose and exposure efficacy relationships from 2 mg/kg Q3W to 10 mg/kg (Q2W), representing an approximate 5 to 7.5 fold exposure range.

KEYNOTE-001 was an open-label phase I study designed to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics, and anti-tumor activity of single-agent pembrolizumab. The dose escalation portion of this study evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks. The dose expansion cohorts evaluated 2 mg/kg every 3 weeks and 10 mg/kg every 3 weeks in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, 2 randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg vs. 10 mg/kg every 3 weeks have been completed, and 1 randomized cohort evaluating 10 mg/kg every 3 weeks vs. 10 mg/kg every 2 weeks has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W.

An integrated body of evidence suggests that 200 mg every 3 weeks should provide similar efficacy to 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks.

In translating to other tumor indications, similar flat exposure-response relationships for efficacy and safety in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types. Thus, the 200 mg every 3 week fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggests that 200 mg every 3 weeks is the appropriate dose and schedule for pembrolizumab.

Pembrolizumab and Carboplatin

Patients will be randomized in a 2:1 ratio to receive either carboplatin AUC 5 IV and pembrolizumab 200 mg IV every 3 weeks for at least 6 cycles (Arm A) followed by pembrolizumab 200 mg IV every 3 weeks if stable or responding disease (Arm Ax) or carboplatin AUC 5 IV every 3 weeks alone (Arm B) until disease progression, at which time they may cross-over (Arm Bx) to pembrolizumab 200 mg IV every 3 weeks with or without carboplatin at the investigator's discretion. Patients with prior thrombocytopenia or prior carboplatin exposure will receive carboplatin AUC 4 IV on Arm A and Arm B. Please see section 3.1.3 for rationale for using carboplatin in this study. In prior studies, carboplatin has demonstrated efficacy when dosed as monotherapy at AUC 6 or in combination at an AUC of 4 or 5 every 3 weeks with efficacy (66, 67). Carboplatin has been dosed at AUC 5 or 6 every 3 weeks in combination with pembrolizumab, (63). For this study, we selected the carboplatin dose of AUC 5 and AUC 4 IV every 3 weeks, in order to minimize potential toxicity in combination with pembrolizumab. If patients are randomized to Arm A and continue on to pembrolizumab only (Arm Ax), carboplatin may be added back into the treatment regimen at the investigator's discretion and with approval from the Study Chair.

Carboplatin Monotherapy

Carboplatin has been used as monotherapy for the treatment of metastatic breast cancer. Response rates range from 10 to 27%, and PFS has been noted to be around 4 months with platinum monotherapy (54-56,57). In this study, carboplatin will be dosed at AUC 5 IV every 3 weeks. Patients with prior thrombocytopenia or prior carboplatin exposure will be dosed at carboplatin AUC 4 IV every 3 weeks. Although carboplatin AUC 6 IV every 3 weeks is standard of care for metastatic breast cancer per the NCCN guidelines, this is often complicated by

toxicity warranting dose reduction and/or delays or discontinuation of treatment. To minimize toxicity to patients in Arm B who may have been pre-treated with prior lines of chemotherapy, and to provide similar carboplatin dosing to the combination arm, carboplatin will be dosed at AUC 4 or 5 IV every 3 weeks in this study.

3.1.6 Rationale for Endpoints

3.1.6.1 Efficacy Endpoints

In this study, we will determine the disease control rate in patients with chest wall disease at 18 weeks of treatment with pembrolizumab and carboplatin vs. carboplatin alone (primary objective), including both chest wall and distant sites of disease as applicable. 18 weeks was selected to assess the primary endpoint as this was the median time to response in a recent phase I trial of pembrolizumab in triple negative breast cancer (31). Additionally, we will determine disease control rates using irRECIST, progression free survival, objective response rate, and toxicity (secondary objectives) after treatment with pembrolizumab and carboplatin vs. carboplatin alone. We will also determine disease control rate based on PD-L1 expression. Disease control has been evaluated as a viable response endpoint in prior studies on patients with unresectable locally advanced breast cancer, given the short period of control of this disease (68, 69).

3.1.6.2 Biomarker Research

Biomarker research will be performed in a companion translational study. Using tissue biopsies and blood collected at baseline and at cycle 3 day 1 of treatment (or at progression if sooner), we will perform immunologic correlative studies to look specifically for changes in PD-L1 expression (75) with treatment. Cytokine expression of interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-alpha), and interferon-gamma will be evaluated before and after treatment in blood (at baseline, at cycle 3 day 1 of treatment) (40, 76, 77). We will also evaluate peripheral T cells for PD-1 expression at baseline and cycle 3 day 1 of treatment (78, 79) to see if these markers correlate with disease control rate.

In addition, we will evaluate serial plasma tumor DNA (80, 81) to assess possible markers of response and resistance, and circulating tumor cells at baseline and cycle 3 day 1 of treatment (82, 83). We will determine whether MYC, an oncogene often over-expressed in triple negative and hormone resistant breast cancer, is associated with high levels of PD-1 and TIM-3 (immune checkpoint receptor) on immune cells in tumor biopsies (84-86). Preliminary data from Andrei Goga's lab has shown that tumor associated T cells demonstrate up-regulation of the PD-1 checkpoint molecule and TIM-3 in response to MYC as a driver oncogene. We will also determine whether these correlative markers correlate with disease control rate.

Altogether, this unique study promises to improve our understanding of pembrolizumab in chest wall disease from the clinical, immunologic, and genomic perspectives.

4.0 OBJECTIVES

4.1 Primary Objective

To determine the disease control rate (including CR, PR and stable disease as defined by RECIST 1.1 at 18 weeks of treatment in breast cancer patients with chest wall disease treated with pembrolizumab and carboplatin or carboplatin alone.

4.2 Secondary Objectives

1. To determine the disease control rate (including CR, PR and stable disease as defined by irRECIST at 18 weeks of treatment in breast cancer patients with chest wall disease treated with pembrolizumab and carboplatin or carboplatin alone.

2. To determine progression free survival in patients treated with pembrolizumab and carboplatin vs. carboplatin alone.

3. To determine the toxicity of pembrolizumab and carboplatin vs. carboplatin alone.

4. To determine 18 week disease control rate based on tumor PD-L1 expression via immunohistochemistry.

5. To determine the overall response rate of patients treated with pembrolizumab and carboplatin vs. carboplatin alone.

6. Support standardized gut microbiome sample collection, storage, preparation and analysis to optimize scientific discovery potential by minimizing variation due to methodologic differences in sample collection, storage, preparation and analysis, as well as permitting cross-study comparisons and testing of multiple analytics platforms to explore gut microbiome associations with the clinical response to immunotherapy.

5.0 METHODOLOGY

5.1 Entry Criteria

This proposed pilot study seeks to investigate the combination of pembrolizumab and carboplatin versus carboplatin alone in patients with breast cancer with chest wall disease. Patients with hormone resistant, triple negative, or HER2+ breast cancer with chest wall disease are eligible regardless of sites of distant metastases. Patients enrolled may have undergone prior surgery and chemotherapy. Prior platinum based chemotherapy is allowed only in patients without evidence of progressive disease while receiving carboplatin; prior radiation therapy is allowed but not required for study entry. Patients with hormone receptor positive disease must have demonstrated progressive disease on at least 2 prior lines of hormone therapy. Patients with brain metastases will be eligible if their intracranial disease has been controlled for at least 1 month. Enrollment will not be contingent on PD-L1 expression although this will be analyzed.

5.1.1 Diagnosis/Condition for Entry into the Trial

Patients must have chest wall disease secondary to breast cancer to be considered for entry into the trial as noted above.

5.1.2 Subject Inclusion Criteria

1. Advanced breast cancer with locally recurrent chest wall disease not amenable to surgical excision with curative intent.
    a. Distant sites of disease are allowed
    b. Prior radiation to the chest wall is not required
2. The following disease subtypes are eligible:
    a. Triple negative disease (defined as ER < 10%, PR < 10%, HER2 negative)
    b. Hormone receptor positive, HER2 negative disease with evidence of progression on at least two prior lines of hormone therapy, unless, per treating investigator's judgement, is not considered a candidate for further endocrine therapy.
    c. HER2 positive disease with evidence of disease progression on trastuzumab, pertuzumab, T-DM1 and oral tyrosine kinase inhibitor unless contraindicated with no other HER2 targeted therapy options available. Patients in this category will be classified by ER status.
        i. Histologically confirmed HER2+ breast carcinoma, with HER2+ defined by in situ hybridization (ISH) or fluorescence in situ hybridization (FISH) or immunohistochemistry (IHC) methodology using standard criteria.
        ii. Cardiac function must be determined within 4 weeks of study entry to be ≥ 50% using ECHO or MUGA.
3. Any number of prior lines of therapy are allowed
    a. Prior platinum based therapy is allowed in the following settings:
        i. Treatment in the neoadjuvant and/or adjuvant setting without clear progression of disease
        ii. Treatment in the metastatic setting without clear progression of disease.
    b. Neo/adjuvant treatment with a checkpoint inhibitor is allowed if the last treatment was at least 12 months from the diagnosis of metastatic disease.

4. At least two weeks from last systemic chemotherapy for breast cancer, with recovery of all treatment related toxicity to grade 1 or less. Subjects with ≤ Grade 2 neuropathy are an exception to this criterion. No specific window is required for hormone therapy.

5. At least two weeks from last radiation therapy, with recovery of all treatment related toxicity to grade 1 or less (excluding alopecia).

6. Prior CNS disease is allowed if stable for at least one month since whole brain radiation therapy, and 2 weeks since stereotactic radiotherapy, and not requiring steroids. Patients whose CNS disease was surgically treated may be enrolled if stable for at least one month, and not requiring steroids.

