MD Anderson IND Sponsor Cover Sheet

Protocol ID	2016-0096
Protocol Title	A phase II study of anti-PD-1 (pembrolizumab) in combination with hormonal therapy during or after radiation in patients with hormone receptor (HR)-positive localized inflammatory breast cancer (IBC) who did not achieve a pathological complete response (pCR) to neoadjuvant chemotherapy.
Phase	Phase II
Protocol Version	17
Version Date	11/17/2023
Protocol PI	Bora Lim
Department	Breast Medical Oncology
Investigational Products	Pembrolizumab
IND Sponsor	MD Anderson Cancer Center
IND #	132505

SPONSOR: MD Anderson Cancer Center

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A phase II study of anti-PD-1 (pembrolizumab) in combination with hormonal therapy during or after radiation in patients with hormone receptor (HR)-positive localized inflammatory breast cancer (IBC) who did not achieve a pathological complete response (pCR) to neoadjuvant chemotherapy.

IND NUMBER: 132505

TABLE OF CONTENTS

1.0 TRIAL SUMMARY

Abbreviated Title	pembrolizumab and hormonal therapy for HR positive IBC as adjuvant therapy
Trial Phase	*II*
Clinical Indication	Anti-PD-1 immunotherapy for primary inflammatory breast cancer
Trial Type	Open label, non- randomized, single center
Type of control	None
Route of administration	IV (pembrolizumab), PO (hormonal agent)
Trial Blinding	No
Treatment Groups	one
Number of trial subjects	37
Estimated duration of trial	*3-4 years*
Duration of Participation	3

2.0 OBJECTIVE(S) & HYPOTHESIS (ES)

Primary Objective:

1. To determine the disease free survival (DFS) at 2 years of patients with maintenance therapy using pembrolizumab in combination with standard adjuvant hormonal therapy.

Hypothesis: Pembrolizumab maintains the disease-free status of patients with HR-positive primary IBC who have less than pathological complete response from neoadjuvant chemotherapy.

2. To determine the safety and toxicity profile of primary IBÇ patients who received combination of pembrolizumab and hormone receptor blockade.

Exploratory Objective

To investigate the association between immune related biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, with safety and efficacy for IBC patients treated with pembrolizumab.

3.0 BACKGROUND & RATIONALE

3.1 Background

3.1.1 Inflammatory breast cancer (IBC)

Definition of IBC

IBC is currently defined, according to the clinical criteria outlined in the seventh edition of the *AJCC Cancer Staging Manual* of the American Joint Committee on Cancer[1, 2] as diffuse erythema, edema (*peau d'orange*) of the breast, often without an underlying tumor mass, in the presence of pathologic evidence of breast cancer. Histologic evidence of dermal lymphatic invasion confirms

the diagnosis but is not mandatory. Given the rarity and complexity of disease, proper management of IBC can be quite challenging. It is challenging for both patient and clinicians. Even after timely diagnosis is successfully made, it is critical to plan ahead before actual implementation of treatment. As team-approached multi-modality treatment is critical in management of this aggressive disease by experienced team, it is recommended for physicians to seek out collaborative approach or early referral of patients to a more experienced center. If the patient is proactively looking for different options of treatment, referral of patients to early phase clinical trials is highly recommended. The frequency of each subtype within breast cancer is different in IBC versus non-IBC. Due to poor survival of patients and heterogeneity of tumor, the designing of clinical trials is challenging while it is mandated.

The largest proportion of breast cancers is hormone receptor (estrogen and progesterone) positive. The incidence hormone receptor positive tumors is up to 75-80% of all breast cancers and rising[3]. The growth and survival of this subtype of breast cancer is largely dependent on female hormone supply[4], and understanding of this biology is essential for treatment design. Breast cancers that express hormone receptors (either estrogen or progesterone) but not HER2 protein are categorized as luminal an intrinsic subtype[5]. Luminal A subtype of breast cancer has the best prognosis amongst all subtypes, but still up to 20% of early stage luminal a breast cancer patients develop breast cancer recurrence by 10 years after completion of initial treatment without adjuvant treatment[3]. Two main adjuvant therapy modalities are cytotoxic chemotherapy and endocrine (hormone receptor blocking) therapy. Both adjuvant treatment modalities improve disease free survival, and overall survival in hormone receptor positive breast cancer patients[6]. The prognosis of hormone receptor positive inflammatory breast cancer patients is worse than that of non-inflammatory breast cancer[7]. Even among hormone receptor (HR) positive subtype, that has the best prognosis among all subtypes, the recurrence rate is still as high as 40%. Pathological complete response (pCR), as in non-IBC, has been shown to be a critical predictive marker of survival in IBC patients. Importantly, while the predictive value of pCR in estrogen receptor (ER) positive non-IBC patients is less clear, the patients with HR positive IBC who did not achieve pCR after neoadjuvant chemotherapy clearly had worse clinical outcome. pCR in IBC is poor in every subtype of breast cancer, as shown in Table 1. Table 1 lists the pCR rate in all subtypes of IBC patients of MD Anderson.

Table 1. Summary of pCR in IBC patients, data collected from 1989 – 2011, MDACC

	TNBC	ER+/HER2-	ER+/HER2+	ER-HER2+
pCR in IBC	12%	7.4%	30%	15%
Historic pCR in non-IBC	30-40%	7-16% *but not clearly related to worse clinical outcome	35%	40-60%

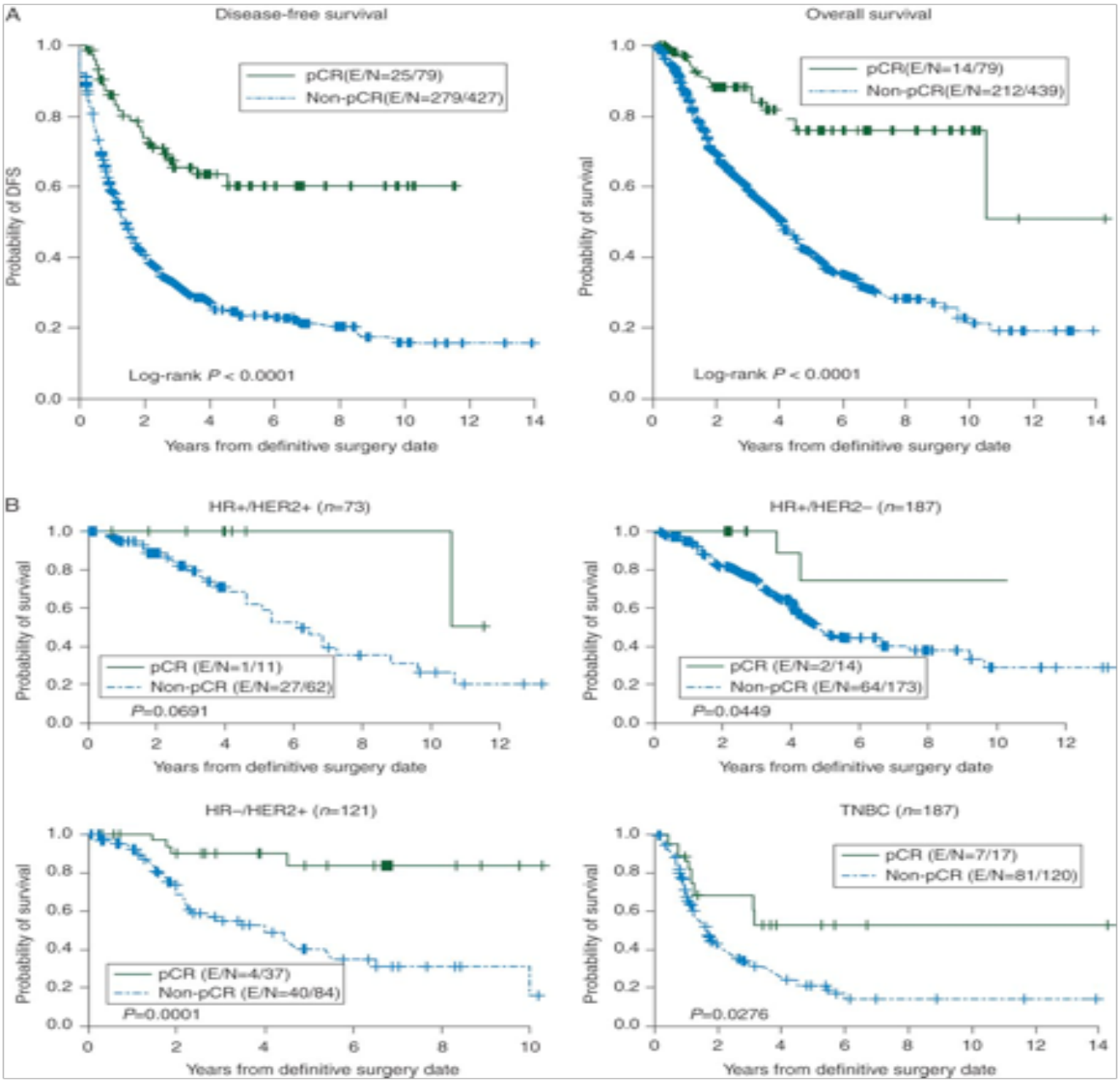


Figure 1.
Disease outcomes as a function of pCR status across molecular subtypes of IBC
Steven J. Van Laere et al. Clin Cancer Res 2013;19:4685-4696

Despite a significantly worse outcome, the standard treatment of HR positive IBC after the completion of neoadjuvant systemic therapy is the same as that of HR positive non-IBC. Selective estrogen receptor modulators (SERM), represented by tamoxifen or aromatase inhibitor (AI), are used for adjuvant endocrine therapy for HR positive HER2 negative IBC patients after surgery regardless of achieving pathologic complete response (pCR). Tamoxifen has been studied over 3 decades among thousands of women, as a primary and secondary preventive therapeutic. It is estimated that 400,000 or more women are alive as a result of tamoxifen therapy worldwide, and

millions of women achieved extended disease free survival[8]. A 15-year review of Early Breast Cancer Triallists' Collaborative Group (EBCTC) concluded that tamoxifen successfully reduced the absolute rate of breast cancer recurrence in HR positive early stage breast cancer by 13% ($p<0.00001$) and breast cancer related mortality by 9.1% ($p<0.00001$)[9]. A 5-year duration of adjuvant tamoxifen has been standard of care for years; however, recently data from the pragmatic ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) trial suggested a change in the duration of adjuvant therapy. This trial accrued 80,000 women and randomized them either to extend the tamoxifen therapy for 10 years or to stop therapy at 5 years, as previously recommended. The extend treatment arm showed a 4% improvement in breast cancer related mortality[10]. In post-menopausal women, AI is the regimen of choice, based on trials that showed an improvement in efficacy compared to tamoxifen. ATAC (anastrazole, tamoxifen, alone or in combination) compared anastrazole and tamoxifen as adjuvant therapy in postmenopausal women. After a median follow-up of 68 months, anastrazole showed significantly prolonged disease-free survival compared to tamoxifen (575 events with anastrozole vs 651 with tamoxifen, hazard ratio 0.87, 95% CI 0.78-0.97, p=0.01), time-to-recurrence (402 vs 498, 0.79, 0.70-0.90, p=0.0005), significantly reduced distant metastases (324 vs 375, 0.86, 0.74-0.99, p=0.04) and contralateral breast cancers (35 vs 59, 42% reduction, 12-62, p=0.01)[11].

The current multi-modal approach to treatment of localized IBC is neoadjuvant chemotherapy, followed by local therapy which consists of modified radical mastectomy and axilla lymph node dissection followed by radiation to the chest wall and regional nodal basins. The approach to radiation therapy in inflammatory breast cancer has been refined over time, largely by the MD Anderson team of IBC-specialist radiation oncologists to include hyperfractionated regimens with a higher total dose delivered in twice-a-day schedules for patients at higher risk of locoregional recurrence. These patients include patients younger than age 45, those with significant residual disease post-chemotherapy and those in whom positive/close margins were left after surgical resection. For patients with IBC, the total dose used at MD Anderson is 66Gy, delivered as either 33 fractions of 2Gy, once per day, or 44 fractions of 1.5Gy delivered in twice-daily sessions over 22 days.

3.1.2 Preclinical and Clinical Trial Data of pembrolizumab (See Investigator's Brochure version 9 for details)

3.1.2.1 Preclinical Data

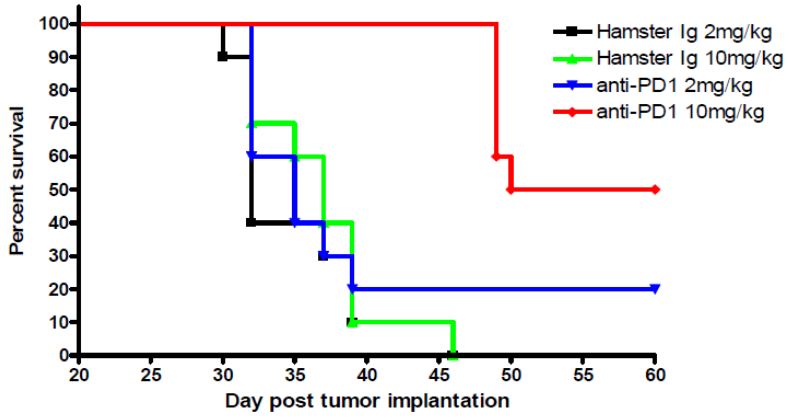
Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with its two receptors, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is being advanced for clinical development as an IV immunotherapy for advanced malignancies.