7. Able to provide tissue from a newly obtained core or excisional biopsy of a chest wall tumor lesion. *Newly-obtained is defined as a specimen any time after the last systemic or local therapy utilized to treat the disease. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Study Chair.*

8. Willing and able to provide written informed consent.

9. ≥ 18 years of age on day of signing informed consent.

10. ECOG performance status of less than or equal to 2

Adequate organ function as defined in Table 1 within 10 business days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR**

	≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

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

12. Female subjects of childbearing potential should be willing to use an acceptable form of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

13. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

1. Treatment with an investigational agent within 4 weeks of the first dose of treatment.

2. A diagnosis of immunodeficiency or is currently receiving systemic steroid therapy at any dose or is receiving any other form of immunosuppressive therapy. Steroid therapy is not allowed within 7 days prior to the first dose of trial treatment. However, topical and intranasal corticosteroids are allowed, and not an exclusion for participation.

3. Known active TB (Bacillus Tuberculosis). Patients with a distant history of tuberculosis that was appropriately treated and have no evidence of active infection are eligible to participate. Patients with a history of latent tuberculosis that was appropriately treated are also eligible to participate.

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Hypersensitivity to carboplatin or cisplatin

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

9. 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 (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/ interstitial lung disease.

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

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

15. Prior checkpoint inhibitor therapy in the metastatic setting.

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

18. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.

Treatment will be continued until clear progression is documented using RECIST, or until unacceptable toxicity or withdrawal of consent. Patients who are believed to have pseudoprogression based on irRECIST may continue on study therapy after consultation with the study PI. Patients on Arm A may stop carboplatin after a minimum of 6 cycles to minimize toxicity if they have stable or responding disease per physician discretion and will continue maintenance pembrolizumab 200 mg IV every 3 weeks. If patients on Arm A discontinue carboplatin before 6 cycles due to reasons other than progressive disease, the possibility of continuing pembrolizumab 200 mg IV every 3 weeks should be discussed with the Study Chair.

Table 2Arm A: Carboplatin AUC 5 IV every 3 weeks and pembrolizumab 200 mg IV every 3 weeks for at least 6 cycles followed by maintenance pembrolizumab 200 mg IV every 3 weeks until progression (Arm Ax). Carboplatin will be dosed at AUC 4 IV every 3 weeks for patients with prior thrombocytopenia or carboplatin exposure. (For HER2+ patients, this arm will also include trastuzumab administered every 3 weeks using standard dosing).

Arm B: Carboplatin AUC 5 IV every 3 weeks alone until progression. Cross over (Arm Bx) to single agent pembrolizumab 200 mg IV every 3 weeks alone is allowed following documented progression. Carboplatin may be continued or added back into the treatment regimen at the investigator's discretion. Carboplatin will be dosed at AUC 4 IV every 3 weeks for patients with prior thrombocytopenia or carboplatin exposure. (For HER2+ patients this will include trastuzumab administered every 3 weeks using standard dosing).

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Arm A and Arm Bx
*Carboplatin	AUC 5 or AUC 4	Q3W	IV infusion	Day 1 of each 3 week cycle	Arm A and Arm B
**Trastuzumab	If needed, 8 mg/kg loading dose followed by 6	Q3W (any dosing schedule allowed)	IV infusion	Coordinate with pembrolizumab if possible, but this is not required.	Arm A and Arm B

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
	mg/kg every 3W				

*The schedule of carboplatin may be modified to weekly dosing given on a 2 week on, one week off schedule as needed to manage hematologic or gastrointestinal toxicity. Patients must start at the study dose and schedule. Any changes to the dosing schedule should be approved by the Study Chair.
**Trastuzumab will only be given to patients with HER2+ disease.

Randomization should occur a maximum of 3 business days prior to C1D1 of trial treatment.

Patients receiving combination therapy will receive carboplatin first followed by pembrolizumab.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 3.1.4.

Dose adjustments are to be made according to the organ system showing the greatest degree of toxicity.

5.2.1.2 Dose Modification and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab and Combination Therapy

Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 3 below. See Section 5.6.1 for supportive care guidelines, including use of corticosteroids.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a

toxicity event to the combination, to carboplatin alone or to pembrolizumab alone, for adverse event listed in Table 3, both interventions must be held according to the criteria in Table 3 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 3.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 3, the combination of carboplatin and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to carboplatin alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Table 3: Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab Monotherapy and IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders

Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal;
bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal;
bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs.

5.2.2 Carboplatin Dose

Carboplatin will be dosed every 3 weeks according to the treatment schedule previously described.

Carboplatin dose in mg = (desired AUC)(GFR + 25)

GFR (estimated) = $\frac{(140 - \text{age in years})\ (\text{weight in kg})}{(\text{SCr in mg/dL})\ (72)}$ (for females x 0.85)

NOTE: Creatinine clearance is capped at 125 ml/min.

5.2.3 Carboplatin Administration

Carboplatin will be prepared and administered as per standard guidelines. Please refer to the package insert for details on carboplatin preparation and administration.

Patients should receive appropriate premedications before each dose of carboplatin including standard antiemetics. Steroid premedication should be avoided or minimized if possible.

5.2.4 Dose Modification of Carboplatin and Management of Toxicity

Every effort should be made to administer study treatment on the planned dose and schedule. Suggested dose reduction criteria are described below for carboplatin administered in this study. These criteria are provided as guidance only. Decisions on dose reduction and resumption of treatment will be determined according to the judgment of the Investigator and per standard guidelines.

Modifying Carboplatin Dosing Schedule

As noted in section 5.2 Table 2 footnote, the schedule of carboplatin may be changed to the 2 week on, one week off schedule as needed to manage toxicity and maintain dosing. Changes to the schedule must be approved by the study Study Chair. The initial Day 1 and Day 8 dose should be at an AUC of 2, but may be modified thereafter for toxicity at the treating investigator's discretion. Re-escalation of carboplatin dose may be discussed with the Study Chair.

Table 4. Carboplatin Dose Modification and Toxicity Management

Event	**Carboplatin Dose Modification**
Neutropenia	
$\geq 1000/mm^3$	• No change to carboplatin

Event	**Carboplatin Dose Modification**
< 1000/mm^3	• Hold carboplatin until ANC >1000/ mm^3 • Dose-reduce carboplatin by 1 dose level (-1 AUC) at the next cycle for all subsequent doses GCSF may be used between days 2–6 according to patient need, at physician discretion, and to avoid dose reduction.
Neutropenic Fever	
ANC ≤ 1000/mm^3, fever ≥ 38.5°C	• Hold carboplatin until resolved (ANC > 1000/mm^3, fever < 38.5°C). • Resume carboplatin with a dose reduction of 1 dose level (–1 AUC) at the next cycle for all subsequent cycles GCSF may be used between days 2–6 according to patient need, at physician discretion, and to avoid dose reduction.
Thrombocytopenia	
≥ 75,000/mm^3	• No change to carboplatin.
50–<75,000/mm^3	• Hold carboplatin until recovery to 75,000/ mm^3 • Dose-reduce carboplatin with a 1 dose level reduction (-1 AUC) at the next cycle for all subsequent cycles.
< 50,000/mm^3	• Hold carboplatin until recovery to ≥75,000/ mm^3 • First episode: Hold carboplatin until platelets are ≥75,000/mm^3. Dose-reduce carboplatin with a 1 dose level reduction (-1 AUC) at the next cycle for all subsequent cycles. • Second episode: Hold carboplatin until platelets are ≥ 75,000/mm^3. Dose-reduce carboplatin with one additional level reduction (-2 AUC from baseline) at the next cycle for all subsequent cycles. • Third episode: Stop carboplatin.
Anemia	
All grades	For all anemia events related to carboplatin regardless of grade, iron studies should be checked and iron should be replaced as indicated. • Red blood cell transfusions can be given at the investigators' discretion as needed for symptom control.
Hepatic	
Grade 0 or 1	No change.
Grade 2	Grade 2 bilirubin: • Hold carboplatin until bilirubin resolves to ≤ grade 1. Resume carboplatin at their previous dose(s).

Event	**Carboplatin Dose Modification**
	A rise in indirect bilirubin with a normal direct bilirubin believed to be attributable to Gilbert's disease does not require change in dose or a drug hold. A note to file should be created. Grade 2 AST or ALT: • Hold carboplatin until AST/ALT resolve to ≤ grade 1. • If AST/ALT resolves to ≤ grade 1, resume carboplatin at previous dose
Grade 3	Grade ≥ 3 bilirubin (not due to Gilbert's disease): • Stop carboplatin. Grade 3 AST or ALT: • Hold carboplatin until AST/ALT resolve to ≤ grade 1. • Resume carboplatin at one dose level reduction (–1 AUC) at the next combined cycle for all subsequent cycles.
Grade 4	Grade 4 AST or ALT: • Stop carboplatin.
Nausea/Vomiting/Anorexia	
Grade 0–2	No change to carboplatin. • Nausea and/or vomiting should be controlled with adequate anti-emetic therapy. Prophylactic anti-emetic therapy (*e.g.,* aprepitant, ondansetron, palonosetron, etc.) should be administered to all patients; specific agents are at the discretion of the treating physician. • Patients are encouraged to take plenty of oral fluids. If symptoms persist despite maximal anti-emetic therapy: • No change carboplatin.
≥ Grade 3	• Hold carboplatin until resolved to ≤ grade 1. • Resume carboplatin at previous dose with modification of premedications. For persistent toxicity ≥ grade 3 despite maximal supportive care, • Dose reduce carboplatin by one dose level (–1 AUC) at the next chemotherapy cycle for all subsequent cycles.
Mucositis/Stomatitis	
Grade 0–2	No change.
≥ Grade 3	Hold carboplatin until symptoms have resolved to ≤ grade 1. • Resume carboplatin at the previous dose with modification of premedications.

Event	**Carboplatin Dose Modification**
	For persistent toxicity ≥ grade 3 despite maximal supportive care: • Dose reduce carboplatin by one dose level for all subsequent doses.
Neurotoxicity	
Grade 0–2	No change.
Grade 3	Hold carboplatin until neuropathy improves to ≤ grade 2. Resume carboplatin based on the number of episodes: • First episode: No change to carboplatin. • Second episode: No change to carboplatin. • Third episode: Stop carboplatin.
Grade 4	Stop carboplatin.
Anaphylaxis/Hypersensitivity	
Mild (*e.g.*, mild flushing, rash, pruritis)	Mild symptoms (grade 1: *e.g.*, transient flushing, rash or fever): • Complete carboplatin infusion. • No treatment required, but observe patient at least until symptoms have resolved.
Moderate (*e.g.*, moderate flushing, rash, mild dyspnea, chest discomfort)	Moderate symptoms (grade 2: *e.g.*, rash, flushing, urticaria, dyspnea, chest discomfort): • Hold carboplatin infusion. • Give intravenous diphenhydramine 25-50 mg and intravenous dexamethasone 10 mg. • Resume carboplatin infusion after recovery of symptoms at half the previous rate for 15 minutes. If no recurrence of symptoms, the planned rate may be resumed. • If symptoms recur after re-challenge, stop carboplatin infusion. Patient should proceed with additional chemotherapy at the discretion of the treating physician. Any moderate hypersensitivity reaction should be discussed with the protocol chair if drug is to be continued.
Severe (*e.g.*, hypotension requiring pressers, angioedema, respiratory distress requiring bronchodilators)	Severe or life-threatening symptoms (grade 3 or 4: *e.g.,* hypotension, angioedema, respiratory distress or anaphylaxis): • Stop carboplatin infusion. • Administer diphenhydramine 25-50 mg and dexamethasone 10 mg IV. Add epinephrine or bronchodilators as needed per institutional guidelines. • Stop carboplatin. Patient should proceed with additional chemotherapy at the discretion of the treating physician.

Event	Carboplatin Dose Modification
Other Clinically Significant Toxicity Excluding Fatigue, Alopecia, and Leukopenia at Physician Discretion	
Grade 0 or 1	No change.
Grade 2	Hold carboplatin until resolved to ≤ grade 1. • Resume carboplatin with no change in dose.
≥ Grade 3	Stop carboplatin and contact the protocol chair for further instructions.

Abbreviations: ANC: absolute neutrophil count; IV: intravenous injection

Grades refer to CTCAE version 4

*All dose reductions will be based on blood counts obtained prior to planned cycle of chemotherapy per study protocol. Nadir counts will not be measured routinely.

The following dose levels will be utilized for the purpose of dose modifications for toxicity:

Table 5. Dose Adjustments for Carboplatin (AUC)

Dose Adjustment	Carboplatin Dose	Carboplatin Dose
Starting dose	AUC = 5	AUC = 4
–1[a]	AUC = 4	AUC = 3
–2[a]	AUC = 3	AUC = 2

[a]Dose to be given only if a dose reduction is required.

5.2.5 Dose Interruptions

Dose interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Study Chair. The reason for interruption should be documented in the patient's study record.

*If carboplatin is held due to toxicity for more than one week, pembrolizumab should be given on schedule.

*In general, missed carboplatin doses should be made-up.

*If carboplatin is held for 3 weeks, cycles will be numbered based on carboplatin and pembrolizumab separately.

5.2.6 Pembrolizumab Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. The +/- 3 day window is based on day 1 of the previous cycle. If carboplatin dosing is changed to two weeks on, one week off, there is a -1/+2 day window for dosing on Day 8.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort 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 of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Details on the preparation and administration of pembrolizumab are provided in the Pharmacy Manual provided with the study drug by Merck.

5.2.7 Trial Blinding/Masking

This is an open-label trial; therefore, the Study Chair, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

84 breast cancer patients with chest wall disease that is hormone resistant or triple negative will be randomized 2:1 to treatment with pembrolizumab and carboplatin (n=56) vs. carboplatin alone (n=28). An additional 9 patients may be accrued (6 Arm A and 3 Arm B) for subject replacement to offset an approximate drop-out rate of 10%.

5.4 Stratification

This study will not be stratified.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

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

Myeloid growth factors may be used at physician discretion to allow on time and safe administration of chemotherapy.

Palliative radiation is permitted on study with PI approval. Carboplatin will be held during radiation therapy and must be restarted within 3 weeks (no greater than 3 weeks) post-radiation.

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.

5.5.2 Prohibited Concomitant Medications

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

- Investigational agents other than pembrolizumab
- Chemotherapy other than carboplatin
- Hormone therapy of any kind
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Study Chair.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents can be considered 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. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **Type 1 Diabetes Mellitus** or **Grade 3-4** Hyperglycemia

        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis (inflammation of pituitary gland)**:
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

  Table 6 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 6 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4:	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Life-threatening; pressor or ventilatory support indicated	deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

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

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

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

OR

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

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

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- male condom or female condom (cannot be used together)

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Hoosier Cancer Research Network (HCRN) within 1 business day. HCRN will report this information within 1 business day to the Study Chair and to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Study Chair. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Study Chair and to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Study Chair if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, using irRECIST.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Sections 7.1.4.3-7.1.4.5. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other

than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up.

5.9 Subject Replacement Strategy

Up to 9 subjects (6 in the pembrolizumab/carboplatin arm and 3 in the carboplatin alone arm) may be replaced if patients drop out of the study for reasons other than disease progression or toxicity, to ensure an adequate sample size to determine the primary endpoint. This replacement strategy accounts for an approximately 10% drop out rate.

5.10 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Screening and Treatment Periods:

6.1.1 Arm A: Pembrolizumab plus Carboplatin, Arm Ax: Pembrolizumab Only

Study Period	Screening period	Treatment Period (3-week, 21-day cycles)				
Treatment Cycle/Title	Screening	1[i]	2	3	4 and Beyond[ii]	Post-completion 6 cycles Carboplatin (maintenance Pembrolizumab, Arm Ax)[iii]
Scheduled Day	-28 to 1 (pre-dose)	1	1	1	1	N/A
Scheduling Window (Days)[iv]	N/A	N/A	±3	±3	±3	N/A
Administrative Procedures						
Informed consent	X					
Informed consent for correlative studies	X					
Inclusion/Exclusion criteria	X					
Demographics and Medical History	X					
Prior and Concomitant Medication Review[v]	X	X	X	X	X	X
Clinical Procedures/Assessments						
Full physical examination[vi]	X	X	X	X	X	X
Vital signs and weight[vii]	X	X	X	X	X	X
Carboplatin administration[viii]		X	X	X	X	
Pembrolizumab administration[ix]		X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X
Adverse Events Monitoring	X	X	X	X	X	X
Child-bearing potential[x]	X					
ECHO/MUGA[xi]	X				X	
Laboratory Procedures/Assessments: Analysis performed by local laboratories						
CBC with Differential[xii]	X	X	X	X	X	X
Chemistry[xiii]	X	X	X	X	X	X
Urinalysis[xiv]	X					
PT/INR and aPTT[xv]	X			X		
TSH[xvi]	X		X		X	X
Pregnancy Test Urine/Serum HCG[xvii]	X					
Correlative Procedures/Assessments: Analysis performed by central laboratory						
Blood, correlative samples[xviii]	X			X		

Study Period	Screening period	Treatment Period (3-week, 21-day cycles)				
Treatment Cycle/Title	Screening	1[i]	2	3	4 and Beyond[ii]	Post-completion 6 cycles Carboplatin (maintenance Pembrolizumab, Arm Ax)[iii]
Scheduled Day	-28 to 1 (pre-dose)	1	1	1	1	N/A
Scheduling Window (Days)[iv]	N/A	N/A	±3	±3	±3	N/A
Tumor biopsy sample[xix]	X			X		
Microbiome Sample Collection[xx]	X					
Tumor Imaging						
CT Chest/Abdomen/Pelvis[xxi]	X			X		X
Bone Scan[xxii]	X			X		X