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 subjects, and nonhuman primates. In T-cell activation assays using human donor blood cells, the half-maximal effective concentration (EC50) has been approximately 0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and levels of other cytokines were 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 (PBMC) 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 anti–murine 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 resulted in increased complete tumor regression rates. Studies also revealed that immunosuppressive doses of dexamethasone in combination with agents used in standard-of-care treatment for non small cell lung cancer (NSCLC) does not reduce the anti-tumor efficacy of an anti–murine PD-1 surrogate antibody. The tumor growth curves in Figure 2 show that anti-mouse PD-1, administered at a dose of 10 mg/kg, potently inhibited the subcutaneous growth of MC38 colon adenocarcinoma tumors in most animals. In addition to inhibiting tumor growth, anti-mouse PD-1 administered at a dose of 10 mg/kg induced complete tumor regression in 50% of the animals, resulting in long-term tumor free survival (Figure 2). At the 2 mg/kg dose, two of 10 mice in this experiment experienced complete rejection of their tumor. None of the mice treated with either dose of the control antibody demonstrated complete rejection of their tumor.

Effects of Anti-PD-1 Monoclonal Antibody Monotherapy on Survival in MC38 Tumor Model



Anti-mouse PD-1, as a monotherapy, demonstrated efficacy in several syngeneic mouse tumor models including MC38 (colon adenocarcinoma, C57Bl/6 mice), C1498 (acute myeloid leukemia, C57Bl/6 mice), PDV6 (squamous cell carcinoma, C57Bl/6), and A20 (B cell lymphoma, Balb/c).

The combined treatment of MC38 colon adenocarcinomas with 5-FU and anti-mouse PD-1 showed a significant increase in anti-tumor efficacy over the individual monotherapy groups. This increased efficacy was reflected in a 60% complete regression rate in the combined treatment protocol. In the monotherapy groups, anti-PD-1 alone induced 20% (two out of ten) complete responses, whereas none of the mice treated with control antibody or 5-FU plus control antibody demonstrated complete regression.

The treatment of MC38 colon adenocarcinomas with combination therapy consisting of gemcitabine and antimouse PD-1 showed a significant increase in anti-tumor efficacy over that of the individual therapies. This increased efficacy was reflected in an 80% complete regression rate in the combined treatment protocol. By comparison, gemcitabine plus control antibody or anti-PD-1 alone resulted in 20% complete regression, whereas control antibody alone did not induce any regressions.

Pembrolizumab administered once every other week over a 6-month duration to cynomolgus monkeys was well tolerated with systemic exposure (area under the curve; AUC) up to approximately 67,500 µg day/mL and the no observed effect level (NOEL) was ≥200 mg/kg/dose (the highest dose tested).

The safety of pembrolizumab was characterized in the 1-month repeat-dose toxicity study in cynomolgus monkeys when administered as IV doses of 6, 40 or 200 mg/kg once a week (a total of five doses) and in the 6-month repeat-dose toxicity study in cynomolgus monkeys when administered as IV doses of 6, 40 or 200 mg/kg every other week (a total of 12 doses). Pembrolizumab was well tolerated in cynomolgus monkeys with a systemic exposure (AUC) of up to approximately 170,000 µg.day/mL over the course of the 1-month study, and with a systemic exposure (AUC) of up to approximately 67,500 µg.day/mL over the course of the 6-month study. No findings of toxicological significance were observed in either 1-month or 6-month toxicity study with pembrolizumab and the NOEL was ≥200 mg/kg. In addition, no findings of toxicological relevance were observed in the in vitro tissue cross-reactivity study using human and cynomolgus monkey tissues. There were no nonclinical findings that would preclude testing of pembrolizumab in clinical trials.

3.1.2.2 Clinical Data

As of November 2014, there are 18 clinical trials studying the safety and efficacy of pembrolizumab treatment in subjects with hematologic malignancies and solid tumors.

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.

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 IPI in subjects with unresectable or metastatic melanoma who had not received prior IPI treatment. Subjects were randomized in a 1:1:1 ratio to receive pembrolizumab at 10 mg/kg Q2W, 10 mg/kg Q3W, or IPI 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 triple negative breast cancer; 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.

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.

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 IPI 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 + IPI (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 + IPI 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 + IPI. 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 IPI 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.

There are several studies underway/completed studying the effects of Pembrolizumab along with radiation. A phase 1 study was performed in patients with metastatic solid tumors and studied the use of a short course of ablative radiation (SBRT) to 1-2 lesions followed by Pembrolizumab within 7 days. This study found the combination to be well tolerated with acceptable toxicity and a median PFS of 3.1 months[14]. In addition, secondary subset analysis of the patients in the

KEYNOTE-001 study showed that NSCLC patients who had received prior radiation had a 44% significantly reduced risk for disease progression and 42% reduction in risk of death compared to non-radiated patients[15]. Of note however, the median interval between radiation and initiation of Pembrolizumab in this study was 9.5 months.

Two other ongoing studies with Pembrolizumab and radiation are described below.

One is the Keynote-412 study, a phase 3 placebo-controlled randomized trial to investigate the efficacy of the combination of Pembrolizumab with chemoradiation in patients with locally advanced head and neck squamous cell carcinoma. The backbone chemotherapy regimen for this study is 100mg/m^2 cisplatin q3w and patients are assigned 1:1 to Pembrolizumab or placebo. Secondly, the PERM study is an investigator-initiated randomized phase II study in the United Kingdom, comparing Pembrolizumab alone to the combination of Pembrolizumab with radiation for patients with advanced melanoma. The goal of the study is to determine whether Pembrolizumab increases the response rate to radiation.

Most recently, McArthur et al reported the result of phase II study using pembrolizumab with radiation. In their study, out of the 17 women enrolled, the median age was 52 y (range 37-73y). and the median number of prior chemotherapies received for metastatic disease was 3 (range 0 to 8). Of the 8 women not evaluable at 13 weeks: 5 died secondary to disease-related complications (at weeks 2, 6, 7, 8, and 9) and 3 came off study due to disease progression prior to week 13. Of the 9 women evaluable at week 13, 3 (33%) had a partial response, 1 (11%) had stable disease and 5 (56%) had disease progression. The 3 partial responses represented 60%, 54%, and 34% decreases in tumor burden by RECIST v1.1 and were durable for 31, 21, and ongoing at 22 weeks, respectively. The stable disease response was durable for 22 weeks. Common toxicities were mild and included fatigue, myalgia and nausea. [Clinical trial information: NCT02730130]

Emerging data suggests that the combination of radiation therapy and immune checkpoint blockade is not only safe but may have synergistic efficacy based on the immune priming hypothesis. Both in animal models as well as patients, radiation therapy may enhance the immune response against tumor cells outside of the radiated field, a phenomenon known as the abscopal effect. The mechanistic basis for this abscopal effect is pleiotropic: (1) RT induced apoptosis of tumor cells results in release of tumor-associated antigens and immunoregulatory cytokines, which function as an in-situ vaccine. Antigen-presenting cells take up the antigen fragments and the cytokines support the maturation and proliferation of activated T cells. (2) RT induces MHC I expression which may abrogate intrinsic resistance to anti-PD1 agents.