[i] Cycle 1, Day 1 may be on same day as randomization or at most 3 business days post randomization
[ii] Starting with Cycle 4, the pattern of study treatment administration and assessments and procedures performed in Cycles 1 through 3 will be repeated, unless stated otherwise, or unless treatment administration schedule is changed for toxicity.
[iii] Upon completing 6 cycles of carboplatin, maintenance pembrolizumab may be given at 200 mg IV every 3 weeks if stable or responding disease (Arm Ax).
[iv] Windows for Day 1 of each cycle are based on Day 1 of the previous cycle. Day 8 windows are based on Day 1 of the same cycle.
[v] Record all medications taken within 30 days prior to randomization and all medications taken during treatment period of the study.
[vi] Full physical examination includes photographs of chest wall disease with measurements within picture. Stick-on rulers should be utilized, and lesions should be named on rulers based on location. The same lesions should be tracked throughout the study.
[vii] Vital sign measurements include temperature, pulse, blood pressure, respiratory rate, and weight (height at screening only).
[viii] For Arm A, Carboplatin AUC 5 IV every 3 weeks in combination with pembrolizumab for at least 6 cycles followed by pembrolizumab maintenance treatment. For patients with prior thrombocytopenia or prior carboplatin exposure: Carboplatin AUC 4 IV every 3 weeks in combination with pembrolizumab for at least 6 cycles followed by pembrolizumab maintenance treatment. In the event of toxicities, at the discretion of the investigator, the carboplatin schedule may be changed to an alternate dosing schedule of two weeks on, 1 week off following the first cycle. If this alternate dosing schedule is used, CBCs and blood chemistries will be repeated on day 8 prior to carboplatin administration. The day 8 dose of carboplatin and the lab tests have a window of -1/+2 days.
[ix] Patients in Arm A will be treated with pembrolizumab 200 mg IV and carboplatin AUC 5 IV every 3 weeks for at least 6 cycles followed by maintenance pembrolizumab 200 mg IV every 3 weeks if stable or responding disease (Arm Ax). Patients with prior thrombocytopenia or prior carboplatin exposure will be treated with pembrolizumab 200 mg IV and carboplatin AUC 4 IV every 3 weeks for at least 6 cycles followed by maintenance pembrolizumab 200 mg IV every 3 weeks if stable or responding disease (Arm Ax).
[x] See section 5.7.2
[xi] For patients with HER2+ disease only: Cardiac function must be determined within 4 weeks of study entry to be ≥ 50% using echocardiogram or MUGA. Frequency of ECHO/MUGA is determined by SOC guidelines.
[xii] Screening laboratory tests must be performed within 10 business days prior to the first dose of study. Labs do not need to be repeated on C1D1 if done within 3 days of first dose.
[xiii] Chemistry includes albumin, sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, glucose, LDH, AST, ALT, alkaline phosphatase, total protein, total bilirubin, and direct bilirubin (if total bilirubin is elevated above the upper limit of normal).
[xiv] Screening laboratory tests must be performed within 10 business days prior to the first dose of study treatment. Labs do not need to be repeated on C1D1 if done within 3 days of first dose.
[xv] PT/INR and aPTT are required for screening (prior to the biopsy) and required prior to the cycle 3 biopsy or the biopsy at cross-over.

[xvi] TSH will be drawn every even cycle of pembrolizumab. If abnormal, TSH will be drawn every cycle.
[xvii] As clinically indicated
[xviii] Blood samples for the correlative study will be collected at screening and at cycle 3 (or earlier, upon progression).
[xix] Tumor biopsy samples for the correlative study will be collected at screening and at cycle 3 (or upon progression).
[xx] Study coordinator will assist patient in completing brief patient survey and provide home stool collection kit as detailed in Section 7.1.2.9
[xxi] A diagnostic CT Chest/Abdomen/Pelvis with contrast to be completed at baseline and then every 6 weeks (+/-7 days) prior to the initiation of a new cycle, for 6 cycles (i.e., weeks 6, 12, 18. After week 18, repeat imaging to be completed every 9 weeks (+/- 7 days). If treatment is held, imaging may be delayed per investigator discretion.
[xxii] A bone scan is to be completed at baseline in all patients. If bone metastases are present on the baseline bone scan, patients will undergo bone scans as clinically indicated. Bone scans in patients with bone metastases may be obtained sooner for staging if a patient is symptomatic from their bone metastases. In patients without baseline bone metastases on bone scan, additional bone scans will not be obtained as part of surveillance unless clinically warranted.

6.1.2 Arm B: Carboplatin ONLY

Study Period	Screening period	Treatment Period (3-week, 21-day cycles)				
Treatment Cycle/Title	Screening	1[i]	2	3	4 and Beyond[ii]	Upon progression, prior to Arm Bx cross-over
Scheduled Day	-28 to 1 (pre-dose)	1	1	1	1	
Scheduling window (days)[ii]	N/A	N/A	±3	±3	±3	N/A
Administrative Procedures						
Informed consent	X					
Informed consent for correlative studies	X					
Inclusion/Exclusion criteria	X					
Demographics and Medical History	X					
Prior and Concomitant Medication Review[iv]	X	X	X	X	X	X
Clinical Procedures/Assessments						
Full physical examination[v]	X	X	X	X	X	X
Vital signs and weight[vi]	X	X	X	X	X	X
Carboplatin administration[vii]		X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X
Adverse Events Monitoring	X	X	X	X	X	X
Child-bearing potential/Menopausal status[viii]	X					
ECHO/MUGA[ix]	X				X	
Laboratory Procedures/Assessments: Analysis performed by local laboratories						
CBC with Differential[x]	X	X	X	X	X	X
Chemistry[xi]	X	X	X	X	X	X
Urinalysis[xii]	X					X
PT/INR and aPTT[xiii]	X			X		X
TSH[xiv]	X					X
Pregnancy Test-Urine or Serum-HCG[xv]	X					X
Correlative Procedures/Assessments: Analysis performed by central laboratory						
Blood correlative samples[xvi]	X			X		X
Tumor biopsy sample[xvii]	X			X		X
Microbiome Sample Collection[xviii]	X					
Tumor Imaging						
CT Chest/Abdomen/Pelvis[xix]	X			X		X
Bone Scan[xx]	X			X		X

[i] Cycle 1, Day 1, may be on same day as randomization or at most 3 business days post randomization
[ii] Starting with Cycle 4, the pattern of study treatment administration and assessments and procedures performed in Cycles 1 through 3 will be repeated, unless stated otherwise, or unless treatment administration schedule is changed for toxicity.

[iii] Windows for Day 1 of each cycle are based on Day 1 of the previous cycle. Day 8 windows are based on Day 1 of the same cycle.
[iv] Record all medications taken within 30 days prior to randomization and all medications taken during treatment period of the study.
[v] Full physical examination includes photographs of chest wall disease with measurements within picture. Stick-on rulers should be utilized, and lesions should be named on rulers based on location. The same lesions should be tracked throughout the study.
[vi] Vital sign measurements include temperature, pulse, blood pressure, respiratory rate, and weight (height at screening only).
[vii] For Arm B, Carboplatin AUC 5 IV every 3 weeks alone until progression. Carboplatin AUC 4 IV every 3 week alone for patients with prior thrombocytopenia or prior carboplatin exposure. Cross over to pembrolizumab 200 mg IV every 3 weeks with or without carboplatin (Arm Bx) is allowed following documented progression (see section 5.2). In the event of toxicities, at the discretion of the investigator, the carboplatin schedule may be changed to an alternate dosing schedule of two weeks on, 1 week off following the first cycle. If this alternate dosing schedule is used, CBCs and blood chemistries will be repeated on day 8 prior to carboplatin administration. The day 8 dose of carboplatin and the lab tests have a window of -1/+2 days.
[viii] See section 5.7.2
[ix] For patients with HER2+ disease only: Cardiac function must be determined within 4 weeks of study entry to be ≥ 50% using echocardiogram or MUGA. Frequency of ECHO/MUGA is determined by SOC guidelines.
[x] Screening laboratory tests must be performed within 10 business days prior to the first dose of study treatment. Labs do not need to be repeated on C1D1 if done within 3 days of first dose.
Pregnancy tests as clinically indicated. TSH on Arm B will only be measured at baseline and prior to crossing over to pembrolizumab only (Arm Bx).
[xi] Chemistry includes albumin, sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, glucose, LDH, AST, ALT, alkaline phosphatase, total protein, total bilirubin, and direct bilirubin (if total bilirubin is elevated above the upper limit of normal)
[xii] Screening laboratory tests must be performed within 10 business days prior to the first dose of study treatment
[xiii] PT/INR and aPTT are required for screening (prior to the biopsy) and required prior to the cycle 3 biopsy or the biopsy at cross-over.
[xiv] For patients on carboplatin only, TSH is only required at screening. Before crossing over to Arm Bx (pembrolizumab only), patients must have a new baseline TSH drawn.
[xv] As clinically indicated
[xvi] Blood samples for the correlative study will be collected at screening and at cycle 3 (or upon progression, prior to Arm Bx cross-over).
[xvii] Tumor biopsy samples for the correlative study will be collected at screening and at cycle 3 (or upon progression, prior to Arm Bx cross-over).
[xviii] Study coordinator will assist patient in completing brief patient survey and provide home stool collection kit as detailed in Section 7.1.2.9
[xix] A diagnostic CT Chest/Abdomen/Pelvis with contrast is to be completed at baseline and then every 6 weeks (+/- 7 days) prior to the initiation of a new cycle, for 6 cycles (i.e., weeks 6, 12, 18). After week 18, repeat imaging to be completed every 9 weeks (+/- 7 days). If treatment is held, imaging can be delayed per investigator discretion. At Arm Bx cross-over, a new set of baseline scans must be obtained prior to pembrolizumab dosing.
[xx] A bone scan is to be completed at baseline in all patients. If bone metastases are present on the baseline bone scan, patients will undergo bone scans as clinically indicated. Bone scans in patients with bone metastases may be obtained sooner for staging if a patient is symptomatic from their bone metastases. In patients without baseline bone metastases on bone scan, additional bone scans will not be obtained as part of surveillance unless clinically warranted, and no bone scan is needed for these patients at Arm Bx cross-over.

6.1.3 Arm Bx: Pembrolizumab (+/- Carboplatin)

Study Period	Pre-crossover[i]	Treatment Period (3-week, 21-day cycles)			
Treatment Cycle/Title		1	2	3	4 and Beyond[iii]
Scheduled Day		1	1	1	1
Scheduling Window (Days)[iv]	N/A	N/A	±3	±3	±3
Administrative Procedures					
Informed consent					
Informed consent for correlative studies					
Inclusion/Exclusion criteria					
Demographics and Medical History					
Prior and Concomitant Medication Review[v]		X	X	X	X
Clinical Procedures/Assessments					
Full physical examination[vi]		X	X	X	X
Vital signs and weight[vii]		X	X	X	X
Pembrolizumab administration[viii]		X	X	X	X
Carboplatin administration[ix]		(X)	(X)	(X)	(X)
ECOG Performance Status		X	X	X	X
Adverse Events Monitoring		X	X	X	X
Child-bearing potential/Menopausal status[x]					
ECHO/MUGA[xi]	X				X
Laboratory Procedures/Assessments: Analysis performed by local laboratories					
CBC with Differential[xii]		X	X	X	X
Chemistry[xiii]		X	X	X	X
Urinalysis[xiv]					
PT/INR and aPTT[xv]	X				
TSH[xvi]	X		X		X
Pregnancy Test-Urine or Serum-HCG[xvii]	X				
Correlative Procedures/Assessments: Analysis performed by central laboratory					
Blood for correlative lab samples[xviii]	X				
Tumor biopsy sample[xix]	X				
Microbiome Sample Collection[xx]	X				
Tumor Imaging					
CT Chest/Abdomen/Pelvis[xxi]	X			X	X
Bone Scan[xxii]	X			X	X

[i] Arm Bx: Pembrolizumab only dosing must begin within 6 weeks of determined progression. All pre-crossover labs must be done within 10 business days of C1D1 of pembrolizumab. Tumor imaging must be done within 4 weeks of first dose of pembrolizumab (C1D1).
[ii] Cycle 1, Day 1, may be on same day as randomization or at most 3 business days post randomization.
[iii] Starting with Cycle 4, the pattern of study treatment administration and assessments and procedures performed in Cycles 1 through 3 will be repeated, unless stated otherwise.
[iv] Windows for Day 1 of each cycle are based on Day 1 of the previous cycle.
[v] Record all medications taken within taken during treatment period of the study.
[vi] Full physical examination includes photographs of chest wall disease with measurements within picture. Stick-on rulers should be utilized, and lesions should be named on rulers based on location. The same lesions should be tracked throughout the study.
[vii] Vital sign measurements include temperature, pulse, blood pressure, respiratory rate, and weight (height at screening only).
[viii] For Arm Bx, pembrolizumab 200 mg IV every 3 weeks with or without carboplatin is allowed following documented progression (see section 5.2).
[ix] All carboplatin dosing and dose modification guidelines apply.
See section 5.7.2
[xi] Frequency of ECHO/MUGA is determined by SOC guidelines.
[xii] Screening laboratory tests must be performed within 10 business days prior to the first dose of study treatment. Labs do not need to be repeated on C1D1 if done within 3 days of first dose.
[xiii] Chemistry includes albumin, sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, glucose, LDH, AST, ALT, alkaline phosphatase, total protein, total bilirubin, and direct bilirubin (if total bilirubin is elevated above the upper limit of normal)
[xiv] Urinalysis only to be repeated pre-crossover if clinically indicated.
[xv] PT/INR and aPTT are required prior to Arm Bx cross-over if progression occurs prior to cycle 3.
[xvi] Prior to Arm Bx cross-over, patients must have a new baseline TSH drawn. TSH will be drawn at every even pembrolizumab cycle, or at every cycle if abnormal.
[xvii]As clinically indicated.
[xviii] Blood samples for the correlative study will be collected prior to Arm Bx cross-over, if progression occurs prior to cycle 3 of Arm B.
[xix] Tumor biopsy samples for the correlative study will be collected prior to Arm Bx cross-over, if progression occurs prior to cycle 3 of Arm B.
[xx] Study coordinator will assist patient in completing brief patient survey and provide home stool collection kit as detailed in Section 7.1.2.9
[xxi] A diagnostic CT Chest/Abdomen/Pelvis with contrast is to be completed at baseline (within 4 weeks of C1D1 of pembrolizumab) and then every 6 weeks (+/- 7 days) prior to the initiation of a new cycle, for 6 cycles (i.e., weeks 6, 12, 18). After week 18, repeat imaging to be completed every 9 weeks (+/- 7 days). If treatment is held, imaging can be delayed per investigator discretion.
[xxii] A bone scan is to be completed at baseline in all patients. If bone metastases are present on the baseline bone scan, patients will undergo bone scans as clinically indicated. Bone scans in patients with bone metastases may be obtained sooner for staging if a patient is symptomatic from their bone metastases. In patients without baseline bone metastases on bone scan, additional bone scans will not be obtained as part of surveillance unless clinically warranted, and no bone scan is needed for these patients prior to crossing over to Arm Bx.

6.2 End of Treatment

Treatment Cycle/Title	End of Treatment	
	At time of Treatment Discontinuation	Safety Follow-up
Scheduled Day	N/A	30 days post last dose[i]
Scheduling Window (Days)	N/A	±3
Administrative Procedures		
Prior and Concomitant Medication Review[ii]	X	X
Subsequent anti-cancer therapy		X
Survival status	X	X
Review Adverse Events[iii]	X	X

[i] 30 days post last dose of study treatment or prior to initiation of new anti-cancer regimen (must be prior to new regimen, no scheduling window).
[ii] Record all medications taken at time of and after treatment discontinuation.
[iii] Record all AEs occurring within 30 days post treatment end. Report all SAEs occurring up to 90 days post treatment end or until subject initiates new anti-cancer therapy.

Clinical Procedures		
Full physical examination[iv]	X	X
Vital signs and weight[v]	X	X
ECOG Performance Status	X	X
ECHO/MUGA[vi]		
Laboratory Procedures/Assessments: Analysis performed by local laboratories		
CBC with Differential	X	X
Chemistry[vii]	X	X
TSH[viii]	X	
Tumor Imaging		
CT Chest/Abdomen/Pelvis[ix]	X	
Bone Scan[x]	X	

[iv] Full physical examination includes photographs of chest wall disease with measurements within picture. Stick-on rulers should be utilized, and lesions should be named on rulers based on location. The same lesions should be tracked throughout the study.

[v] Vital sign measurements include temperature, pulse, blood pressure, respiratory rate, and weight (height at screening only).

[vi] For patients with HER2+ disease only: Cardiac function must be determined within 4 weeks of study entry to be > 50% using echocardiogram or MUGA. Frequency of ECHO/MUGA is determined by SOC guidelines.

[vii] Chemistry includes albumin, sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, glucose, LDH, AST, ALT, alkaline phosphatase, total protein, total bilirubin, and direct bilirubin (if total bilirubin is elevated above the upper limit of normal)

[viii] For patients most recently on pembrolizumab only.

[ix] Study discontinuation scans must be completed. If progression is noted in chest wall, scans must be completed to document systemic treatment response. If patients progress on imaging prior to their EOT visit, scans do not need to be repeated.

[x] Bone scan to be completed as clinically indicated.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Study Chair and/or Merck for reasons related to subject 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 subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

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

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 Study Chair requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Screening Number

Patients will be screened by the medical oncologists in the oncology practice clinics at participating sites. Patients to be screened will include those currently followed in these practices, as well as those referred from outside providers.

For each potential patient who signs informed consent to this study, demographic and consent process information will be entered into the Hoosier Cancer Research Network (HCRN) electronic data capture (EDC) system. Subjects will be automatically assigned a screening number (see study procedure manual (SPM) for details). The patient must have signed and dated the currently approved consent form before any study-related screening procedures are performed.

7.1.1.7 Registration and Assignment of Randomization Number

The UCSF Coordinating Center for this study will be working with Hoosier Cancer Research Network (HCRN). As above, all patients who are consented will be entered into the electronic database capture system (EDC), which is password protected and meets HIPAA guidelines. All data will be collected and entered into the EDC system by Clinical Research Coordinators (CRCs) from UCSF and other participating centers.

Registration and randomization of eligible patients may occur only after the pretreatment evaluation is complete and all eligibility criteria have been met.

Prior to registration and randomization, the Study Chair at UCSF (or her designee) must review and approve each patient. When a participating site determines that a patient meets eligibility criteria; the study site will send a completed eligibility checklist and de-identified supporting source documentation to the UCSF study team (see study procedures manual for details) for review; UCSF will check the forms for completeness and contact the site regarding any discrepancies. The approval of the Study Chair will be communicated back to the participating site prior to registration/randomization; documentation of this approval will be provided to HCRN at the time of registration/randomization.

Eligible and approved patients for enrollment may then be registered through the Hoosier Cancer Research Network (HCRN) electronic data capture (EDC) system. Successful registration is when an “On Study” date is entered into the EDC system. HCRN’s EDC system will automatically assign a study-specific sequence number. All future study documentation related to the patient should include the assigned sequence number. Randomization will occur at the Hoosier Cancer Research Network after registration is complete. Subjects will be randomized 2:1 to receive treatment with pembrolizumab and carboplatin (n=56, Arm A) or carboplatin alone (n=28, Arm B) until documented disease progression.

Any required local patient registration or tracking should occur per each participating site’s local requirements.

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

Patients will be assessed at each study visit for compliance to trial procedures including medications, diet, and activity. Activity and diet are as tolerated.

Subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous 4 weeks prior to their screening visit. The investigator must be informed as soon as possible about any new medication taken from the time of screening until the end of the clinical phase of the study.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 13b). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. Grade 1 laboratory abnormalities and white blood cell differential abnormalities excluding neutrophils (i.e., lymphocytes, monocytes, basophils, etc.) do not need to be recorded as AEs.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is an event of a potentially immunologic etiology.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the

Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 13a) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Patients will undergo tumor imaging and disease assessment with a diagnostic CT chest, abdomen, and pelvis with contrast at baseline, and every 6 weeks (+/- 7 days) prior to the initiation of a new cycle, for 6 cycles (i.e., weeks 6, 12, and 18- prior to cycles 3, 5, and 7). After week 18, patients will be scanned every 9 weeks (+/- 7 days) moving forward. Per the NCCN guidelines 3.2015 (section "Principles of monitoring metastatic disease"), imaging in patients with metastatic disease receiving chemotherapy (such as those enrolled in this study) may occur as frequently as every 2-4 cycles of treatment, so this is the standard of care. A PET/CT can be used if the CT is diagnostic.