3.1.3 Rationale for the Trial and Selected Subject Population

Molecular subtypes defined by hormonal receptor (HR) and HER2 status have not been well studied in inflammatory breast cancer (IBC). We characterized clinical parameters and long-term outcomes, and compared pathological complete response (pCR) rates by HR/HER2 subtype in a large IBC patient population. We retrospectively reviewed the records of patients diagnosed with IBC and treated at MD Anderson Cancer Center from January 1989 to January 2011. Of those, 527 patients had received neoadjuvant chemotherapy and had available information on estrogen receptor (ER), progesterone receptor (PR), and HER2 status. The overall pCR rate in stage III IBC was 15.2%, with the HR-positive/HER2-negative subtype showing the lowest rate (7.5%) and the

HR-negative/HER2-positive subtype, the highest (30.6%). The HR-negative, HER2-negative subtype (triple-negative breast cancer, TNBC) had the worst survival rate. HR-positive disease, irrespective of HER2 status, had poor prognosis that did not differ from that of the HR-negative/HER2-positive subtype with regard to OS or PFS[7]. The two year PFS is only 60% at two years for patients with HR-positive/HER2-negative subtype. These findings identify an unmet medical need and justify exploring a novel treatment in this population at high risk for disease relapse.

The extensive invasion of lymphatic vessels by tumor emboli in IBC patients suggests that the host immune surveillance system is suboptimal or that the tumor cells have lowered their immunogenicity through immunoediting resulting in their ability to avoid detection by the host. In the immunocompetent host, tumor cells must overcome both innate and adaptive immunologic defenses of the host. A recent publication from our group also suggests that immune pathways are active in IBC[4]. Consistent with our findings, other groups have shown that several major inflammatory signaling pathways are constitutively active in IBC and breast cancer. Among them, the NF-κB, COX-2, and JAK/STAT signaling systems seem to play a major role in the tumorigenesis of IBC. Inflammatory molecules such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ) have been shown to contribute to malignant transformation in preclinical studies of IBC, while transforming growth factor beta (TFF-β), interleukins 8 and 1β, as well as TNF-α appear to play a role in proliferation, survival, epithelial-mesenchymal transition, invasion, and metastasis.

In an ongoing study to evaluate immune function in IBC patients, we found that the median number of dendritic cell (DC) precursors was significantly lower in breast cancer patients than in healthy female donors (HFDs). Moreover, the median number of myeloid-derived dendritic cells (mDCs) in the peripheral blood of locally advanced breast cancer (LABC), IBC, and metastatic IBC (MIBC) patients was lower than the number of mDCs in the peripheral blood of HFDs. Because mDC and plasmacytoid dendritic cell (pDC) subsets determine the type of helper (Th1/Th2) or cytotoxic (Tc1/Tc2) effector responses, our data suggest that Th1 and Tc1 responses are compromised in patients with LABC, IBC, and MIBC. We observed a significantly lower median number of pDCs in IBC and MIBC patients than in HFDs, but the same was not true for the median number of pDCs in LABC and MBC patients compared with the number of pDCs in HFDs. These data suggest that Th2 and Tc2 responses may be lower in IBC and MIBC patients than in HFDs[5].

In addition, a total of 87 IBC patients treated with neoadjuvant chemotherapy were eligible for gene expression analysis: 59 patients had RD [residual disease (no pCR)] and 28 (32%) had a pCR. We compared the pCR and RD groups with respect to histoclinical features, molecular subtypes, and several GES. We identified two immune pathways (IFNα- and INFγ-pathways) as hyperactivated in samples from patients with pCR (P = 0.015 and P = 0.001 respectively, Mann−Whitney test), as well as three pathways (EGFR, P53, TGBβ) as hypoactivated in patients with pCR (P = 0.015, P = 0.015, P = 0.004, respectively). Transcription factor (TF) analysis revealed three transcription factors (STAT5: P = 3.6E- 05, GLI: P = 8.7E−04, SMAD: P = 9.6E−04, Mann–Whitney test) as hypoactivated in samples from patients with pCR after correction with false discovery rate (FDR) inferior to 20%. In the learning set, significant analysis of microarrays (SAM) (FDR inferior to 25%) identified 124 differentially expressed probe sets (107 unique genes), between responders and nonresponders, all of which were overexpressed in samples with

pCR. Several processes related to T-cell- dependent immune responses were strongly overrepresented in this gene list, including the 'T-cell receptor signaling' canonical pathway[6].

These data provide the rationale for using anti-PD-1 maintenance therapy to maintain the progression-free status for IBC patients with HR-positive/HER2-negative subtype. Chemotherapies, surgery, radiation therapy can debulk the disease volume but cannot be used for maintenance. Therefore, using an anti PD-1 monoclonal antibody combined with standard adjuvant hormonal therapy is a very promising approach for these patients for whom currently nothing else has been proven to sustain the initial response to treatment and is a significant unmet need for patients with HR positive primary inflammatory breast cancer.

3.1.4 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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.

Apart from the phase 1 study with Pembrolizumab and SBRT that is already published, there is published safety data from the phase 3 study PACIFIC in non-small-cell lung cancer with the PD-1 antibody Durvalumab[16]. The PACIFIC study included stage III NSCLC patients who had not progressed following definitive chemoradiation and showed both an increase in PFS by 11 months in the Durvalumab group as well as no significant difference in toxicity between groups. Of specific note, the incidence of grade 3/4 pneumonitis was 3.4% versus 2.6% in the placebo arm. This is encouraging given that the majority of patients in that study received definitive lung radiation to a dose of 54-66Gy. For patients with IBC, post-mastectomy radiation is a key part of trimodality treatment, and our typical target dose for the chest wall is in this range, hence lung dose would be considerably less, so we would not expect significantly higher rates of pneumonitis as a result of the concurrent radiation.

3.1.5 Study Endpoint

Up to 40% of patients with HR positive IBC who received pre-operative chemotherapy who did not achieve pCR will eventually have disease progression. The goal of this clinical trial is to observe clinical activity signals of pembrolizumab for disease stabilization or control as a maintenance therapy when given with combinatorial adjuvant HR blockade. The efficacy endpoint is to evaluate pembrolizumab[12].