A bone scan will be completed at baseline in all patients. If bone metastases are present on the baseline bone scan, patients will undergo bone scans as clinically indicated. Bone scans in patients with bone metastases may be obtained sooner for staging if a patient is symptomatic from their bone metastases. In patients without baseline bone metastases on bone scan, additional bone scans will not be obtained as part of surveillance unless clinically warranted.

Study discontinuation scans must be completed to document systemic treatment response.

If cycles are delayed, tumor assessments may be delayed per investigator discretion.

Patients will undergo photography of their chest wall disease every 3 weeks (or more frequently, depending on clinic visits) prior to scheduled treatment.

Arm B: Before crossing over to pembrolizumab only (Arm Bx), all patients will complete a diagnostic CT of chest, abdomen, and pelvis with contrast, and bone scan (if clinically indicated) to establish a new baseline and verify disease progression.

7.1.2.7 Assessments for Arm B patients prior to crossing over to pembrolizumab only (Arm Bx)

Cross-over to pembrolizumab only (maintenance pembrolizumab, Arm Bx) is allowed for Arm B patients with documented disease progression. On Arm Bx, carboplatin may be continued or added back into the treatment regimen at the investigator's discretion. Disease progression can be clinically verified with photos and measurements of chest wall disease, or increase in symptoms associated with evidence of progression on imaging, but does not need to meet RECIST criteria for PD.

Tumor imaging must be completed prior to pembrolizumab dosing. All patients will complete a diagnostic CT of chest, abdomen, and pelvis with contrast, as well as a bone scan (if clinically indicated).

All patients will have a new baseline TSH drawn. Thereafter, TSH will be drawn every even cycle of pembrolizumab dosing. If abnormal, TSH will be drawn every cycle.

If progression occurs before cycle 3 (on Arm B), a biopsy and correlative blood samples should be obtained at end of study treatment (on Arm B) or at cross-over.

At cross-over, the first dose of pembrolizumab will be considered Cycle 1 Day 1 of pembrolizumab. Prior to pembrolizumab dosing, all AEs must be recovered to Grade 1, except peripheral neuropathy and alopecia. Cycle 1 Day 1 of pembrolizumab dosing must occur within 6 weeks of progression on carboplatin.

7.1.2.8 Tumor Tissue Collection and Correlative Studies Blood Sampling

1. **Tumor Tissue-**Fresh tumor tissue will be collected for correlative studies. All patients will undergo tumor biopsies (4 excisional biopsies of chest wall tumor lesion or 4 core biopsies) at baseline and at cycle 3 day 1 of treatment (or sooner, should progression occur). Tumor tissue from chest wall disease preferred. Correlative studies will be performed on tumor tissue in a companion trial.

Participants will be given information as part of the informed consent process that samples will be used for research tests that will include genetic studies and testing. The intent is not to give participants (or his/her medical providers) the results of any testing done for research purposes; however, incidental germline (heritable) mutations may be identified of which a participant may or may not already be aware. In the case that an incidental genetic finding is identified, the Protocol Chair of this project will be notified. The possible decisions for handling incidental findings may include notification of the participant (and provider); recommendation for genetic counseling, which may or may not include genetic testing (e.g., if the finding was not done in a CLIA certified laboratory); or, neither. In general, a member of the participant's treating team will be given the information to help with notification. In all cases, the current policy of the Johns Hopkins and local/participating site IRB, as applicable, will be followed and any additional approvals that may be required prior to participant notification will be secured in advance.

Any leftover study tissue or blood samples may be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. The study PI and collaborators have approval by the TBCRC, which has custodial oversight of all

biospecimens collected as part of a TBCRC trial, to address the research questions described in the protocol document. All future use as part of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the TBCRC according to its established policies, whether the specimens are stored in a central site or at a local institution or in a virtual repository.

7.1.2.9 Stool Collection for Microbiome Studies

1. Patient Survey, Specimen Collection and Handling
Prior to initiation of protocol treatment, the study coordinator will complete with the patient a brief patient survey (Appendix 4) that addresses antibiotic use and diet and provide the patient with a stool collection kit and mailer and instructions for use (Appendix 5). The Mawi kit iSWAB-Microbiome will be used to collect stool in one tube and may remain at room temperature for up to 40 days. Study patients will mail the sample directly to CosmosID [redacted] after collection. Study coordinators will return the completed patient survey after dispensing the stool collection kit to the Mayo Clinic Surgical Research Office via mail or email to:

Department of Surgery Research Office
[redacted]

Or

Study Coordinator:
[redacted]

Study Coordinator Supervisor:
[redacted]

2. Specimen Banking, Data Collection and Laboratory Analyses
Patient survey information linked to TBCRC patient study ID and demographic data will be maintained in a secure password-protected database in the Mayo Clinic Surgery Research Office. A study coordinator will be responsible for data collection including demographic and patient survey information, linking data with TBCRC trial identifiers and central coordination among sites and studies.

Samples mailed directly to CosmosID will be stored at -70 and DNA extraction and V3-V4 16S sequencing will be performed on batched aggregated samples. Raw samples and extracted samples will be maintained under appropriate conditions at CosmosID. Raw sequencing output will be provided to investigators to link with clinical metadata and to perform analyses using various microbiome analysis pipelines.

Secondary use of bio-specimens for new endpoints must be submitted to the TBCRC Central Office for possible review by the TBCRC Correlative Science Review Committee.

7.1.3 Laboratory Procedures/Assessments

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Creatinine		
	Calcium		
	Chloride		
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

Laboratory tests for screening should be performed within 10 business days prior to the first dose of treatment. Pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. Grade 1 laboratory abnormalities and white blood cell differential abnormalities excluding neutrophils (i.e., lymphocytes, monocytes, basophils, etc.) do not need to be recorded as AEs.

7.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.4.4) and then proceed to the Follow-Up Period of the study (described in Section 7.1.4.5).

7.1.3.2 Blinding/Unblinding

This study will not include blinding.

7.1.4 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.4.1 Screening

Potentially eligible patients will sign a screening consent in order to be screened for the study.

7.1.4.1.1 Screening Period

Eligible patients will have the following procedures performed within 3 weeks prior to study drug dosing:

1. Informed consent
2. Medical history and demographics
3. Record all medication(s) received within 30 days prior to the first dose of study treatment and note if the medication is ongoing.
4. Physical examination including photographs of chest wall disease.
5. Vital signs including height and body weight.
6. ECOG Performance Status
7. Laboratory assessments including

a. Pregnancy test: urine hcg (serum hcg to be performed if urine hcg uninterpretable)

b. Complete blood count including hematocrit, hemoglobin, platelet count, white blood cell count and differential

c. Comprehensive serum chemistry panel: albumin, sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, glucose, LDH, AST, ALT, total bilirubin, total protein, direct bilirubin (if total bilirubin is elevated above the upper limit of normal), and alkaline phosphatase.

d. PT/aPTT

e. Thyroid function test: TSH

f. Urinalysis

8. Disease assessment: diagnostic CT chest, abdomen, pelvis with contrast and bone scan (all patients are required to have a bone scan at screening)

9. Tumor biopsy: Fresh tissue –see correlative lab manual requirements

10. Microbiome sample collection

7.1.4.2 Treatment Period

Every 3 weeks during treatment period
1. Prior and concomitant medication review
2. Adverse Event Assessment
3. Physical Examination including photographs of chest wall disease.
4. Vital signs
5. ECOG Performance Status
6. Laboratory assessments including

a. Complete blood count including hematocrit, hemoglobin, platelet count, white blood cell count and differential

b. Comprehensive serum chemistry panel: albumin, sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, glucose, LDH, AST, ALT, total bilirubin, total protein, direct bilirubin (if total bilirubin is elevated above the upper limit of normal), and alkaline phosphatase.

Every even cycle of pembrolizumab (2, 4, 6, etc.)

Thyroid function test: TSH

Every 6 weeks until week 18 (weeks 6, 12, 18) and every 9 weeks thereafter

(At time of crossover, new baseline scans should be obtained. Scans should then be obtained at 6 week intervals following C1D1 of pembrolizumab.)

CT Chest/Abdomen/Pelvis

Cycle 3, Day 1

Repeat tumor biopsy

As Clinically Indicated

Bone scan

7.1.4.3 Post-Treatment Visits

1. Review adverse events

2. Physical Examination including photographs of chest wall disease

3. Vitals signs

4. ECOG Performance Status

5. Laboratory assessments (30 days post last treatment dose) including:

a. Complete blood count including hematocrit, hemoglobin, platelet count, white blood cell count and differential

b. Comprehensive serum chemistry panel: albumin, sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, glucose, LDH, AST, ALT, total bilirubin, total protein, direct bilirubin (if total bilirubin is elevated above the upper limit of normal), and alkaline phosphatase.

6. Record all concomitant medications(s) added and/or changed.

Patients will be followed for four weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.1.4.4 Safety Follow-Up Visit

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

7.1.4.5 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should return for the 30 day safety follow-up as outlined above.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-

specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, the onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. Grade 1 laboratory abnormalities and white blood cell differential abnormalities excluding neutrophils (i.e., lymphocytes, monocytes, basophils, etc.) do not need to be recorded as AEs.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Study Chair and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 1 business day to HCRN who will then report this information within 1 business day to the Study Chair and Merck Global Safety. [redacted]

7.2.2 Reporting of Pregnancy and Lactation to the Study Chair and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 1 business day to HCRN who will then report this information within 1 business day to the Study Chair and Merck Global Safety. [redacted]

7.2.3 Immediate Reporting of Adverse Events to the Study Chair and to Merck

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 8 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time of start of study treatment through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be

reported within 1 business day to HCRN [redacted] who will then report this information within 1 business day to the Study Chair and Merck Global Safety [redacted]

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to HCRN who will then report this information to the Study Chair and Merck [redacted]

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. [redacted] at the time of submission to FDA. UCSF will coordinate all submissions to the FDA.