4.0 METHODOLOGY

4.1 Entry Criteria

In order to be eligible for participation in this trial, the subject must meet the following criteria:

4.1.1 Inclusion Criteria

1. Is willing and able to provide written informed consent for the trial.

2. Is a female or male and >/= 18 years of age

3. Has histological confirmation of breast carcinoma.

4. Has confirmed inflammatory breast cancer by using international consensus criteria:

Onset	Rapid onset of breast erythema, edema and/or peau d'orange, and/or warm breast, with/without an underlying breast mass
Duration	History of such findings no more than 6 months
Extent	Erythema occupying at least 1/3 of whole breast
Pathology	Pathologic confirmation of invasive carcinoma

5. Did not achieve pathological complete response (pCR) to any chemotherapy that was given with the intention to induce best response prior surgery. pCR is defined as the current American Joint Committee on Cancer (AJCC) breast cancer staging.

6. Is HER2 normal, defined as HER2 0 or 1+ by IHC and negative by FISH if performed; or HER2 is 2+ by IHC and negative by FISH; or HER2 negative by FISH if IHC is not performed.

7. Has positive ER or PR status. ER or PR >/= 10%

8. Has a performance status of 0-1 on the ECOG Performance Scale.

9. Has adequate organ function as determined by the following laboratory values:
   ANC >/= 1,500 /mcL, Platelets >/=100,000 /mcL, Hgb >/= 9 g/dL, creatinine levels < 1.5 x ULN, Total bilirubin </= 1.5 x ULN, ALT and AST </= 2.5 x ULN

10. 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): (1) intrauterine device (IUD); (2) vasectomy of a female subject's male partner; (3) contraceptive rod implanted into the skin. Combination method (requires use of two of the following): (1) diaphragm with spermicide (cannot be used in conjunction with cervical

cap/spermicide); (2) cervical cap with spermicide (nulliparous women only); (3) contraceptive sponge (nulliparous women only); (4) male condom or female condom (cannot be used together); (5) hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

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.

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).

11. Has negative serum or urine pregnancy test for subjects of childbearing potential within 10 days before first dose.

12. Have completed radiation (if candidate for post-mastectomy radiation) or plans to begin radiation and endocrine therapy within 28 days.

13. If the patient has already started hormonal blockade therapy after radiation as adjuvant therapy, the patient is eligible as long as the hormonal therapy was initiated no more than 6 months before the screening day and the patient can start the study drug within 4 weeks since the completion of screening.

4.1.2 Exclusion Criteria

1. Is currently participating in a study of an investigational anti-cancer agent.

2. Has a diagnosis of immunodeficiency or any other form of immunosuppressive therapy.

3. Has not recovered from adverse events due to prior therapies, i.e. monoclonal antibody, chemotherapy, targeted small molecule therapy, radiation therapy, or surgery.

    - Note: Subjects with ≤ Grade 2 neuropathy, alopecia and general disorders and administration site conditions (per CTCAE version 4.0) are an exception to this criterion and may qualify for the study.

4. Has a known history of prior malignancy with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or in situ cervical cancer, and has undergone potentially curative therapy and has no evidence of recurrence over the last 1 year since completion of curative therapy.

5. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators, inhaled steroid or local steroid injections to the skin would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjögren's syndrome will not be excluded from the study.

6. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

7. Has an active infection requiring systemic therapy.

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

9. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

10. Has a known history of Human Immunodeficiency Virus (HIV).

11. Has a known active Hepatitis B or Hepatitis C

12. Have received a live vaccine within 30 days prior to the first dose of trial treatment.

13. Gastrointestinal tract disease or defect or previous history of colitis.

14. Has proven or suspected distant metastasis that involves occurrence of breast cancer outside of loco-regional breast and lymph nodes area.

15. Subjects requiring daily corticosteroids either via po or infusion

16. Myocardial infarction within 6 months before starting therapy, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or unstable cardiac arrhythmia requiring medication.

4.2 Treatment Plan

The treatment to be used in this trial is outlined in Table 1 below.

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
pembrolizumab	200 mg	Every 3 weeks	IV infusion	Up to 24 months or until meet drug discontinuation criteria (See 4.5)	Experimental

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
The pembrolizumab dosing interval may be increased due to toxicity described in 4.2.2.					

Based on our experience with very minimal side effects observed in the first 3 evaluable patients (see Table 2) as well as the design of another adjuvant Pembrolizumab study ongoing in triple negative breast cancer, physician follow-up will be reduced to every 2 cycles during the study due to the known side effect profile of Pembrolizumab.

Table 2: Interim safety analysis (3 evaluable patients, as of November 2017)

AE	Grade	Total # of patients
Fatigue	Grade 1	2
Nausea	Grade 1	1
Hot flashes	Grade 1	2
Headaches	Grade 1	1
Agitation	Grade 1	1
Skin itching	Grade 1	2
Vomiting	Grade 1	1
Dizziness	Grade 1	1
Eye disorders - eyelash thinning	Grade 1	1
Arthalgia	Grade 1	1
Rash	Grade 1	1

Based on emerging safety and efficacy data, as described in section 3.1.4, study treatment may be given concurrently with radiation based on physician and/or patient preference, but is not required. For patients consented prior to radiation who meet other eligibility criteria to allow concurrent radiation, pembrolizumab treatment will begin 7 days (±3 days) after initiating radiation. During radiation, adverse events will be collected weekly, and patients will continue twice-weekly/weekly follow up visits with radiation oncologists as per standard procedure at MD Anderson for IBC patients receiving radiation. Special attention will be placed to minimize off-target dose to the lung, owing to the risk for pneumonitis in patients receiving immune checkpoint therapy.

4.2.1 Dose Selection

4.2.1.1 pembrolizumab: Each cycle is defined as 3-week interval. pembrolizumab 200 mg will be administered on day 1 of each cycle as approximately 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 4.2.2). Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

The Procedures Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

4.2.1.2 Hormonal Therapy: The hormone receptor blockade agent would be on physicians' discretion including tamoxifen, exemestane, anastrozole, letrozole, LHRH agonist and combination with any of above.

4.2.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 4.4 for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification Guidelines for pembrolizumab Related Adverse Events:

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[a]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[b]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[a] 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; Refer to section 4.4 Table 4 – Infusion Treatment Guidelines for further management details.
[b] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing 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 Sponsor. The reason for interruption should be documented in the patient's study record.

In case toxicity does not resolve to Grade 0-1 or baseline within 12 weeks after last infusion, trial treatment will be discontinued. Subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab will be discontinued from trial treatment.

4.3 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 final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.3.1 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. Concomitant medication will be recorded as standard of care in clinic database.

4.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the study.

- 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral)

vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Glucocorticoids for any purpose other than to modulate symptoms of suspected immunologic etiology.

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.

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

4.4 Rescue Medications & Supportive Care

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

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Table 3 for dose modification.

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 **T1DM** 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**:
  - 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 3-4** 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 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 4 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	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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.**	
<u>Grades 3 or 4</u> 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: Life-threatening; pressor or ventilatory support indicated	**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 deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.5 Subject Withdrawal/Discontinuation Criteria

In this study, pembrolizumab administration will continue until one of the following conditions is observed.

4.5.1. Disease progression [RECIST Criteria 1.1.]

Disease progression is defined as rapid growth of multiple measurable or non-measurable lesions. (Note: the appearance of one or more new lesions is also considered progression).

4.5.2 Noncompliance:

If the patient is not able to remain compliant with the treatment schedule in the absence of toxicity, the study treatment should be discontinued for the patient.

4.5.3. Sustained side effects:

Study treatment will be discontinued for patients who have sustained toxic effects that are attributed to the study drug and require a dose interruption lasting more than 12 weeks.

4.5.4. Initiation of new anticancer treatment:

In patients for whom the investigator, in his or her judgment, determines new treatment for breast cancer is warranted, the study treatment may be discontinued.

4.5.5. Patient withdraws consent.

In the event that a patient withdraws consent, the reason(s) for withdrawal must be documented. Patients must be informed that their participation in the study is voluntary and that they may choose not to take part in the study or to stop taking part at any time. If a patient chooses not to take part in the study or to stop at any time, his/her future medical care or medical benefits will not be affected.

4.5.6. Patient has completed 24 months of treatment. However, if the patient remains progression free, she/he will continue the hormonal blockade therapy to complete a total of 5 years to 10 years based on the risk stratification and the discretion of the physician. Patient will be taken off-study after completion of Pembrolizumab.

4.6 Criteria for Disease Control

The purpose of this study is to maintain progression free status by additional immune modulation with pembrolizumab to enhance the surveillance and suppression of tumor that is currently done only by hormone receptor blocking agents.

4.6.1. Response will not be considered evaluable in the following categories:

4.6.1.1. Early Deaths: Patients who die within the first 2 weeks of the initiation of drug therapy owing to concurrent disease. These cases will be considered treatment failures in the intent-to-treat analysis.

4.6.1.2. Lost to Follow-up: Patients for whom there is inadequate information to judge tumor response because of loss of contact with our institution (>2 months after a missed appointment) and with referring physician in spite of repeated attempts to locate them. These cases will be considered treatment failures in the intent-to-treat analysis.

4.6.1.3. Major Protocol Violation: Patients who significantly deviate from the treatment program by either adding or deleting another agent or another therapeutic maneuver or by modifying schedule substantially (delay treatment ≥7 days without administration reason) of the drug under evaluation. Patients who do not fulfill the requirements outlined under Patient Eligibility are also included in this category. Patients on the concurrent radiation arm due to excess toxicity who do not complete the planned radiation will not be considered violations if they continue systemic therapy per protocol plan

5.0 STUDY FLOW CHART

Trial Period:	**Screening Phase**	**Treatment Cycles**								**End of Treatment** [h]	**Post-Treatment**	
						8 cycles and beyond						
Treatment Cycle/Title:	Screening /Baseline	1	2	3	4	5	6	7	8	If patient returns to clinic	Safety follow up f	Follow Up [g]
Scheduling Window (Days):			± 3	± 3	± 3	± 3	± 3	± 3	± 3		1 month after last dose	24 months
Informed Consent	x											
Inclusion/Exclusion Criteria	x											
Demographics and Breast Cancer History [a]	x											
Concomitant Medication Review per SOC	x											
Physical Exam [b], V/S	x	x		x		x		x		x		
Adverse Events [b]	x	x	x	x	x	x	x	x	x	x	x	
ECOG Performance Status [b]	x	x	x	x	x	x	x	x	x	x		
Pregnancy Test – Urine or Serum β-HCG (for women with childbearing potential)	x											
CBC and Biochemical Profiles [c]	x	x	x	x	x	x	x	x	x	x		
TSH, Free T4 and Total cortisol[i]	x			x		x		x		x		
Radiological Evaluation as clinically indicated and as SOC [d]	x									x		
Archived biopsy and/or surgical specimens (block or unstained slides) obtained at any time prior to treatment.	x											
Correlative Studies Blood Collection [e]	x				x			x		x		
Optional tumor sample collection at disease progression, if the site is accessible										x		
Disease Progression Status												x
Pembrolizumab Administration		x	x	x	x	x	x	x	x			
Hormonal Therapy		x	x	x	x	x	x	x	x			
Radiation Therapy [j]		x	x									

a. Demographics include patient's age, gender and race. Medical history includes primary breast cancer pathological diagnosis, ER/PR/HER2 status. Prior therapies and procedures for breast cancer,

b. Complete physical exam, ECOG performance status and adverse events assessment during the screening period will not be repeated if done within 30 (+/- 3 days) days before the start of treatment. Physical exam will be performed every 2nd cycle throughout the study unless the patient is having side effects that require more frequent monitoring. Adverse events will be collected each cycle – on cycles when a physician follow-up is not scheduled, the study coordinator will meet with the patient to review these. For patients who are receiving concurrent radiation with study treatment, adverse events will be monitored on a weekly basis during the radiation therapy period.

c. Hematologic and biochemical profiles (CBC, albumin, alkaline phosphatase, ALT, AST, LDH, uric acid, calcium, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, total protein, BUN, as standard of care (will not be repeated if done within 30 (+/- 3 days) days before the start of treatment). During treatment, an earlier evaluation will be performed if clinically indicated.

d. Radiological evaluation may include CT of the chest, and/or abdomen, and/or pelvis, ultrasound, bone scan and X-Rays as clinically indicated for standard of care. PET/CT, chest wall/breast photos, EKG and ECHO or MUGA may also be performed as indicated for standard of care. If follow up evaluations are necessary, the same method of evaluation, specific to the subject's condition, will be performed as clinically indicated. Patients without symptoms of recurrent or cardiac toxicity will not receive imaging per national guidelines.

e. Peripheral blood and serum for correlative studies. Approximately 50 cc of blood will be drawn at baseline, and after every 3 cycles (i.e. after 3rd, 6th, 9th, 12th, etc) and at disease progression (if applicable). Patients who remain on study for all 34 cycles will not have the last sample drawn before cycle 34. The last blood collection for these patients who complete all 34 cycles of study treatment will be at the end of study visit after the 34th cycle of Pembrolizumab

f. 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. Safety Follow-Up Visit can be done in the clinic, or by phone if patient is not willing to come to the clinic for follow up.

g. Disease progression status follow up: 24 months after the first treatment of the study regimen for patients who were taken off study treatment for reasons other than disease progression.

h. The end of 24 months of treatment or until meet drug discontinuation criteria, whichever occurs first.

i. TSH, Free T4 and Total cortisol level will be monitored at baseline, then every 2 cycles and at disease progression as standard of care.

j. Patients may begin Pembrolizumab and endocrine therapy concurrently with radiation or after radiation based on physician discretion. For patients receiving concurrent radiation and study treatment, radiation will begin 7 days (+/- 3 days) prior to administration of pembrolizumab and initiation of endocrine therapy. Concurrent pembrolizumab and radiation is not required.