All subjects with serious adverse events must be followed up for outcome.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 8 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	

Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)

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

7.2.5 Study Chair Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.2.6 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 1 business day to HCRN [redacted]. HCRN will then report this information within 1 business day to the Study Chair and Merck Global Safety. [redacted]

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI or follow up to an ECI must be reported within 1 business day to HCRN [redacted]. HCRN will then report this information within 1 business day to the Study Chair and Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 1 business day to HCRN. HCRN will then report this information within 1 business day to the Study Chair and Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Study Chair and to Merck, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The primary endpoint in this study is to determine the arm specific disease control rate (CR/PR/SD) at 18 weeks of therapy with pembrolizumab and carboplatin vs. carboplatin alone.

Patients will be randomized 2:1 to treatment with pembrolizumab and carboplatin vs. carboplatin alone.

Table 9 Statistical Analysis Summary

	Carboplatin	**Carboplatin & Pembrolizumab**	**Inter Group Differences**
Cycle-6 disease control rate	0.10	0.30	Difference 0.20
Median number of cycles with disease control	1.81	3.45	Difference 1.65
Hazards	0.384	0.201	Hazards Ratio 0.52
Events needed	--	--	59
Patients needed per arm	28	56	Total 84
For n=28 Carboplatin arm and n=56 Pembrolizumab/ Carboplatin: Within-arm rate (95% CI)	10.0% (2.99%-20.80%)	30.0% (20.39-40.11%)	

We will accrue a total of 84 patients (56 in Arm A and 28 in Arm B) for efficacy assessments. Up to 9 subjects (6 in Arm A and 3 in Arm B) may be replaced (accounts for an approximately 10% drop out rate) if patients drop out of the study for reasons other than disease progression or toxicity, to ensure an adequate sample size to determine the primary endpoint.

With this sample size, a 20% difference in disease control rate between arms with a hazard ratio difference of 0.52 can be detected. This calculation assumed a 2:1 allocation to the study arms as described above, and was determined using a 2-sided log rank test with $\alpha = 0.10$ and $\beta = 0.20$ (power = 80%). The within arm 18 week disease control rate estimates use $\alpha = 0.10$, and are based on the Kaplan-Meier method, accounting for timing of assessments of new disease.

The rate of disease control with carboplatin alone was estimated as 10%, based on prior data with platinum agents in pre-treated metastatic breast cancer (65). The estimated rate of disease

control in the pembrolizumab/carboplatin arm was estimated at 30% based on 2 recent phase I studies with anti-PD-1/PD-L1 antibodies in breast cancer showing clinical benefit rates between 27-44% in breast cancer (31, 46, 47). The response rate of patients with chest wall disease has been reported to be between 25-52% in prior studies (33). Based on this data, we selected use a cutoff of 30% for disease control in the pembrolizumab/carboplatin arm, so as not to exclude the potential efficacy of a novel agent in an aggressive, rapidly progressing disease. 18 weeks was selected as the time frame to determine the primary endpoint based on a recent phase I trial with pembrolizumab in breast cancer showing that the median time to response was 18 weeks (31), and also because prior studies have shown that the period of control of chest wall disease is relatively short (<3-4 months) (82).

Patients with early progressive disease in the control arm (carboplatin alone) before 18 weeks are unlikely to have disease control at 18 weeks, so this should not create much bias favoring the pembrolizumab/carboplatin arm.

8.2 Statistical Analysis Plan

8.2.1.1 Primary Efficacy Analysis

The primary variable for assessment of the treatment is the disease control rate (CR/PR/SD) by RECIST 1.1 at week 18. A disease control rate of <10% would be considered undesirable at week 18 and >30% would be considered clinically meaningful. The study hypothesis is defined as: H0: $\pi 1 \leq \pi 0$ (The disease control rate of the pembrolizumab/carboplatin arm is assumed to be smaller than the disease control rate of the carboplatin alone arm versus H1: $\pi 1 > \pi 0$ (The disease control rate of the pembrolizumab/carboplatin arm is assumed to be greater than the disease control rate of the carboplatin alone arm). Efficacy outcomes (rate of disease control, and progression free survival) will be evaluated at the end of each treatment cycle. The primary endpoint will be determined at 18 weeks of treatment. The 2 sided logrank test with $\alpha = 0.10$ and $\beta = 0.20$ (power = 80%) will be used to determine the statistical significance of arm specific efficacy. Supportive analyses will be done using estimates of progression free survival at week 18 between treatment arms by the Kaplan-Meier method in order to account for any censoring patients.

8.2.1.2 Futility analysis for carboplatin arm

An interim analysis for futility will be performed after enrolling 18 patients in the carboplatin arm. Disease control is defined as evaluable patients who are observed with CR, PR and SD during the assessment period. Patients, who drop out, terminate the study early or crossover due to progression will be considered as non-responders. Because the efficacy endpoint is disease control, patients who are crossed-over in the study will be separately reported and also considered as non-responders or progressive-disease in the efficacy analyses (including progression free survival, in 8.2.2). If ≤ 2 patients are observed with disease control at week 18, then the null hypothesis may not be rejected, indicating that no further enrollment of carboplatin arm is warranted. If the disease control rate of carboplatin alone arm is indeed < 10%, the probability of terminating the carboplatin/control arm is 73.4%.

8.2.1.3 Safety/toxicity analysis for pembrolizumab/carboplatin arm

An interim analysis for safety and toxicity will be performed in the pembrolizumab/carboplatin arm. The study will be stopped for safety/toxicity if the number of patients experiencing treatment-related SAE or toxicities in pembrolizumab/carboplatin arm is excessive, and this toxicity is not thought to be related to carboplatin alone. A probability of treatment-related SAE/toxicity exceeding 0.33 will be considered prohibitively high. The table below (Table 10) shows the stopping rules of safety and toxicity based on a continuous Bayesian beta-binomial monitoring.

Table 10: Stopping rule for toxicity: for given number of patients in the pembrolizumab/carboplatin arm, the study is suspended if the number of patients with treatment-related SAE or toxicities is achieved

Number of patients in study	3-5	6-9	10-12	13-15	16-18
Number of treatment-related SAE/Toxicity	2	3	4	5	6

8.2.1.4 Futility analysis for pembrolizumab/carboplatin arm

An interim analysis for futility will not be done in the pembrolizumab/carboplatin arm as prior studies have shown efficacy of pembrolizumab in breast cancer (31).

8.2.2 Secondary Efficacy Analyses

Secondary efficacy variables will include disease control rate by irRECIST, objective Response Rate (ORR) and progression free survival at week 18.

The disease control rate (CR/PR/SD) by irRECIST will be determined at week 18. ORR will be presented as the percentage of patients with CR/PR by RECIST for the primary endpoint as noted above, and by irRECIST for the secondary endpoint. Disease control of chest wall disease will be calculated it will be defined as the time from the baseline until the chest wall disease progression or death from any cause. Patients who have no chest wall disease at the time of the analysis will be censored at the time of last assessment demonstrating lack of progression. Disease control will also be based on PD-L1 expression via immunohistochemistry.

Time to event variables (Disease Control and ORR) and Progression Free Survival will be summarized by treatment arms using the Kaplan-Meier method, including graphical displays and incidence estimates at 4, 8 12, and 18 weeks.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 11.

Table 11 Product Descriptions

Product Name & Potency	**Dosage Form**
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Patient confidentiality will be maintained in accordance with standard HIPAA guidelines. In addition, all patients will be assigned a screening and randomization number as outlined in sections 7.1.1.6 and 7.1.1.7 above.

10.2 Compliance with Financial Disclosure Requirements

This trial will comply with financial disclosure requirements as outlined by the respective centers and states in which the trial occurs.

10.3 Compliance with Law, Audit and Debarment

This trial will comply with all policies outlined by the respective centers and states in which the trial occurs.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Data Management

Each patient will be assigned a study identification number as outlined in sections 7.1.1.6 and 7.1.1.7 above. All patients will then be entered into the EDC system, which is password protected and meets HIPAA guidelines. All data will be collected and entered into the EDC system by Clinical Research Coordinators (CRCs) from UCSF and other participating centers.

Study meetings will occur at the coordinating center bimonthly, and updates will be provided to the TBCRC monthly. At these meetings, preliminary data will be reported.

All serious adverse events, regardless of causality to study drug, will be reported to HCRN, the Site Investigator and/or the Study Coordinator at each institution, and also to the Study Chair.

All serious adverse events must be reported to HCRN [redacted] within 1 business day after the investigator becomes aware of the event. Events should be reported using an HCRN SAE Submission Form. HCRN will then report this information to the Study Chair within 1 business day.

Follow-up information must also be reported to HCRN [redacted]. within 1 business day of receipt of the information by the investigator. HCRN will then report this information to the Study Chair within 1 business day of receipt of the information by the investigator.

HCRN will disseminate information regarding serious adverse events to the participating sites within 5 days of review of the information by the Study Chair (or her designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly,

probably, or definitely) to the study medication. UCSF will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

The UCSF DSMC will conduct remote data monitoring visits at the participating sites, as per DSMP and monitoring SOPs. Upon request, redacted source documents must be available for remote review. HCRN will perform remote data validation throughout the lifecycle of the study. If there are significant issues with the data identified at these sites, an onsite monitoring visit may be performed by HCRN (see appendix 3.0).The trial site may also be subject to quality assurance audit by Merck as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

10.6 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation.