6.0 COLLATERAL RESEARCH

Correlative research will be performed on biologic specimens from patients enrolled. Original tumor tissue will be collected prior to treatment [primary tumor biopsy, mastectomy, skin biopsy which has been already being archived]. Peripheral blood will be collected prior to beginning pembrolizumab at baseline & after every 3 cycles (i.e. after 3rd, 6th, 9th, 12th, etc), and at the time of progression, whichever occurs first. Tumor collection at the time of progression is an optional procedure. These samples will be used to perform correlative studies aimed at identifying predictive markers and to enhance understanding of disease biology.

6.1 Biomarker assessments

Tumor tissue and peripheral blood will be collected prior to therapy and at selected time points on treatment. Residual sample material available after completion of the designated analyses may be used in the future for identification of additional predictive markers or to enhance understanding of disease biology. If biomarker samples are drawn but study drug is not administered, samples will be retained. A description of each assay system is described below.

6.1.1 Tumor samples

Archived biopsy and/or surgical specimens (block or unstained slides) obtained at any time prior to treatment will be collected from all consenting subjects. Optional biopsies will be obtained from patients who have disease progression and have accessible lesions.

Immunohistochemistry (IHC) will be used to assess the immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin-embedded tumor tissue. PD-L1 IHC will be performed by both MD Anderson and QualTek.

These IHC analyses will include but not necessarily be limited to:

1) Characterization of immune cells (CD3, CD4, CD8, CD25, FOXP3, CD68);

2) Expression of co-stimulatory and co-inhibitory markers (PD-1, PD-L1, LAG-3, TIM-3, ICOS, OX40);

3) Genomic mutations,

4) T cell clonality.

6.1.2 Blood samples

<u>Collection and processing</u>

Multiple blood draws will be required for this trial. All blood tubes will be labeled only with the patients' unique study number. Approximately 50cc will be drawn for each immunologic

assessment (at baseline; after every 3 cycles & prior to next dosing; and at disease progression). 10cc will be collected into a BD Vacutainer Rapid Serum tube (BD, Franklin Lakes, NJ) which contains a clot activator and silicone coated interior. After centrifugation, serum will be collected, aliquoted in 1cc vials and frozen. 20cc will be collected into BD Vacutainer CPT Cell Preparation tubes which contain an anticoagulant (sodium heparin or sodium citrate) with FICOLL HYPAQUE density gradient fluid and a polyester gel barrier. The density gradient fluid and the gel barrier allow for the separation of peripheral blood mononuclear cells (PBMC) from the red blood cells by a single step centrifugation process. The PBMC fraction will be collected by centrifugation and suspended in RPMI-1640 (GIBCO, Invitrogen Corporation, Carlsbad, CA) with 10% FCS (Gemini Bio-Products, West Sacramento, CA) and antibiotics. 20cc blood will be collected in EDTA 10 ml purple top tubes for FACS assay and CTC.

Assays

Serum:

• Soluble factors such as cytokines and chemokines present in serum collected at baseline, during, and after treatment will be quantified using a multiplex assay which has the capability to simultaneously measure multiple analytes from a single sample. Factors to be evaluated may include but not necessarily be limited to IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-7, IL-10, IL-12, IL-15 and IL-17.

• Additional immunoassays will be performed to quantify soluble receptors present in the serum. Analyses may include but not necessarily be limited to soluble CD25, soluble PD-1, and soluble LAG-3.

Peripheral blood mononuclear cells:

• The proportion of specific lymphocyte subsets to include T cells, B cells, and the proportion of memory and effector T cell subsets will be quantified by flow cytometry.

• The expression levels of T cell co-stimulatory and co-inhibitory markers including but not necessarily limited to PD-1, PD-L1, other B7 family members, and ICOS will be quantified by flow cytometry.

FACS assay:

- Intracellular cytokine synthesis by T-cells activated through the T-cell receptor (TCR).
- Cytokine production by dendritic cells activated with Toll-like receptor (TLR) agonist.
- The NK cell assay.

7.0 SAFETY MONITORING AND REPORTING

7.1 Assessing and Reporting Adverse Event

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 pembrolizumab, is also an adverse event.

Adverse events may occur during the course of the use of pembrolizumab in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded 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 7.6**.** The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period as long as that subject has not undergone any protocol-specified procedure or intervention.

Adverse events will be assessed according to the CTCAE version 4.0. All study patients who have received any dose of pembrolizumab will be evaluable for safety. Unexpected adverse events including laboratory adverse events deemed clinically significant by the investigator will be graded and recorded.

The ongoing review of safety data will include review of clinical AEs and SAEs. The NCI-CTC version 4.0 will be used to grade all AEs.

The investigator will monitor subjects' AEs closely by providing Toxicity Diary to the subjects to record adverse events daily, educating the subjects to report any severe toxicities to the investigator at any time during the trial, and evaluating all AEs at each clinic visit prior to next dosing. All AEs whether observed by the investigator or reported by the subjects will be collected and reviewed,

and its association to the study drug will be determined. If a subject experiences an AE, the subject may receive appropriate treatment and supportive care as clinically indicated, or if grade a 3 non-hematological AE is deemed to be related to study drug, study drug should be held, the Investigator will continue to follow up until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution is achieved.

AEs (>/= Grade 2 non-hematological and >/= Grade 3 hematological AEs) occurring after informed consent signing observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be documented and recorded. Grade 1 non-hematological abnormal laboratory values will not be reported as AEs; however, any clinical consequences of the abnormality should be reported as AEs.

7.2 Definition of an Overdose for This Protocol and Reporting of Overdose 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 pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX: +1-215-661-6229-)

7.3 Reporting of Pregnancy and Lactation 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) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of investigational product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by

the investigator. All reported pregnancies 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 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX +1-215-661-6229)

7.4 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints of this trial will not be reported to Merck as described in Section 7.6.3. - Immediate Reporting of Adverse Events to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to Merck Global Safety within 2 working days either by electronic or paper media.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

7.5 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.

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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); 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) **(**although not serious per ICH definition, is reportable to the Sponsor and Merck); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be to the sponsor and Merck.	
	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 Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that 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 Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to 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 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

7.6 SERIOUS ADVERSE EVENT REPORTING

7.6.1 Reporting to IND Office

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

- Notable events must be recorded in the eSAE program in order to be submitted to sponsor. Reporting of notable events is the responsibility of the investigator.

7.6.2 Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.6.3 Investigator Communication with Supporting Companies:

The MDACC Internal SAE Report Form will be used for reporting to Merck Global Safety (FAX: +1-215-661-6229).

Reporting Timeline:

- Deaths that is unanticipated and definitely, probably or possibly related to study intervention that occur during and within 30 days after the last day of active study intervention will be reported to Merck within 24 working hours.

- All other SAEs that are serious, unanticipated, and definitely, probably or possibly related to study drugs will be reported to Merck within 2 working days.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Immediate Reporting of Adverse Events to Merck:

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 another important medical event

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

For the time period beginning when the consent form is signed until treatment allocation, 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 must be reported within 2 working days to 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 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 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 must be reported within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Pembrolizumab that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

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 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX +1-215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 2 working days to 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 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Pembrolizumab, as defined in Section 7.2. - Definition of an Overdose for This Protocol and Reporting of Overdose 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

Overview

This is a single-arm Phase II study of pembrolizumab in combination with standard adjuvant hormonal therapy in patients with inflammatory breast cancer (IBC). The primary endpoint is Disease-free survival (DFS) as evidenced by the patient remaining alive with continued disease control. We will use a Bayesian time-to-event monitoring design to monitor DFS to ensure patient safety. Continued disease control will be defined as no disease by imaging.

Sample Size and Power

With a total of 37 patients, assuming 80% are alive and disease-free at two years, and all patients are followed for more than 2 years after study enrollment with no dropout, a 95% confidence interval around the 2-year estimate of disease-free survival will be approximately 25% wide.

Disease-Free Survival Monitoring Rule

The primary outcome is T = the time to disease relapse. The Bayesian method of Thall, et al.[1] will be used for safety and efficacy monitoring. For the purpose of safety and efficacy monitoring, "failure" will be defined as F2YR = [T < 2 years]. The historical DFS rate in this population treated in MD Anderson Cancer center (1989-2011) for standard therapy is 60% at two years, corresponding to a failure (disease relapse) rate of 40% at two years[13]. Assuming exponential DFS times, this corresponds to m_S=median time to failure for standard therapy of 32.6 months[13]. We will then assume that m_S follows an inverse gamma (31.52, 994.99) distribution, which corresponds to a median time to failure of 32.6 months and a corresponding standard deviation of 6 months. For the experimental group, m_E= median time to failure with the experimental therapy will be assumed to have the same mean but large variance: a_E=3 and b_E=65.2. Monitoring possibly right-censored T continuously, the trial will be terminated early if $Pr(m_S < m_E \mid data) < 0.1878$. The expected accrual rate is 1 patient per month, and a maximum of 37 patients will be treated. The monitoring rules were conducted by using the MDACC Department of Biostatistics software: TTEDesigner program v1.2.2. The operating characteristics of this safety monitoring rule are summarized in Table 5, based on 2000 replications per scenario.

Table 5. Operating characteristics of the safety and efficacy monitoring rule

True Pr(F2YR)	True Median Time to Failure (Months)	Pr(Stop Early)	Mean Sample Size
0.20	74.5	0.100	34.0
0.30	46.6	0.238	30.5
0.40	32.6	0.470	25.4
0.50	24.0	0.775	19.0
0.60	18.2	0.947	13.7

Safety Run-in

At any time within first 6 patients are treated, if >=2 patients experience serious adverse events (SAE) within first 3 cycles of treatment, we will stop the trial and claim that the regimen is too toxic. An SAE is defined as an adverse event that is serious, unexpected, and related to the study drug. This study will be monitored by the IND Office. During the safety run-in and throughout the study, patients who have completed 3 cycles of treatment will be considered as evaluable for safety and response.

Analysis of Primary and Secondary Endpoints

The primary endpoint of DFS will be summarized at 2 years with a corresponding 95% confidence interval. DFS will be compared with the historical control rate of 60% at year two by using a one-sided exponential MLE test. Cox proportional hazards regression analysis will be used to model the association between DFS and disease and demographic covariates of interest, including immune-related biomarkers in the peripheral blood and tumor tissue. Overall survival (OS) from the start of the study will be analyzed similarly to DFS. Adverse events will be summarized by grade and category.

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 6 Product Descriptions

Product Name & Potency	**Dosage Form**
pembrolizumab 100 mg/ vial	Solution for Infusion

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 Sponsor 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 DATA MANAGEMENT

The Principal Investigator is responsible for assuring that the data entered into the database are complete and accurate and that data entry is performed in a timely manner.

10.1 Data collection for this study including:

1) demographic information (sex, race, and date of birth),

2) date of initial breast cancer diagnosis, pathology report of primary breast cancer, biomarker status, and date and location of distant metastases at disease progression;

3) history of breast cancer surgery, and radiation therapy, if applicable; radiation therapy timing with respect to initiation of pembrolizumab

4) date and type of chemotherapy and/or hormonal therapy for metastatic disease;

5) All AEs will be collected, however only >/=2 non-hematologic AEs and >/=3 hematological AEs will be recorded. Other abnormal laboratory values will not be reported as AEs; however, any clinical consequences of abnormality should be reported as AEs.

6) Concomitant medication will be recorded per standard of care in the electronic medical record, and will not be recorded in the study database.

7) All data collected for this study will be shared with Baylor College of Medicine (Bora Lim) with compliance of data confidentiality plan.

10.2 Data confidentiality plan

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity will be possible only after accessing a password-protected database. Access to the database will be available only to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

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APPENDIX A NEW YORK HEART ASSOCIATION'S (NYHA) FUNCTIONAL CRITERIA

Overview: The New York Heart Association (NYHA) developed a functional classification for patients with heart disease.

Patients: Heart disease must be present.

Parameters:

(1) limitations on physical activity

(2) symptoms (undue fatigue palpitations dyspnea and/or anginal pain) with ordinary physical activity

(3) status at rest

Limitations on Physical Activity	Symptoms with Ordinary Physical Activity	Status at Rest	Class
none	none	comfortable	I
slight	symptomatic with ordinary activities	comfortable	II
marked	symptomatic at less than ordinary levels of activity	comfortable	III
unable to perform any activity	discomfort with any activity	symptomatic at rest	IV

In addition the level of objective evidence was also classified:

Objective Evidence of Cardiovascular Disease	Class
no evidence of disease	A
minimal disease	B
moderate disease	C
severe disease	D

Previous Classification (1964)

The NYHA classification above was introduced with the seventh edition of the manual. The AMA criteria for permanent impairment still uses an older classification.

Limitations on Physical Activity	Symptoms with Physical Activity	Findings at Rest	Class
none	none	comfortable at rest	I

slight	symptomatic with greater than ordinary activities	comfortable at rest	II
marked	symptomatic with ordinary activities	comfortable at rest	III
any activity increases symptoms	symptomatic at less than ordinary levels of activity	may or may not be symptomatic at rest	IV

where:

• Symptoms include undue fatigue palpitations dyspnea heart failure or anginal pain.

NOTE: If you combined both the old and newer classifications you would end up with 5 classed (class I = asymptomatic at increased activity levels; class V = symptomatic at rest).

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