The Protocol Chair (or designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

11.0 MULTI-CENTER GUIDELINES

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Hoosier Cancer Research Network (HCRN). The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. HCRN will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to HCRN.

The requirements for data management, submissions, and monitoring are outlined below.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. HCRN will inform the investigator at each site at such time that the records may be destroyed.

It is understood that any manuscript or releases resulting from the collaborative research must be approved by the Study Chair and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation.

Additionally, any publication of study data and results must conform to the publications policy as stated the Translational Breast Cancer Research Consortium's (TBCRC) "Policies and Procedures".

12.0 ETHICS AND GOOD CLINICAL PRACTICE ETHICS AND GOOD CLINICAL PRACTICE

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.

2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

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APPENDIX 1 ECOG

a. ECOG Performance Status

Table 12. ECOG Performance Status

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

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

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

APPENDIX 2 Response evaluation

13.1 Response evaluation

Both RECIST 1.1 and irRECIST will be used in this study. The irRECIST criteria are outlined by Bohnsack O, Ludaji K, and Hoos A. (Adaptation of the immune-related response criteria: irRECIST. 2014. ESMO; Abstract 4958).

The irRECIST criteria refer to RECIST 1.1:

Eisenhauer EA et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47 (83).

13.2 Chest wall disease assessment

Clinical assessment of chest wall disease will occur by the treating provider and/or the study site coordinator. Chest wall disease assessment will occur in accordance with RECIST 1.1. These guidelines are also summarized here for ease of reference.

Measurable disease is defined as a superficial lesion with a minimum size of 10 mm by caliper measurements by clinical exam or at least 10 mm in longest diameter by CT scan. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. Documentation by color photography including a ruler to estimate the size of the lesion will be done. When lesions can be evaluated by both clinical exam and imaging, the imaging evaluation will be used for target lesion assessment.

Non measurable lesions will not be selected as target lesions, but will be selected and followed as non-target lesions. These lesions will also be documented by color photography.

APPENDIX 3 - Data and Safety Monitoring Plan for Multicenter Institutional Study (Phase 2 or 3)

Data and Safety Monitoring Plan for a Multicenter Study Phase II or III Trial

1.Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on accrual).
- Review of serious adverse events.
- Minimum of a biennial regulatory auditing visit.

Hoosier Cancer Research Network will work with the DSMC to provide requested reports at the intervals agreed upon by UCSF and HCRN.

2.Monitoring and Reporting Guidelines

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair; HCRN provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. HCRN will work with the UCSF Coordinating Center to conduct quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters. The Study Chair is responsible for the overall conduct of the trial and for auditing its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and participant safety at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

All institutional Phase II or III therapeutic trials are designated with a moderate risk assessment. The data is audited by a DSMC Monitor/Auditor on a semiannual basis with a random selection of twenty percent of the participants (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the CRA console of OnCore and/or via access to the site's

electronic medical records. The DSMC Monitor/Auditor will audit no more than three participant charts at each participating site during the course of auditing this trial.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

Multicenter communication

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. The UCSF Coordinating Center and HCRN provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. HCRN and the UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

•Enrollment information.

•Adverse events (i.e., new adverse events and updates on unresolved adverse events and new safety information).

•Protocol Violations.

•Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center and HCRN, as well as the participating sites. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable FDA regulations.

3Review and Oversight Requirements

3.1Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), regardless of being unexpected or considered to be associated with the use of the study drug will be entered into OnCore®, UCSF's Clinical Trial Management System.

All clinically significant adverse events must be reported to HCRN by the participating sites who will then report the clinically significant AEs to Merck and the Study Chair within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.

- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.

- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.

- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center Site Committee meetings. All grade 3-5 adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment from the UCSF Coordinating Center and the participating sites.

3.2Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.

- Life-threatening (i.e., results in an immediate risk of death).

- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Permanent or significant disability/incapacity.

- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.

- Event occurring in a gene therapy study.

- Event that changes the risk/benefit ratio of a study.

• Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All Serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within one business days of becoming aware of the event. The SAEs are reviewed and audited by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, HCRN will report this information to the Study Chair at the UCSF Coordinating Center or the assigned designee within 1 business day. The Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

3.3Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying HCRN and the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, HCRN, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified within their reporting guidelines.

HCRN

In addition, all suspected adverse reactions considered “serious” must be sent electronically to [redacted] HCRN within 1 business day of becoming aware of the event and

HCRN will report this information within 1 business day to the Study Chair and Merck. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
[redacted]

UCSF HDFCCC

San Francisco, CA 94158

John McAdams (DSMC Director)
[redacted]

UCSF HDFCCC

San Francisco, CA 94143

(Version 12Oct2020)

Appendix 4 TBCRC (Translational Breast Cancer Research Consortium)

Collection of Microbiome Samples in Immuno-Oncology Studies

Patient Survey

Study Patient ID# _____

Age: _____ Sex: ☐ Male ☐ Female **Zip Code of primary residence: _____**

Race:
❑ White
❑ American Indian/Alaskan Native
❑ Black or African American
  ❑ African American ❑ African
  ❑ American-born African ❑ Caribbean Black
❑ Native Hawaiian/Pacific Islander
  ❑ Guamanian or Chamorro ❑ Samoan
  ❑ Native Hawaiian ❑ Other Pacific Islander
❑ Asian
  ❑ Chinese ❑ Indian ❑ Laotian ❑ Thai
  ❑ Cambodian ❑ Japanese ❑ Pakistani ❑ Vietnamese
  ❑ Filipino ❑ Korean ❑ Taiwanese ❑ Other
❑ Some other race
❑ Choose not to disclose

Proton Pump Inhibitor (PPI) use within 30 days: ☐ Yes ☐ No

If yes – medication name

_____

Antibiotic use within 30 days: ☐ Yes ☐ No

If yes – antibiotic name, dose, duration

_____

Probiotic use within 30 days: ☐ Yes ☐ No

If yes – frequency (daily, weekly)

_____

Steroid use (other than inhaled or topical) within 30 days: ☐ Yes ☐ No

If yes – medication name, dose, duration

_____

Primary diet (select one):

☐ Vegetarian (vegetables and some animal products such as eggs and milk)

☐ Vegan (no animal products)

☐ Omnivore (both animal and plant products)

High fiber (>20 g fiber/day) diet: ☐ Yes ☐ No

Please scan and e-mail to Pam Skaran (skaran.pamela@mayo.edu)

APPENDIX 5 TBCRC Stool Collection Kit

Instruction

KIT CONTENTS

1. Fecal collection tube (with pre-affixed barcode)
2. Coring brush
3. Plastic bulb pipette (for collection of loose stool)
4. 2 Feces Catchers (1 is a spare)
5. Plastic Ziploc bag
6. "Biohazard" bag
7. Extra Barcode label (for lab/physician use only)
8. Return padded envelope with return label and barcode

STOOL COLLECTION WITH FECES CATCHER

Feces Catcher

1. Open the Feces Catcher in the direction of the arrows.
2. Paste the Feces Catcher on the back of the toilet seat, as shown in the second image on the Feces Catcher.
3. Avoid water coming in contact with the Feces Catcher.
4. After defecating, take the sample as indicated in the subsequent instructions for the Fecal Collection Tube.
5. After taking the sample, loosen the Feces Catcher on both ends and press the ends together.
6. Drop the Feces Catcher in the toilet, wait until the paper is soft and can easily be flushed down the toilet

CORING BRUSH

FECAL COLLECTION TUBE

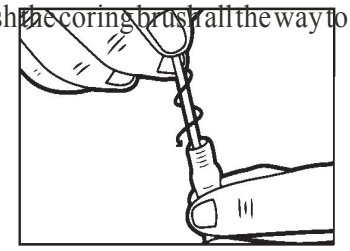
RETURN ENVELOPE

PLASTIC BULB PIPETTE

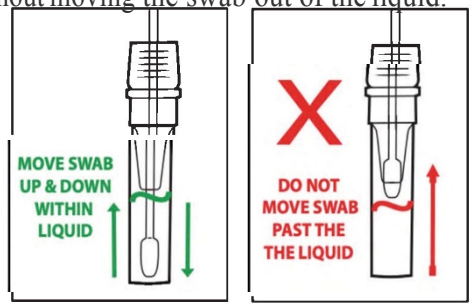
FECAL COLLECTION TUBE INSTRUCTIONS

1. Remove the pre-sterilized coring brush from its package.
2. Use the coring brush to poke stool repeatedly (10-12 consecutive pokes) in multiple different locations to get a representative sample of the entire stool.
3. Once the sample is collected on the coring brush (after all pokes of the stool have been

completed), Pickup the fecal collection tube and hold steady in one hand. Slowly twist the coring brush into the vial with a corkscrew motion. There will be resistance but push the coring brush all the way to the bottom of tube.



4. Hold vial steady and move coring brush up and down rapidly inside the tube 10-15 times without moving the swab out of the liquid.



5. At this point remove and discard the coring brush: Hold vial firmly and remove swab by slowly twisting out with a corkscrew motion.
6. Discard brush in the trash. DO NOT PLACE SWABS IN THE BIOHAZARD BAG.

SAMPLE RETURN SHIPMENT

1. Place the Fecal Collection Tube into the plastic Ziploc bag and seal the bag.
2. Place the bagged tube into the "biohazard" bag and seal the bag.
3. Place the "biohazard" bag into the provided pre-addressed FedEx mailer, seal the mailer, call for FedEx pick-up or drop off at FedEx location convenient for you

[redacted]

NSTRUCTIONAL VIDEO:

[redacted]