MD Anderson IND Sponsor Cover Sheet

Protocol ID	2014-0533
Protocol Title	A phase II study of anti-PD-1 (MK-3475) therapy in patients with metastatic inflammatory breast cancer (IBC) or non-IBC triple negative breast cancer (TNBC) who have achieved clinical response or stable disease to prior chemotherapy
Protocol Version	30
Version Date	3/10/2023
Protocol PI	Clinton Yam
Department	Breast Medical Oncology
IND Sponsor	MD Anderson Cancer Center
IND #	125866

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1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 for metastatic IBC or non-IBC TNBC
Trial Phase	*II*
Clinical Indication	Anti-PD-1 immunotherapy for metastatic IBC or non-IBC TNBC
Trial Type	Open label, non- randomized, single center
Type of control	None
Route of administration	IV
Trial Blinding	No
Treatment Groups	one
Number of trial subjects	50
Estimated duration of trial	*3-4 years*
Duration of Participation	3

2.0 OBJECTIVE(S) & HYPOTHESIS(ES)

2.1 Primary Objective(s) & Hypothesis(es)

Primary Objective: To assess the efficacy of MK-3475 as a single agent in patients with metastatic IBC or non-IBC TNBC

Hypothesis: MK-3475 maintains disease control status of patients with metastatic IBC or non-IBC TNBC who have achieved clinical response or stable disease from prior systemic therapy for metastatic disease.

2.2 Exploratory Objective

(1) To investigate the association between biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, with safety and efficacy for IBC or non-IBC TNBC patients treated with MK-3475.

(2) To determine the disease control rate of metastatic IBC or non-IBC TNBC patients who have achieved clinical response or stable disease to the systemic therapy.

(3) To investigate the association between biomarkers and efficacy by RNA-sequencing of exosomes in blood and tumor for IBC or non-IBC TNBC patients treated with MK-3475.

(4) To investigate the 5-year OS for IBC or non-IBC TNBC patients treated with MK-3475

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.

Metastatic IBC

Although IBC accounts for a mere 2-6% of all breast cancers in the United States, IBC is responsible for a disproportionate 7% of breast cancer-related deaths.[3-5] Approximately 20% to 30% of patients with IBC present with distant metastasis at diagnosis (*de novo* metastasis, classified as stage IV disease),[6-8] compared to 6% to 10% of patients with non-inflammatory breast cancer (non-IBC).[9,10]

We have tested the hypothesis that overall survival (OS) is worse in patients with IBC than in those with non-IBC among patients with distant metastasis at diagnosis (stage IV disease). Survival curves were compared among 1504 consecutive patients with stage IV breast cancer (IBC: 206; non-IBC: 1298) treated at our institution from 1987 through 2012[39]. The Cox proportional hazards model was used to determine predictors of OS. IBC was associated with shorter median OS time than non-IBC (2.3 years vs. 3.4 years; *P*=.01, log-rank test). In a multicovariate Cox model that included 1,389 patients, the diagnosis of IBC was a significant independent predictor of worse OS (hazard ratio = 1.4, *P*=.00). In summary, IBC is associated with shorter OS than non-IBC in patients with distant metastasis at diagnosis. (Unpublished data) *These data support the prognostic impact of IBC among patients with stage IV breast cancer.*

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 decreased immunogenicity through immune editing to avoid detection by the host. In the immunocompetent host, tumor cells must overcome both innate and adaptive immunologic defenses of the host.

We have also shown 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 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 cells (pDC) subsets determine the type of Th1/Th2 or Tc1/Tc2 responses, our data suggest that Th1 and Tc1 responses would be 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.[12]

3.1.2 Metastatic TNBC

Despite exciting progress in the understanding of breast cancer development and progression, and in the development of novel therapeutic strategies, breast cancer remains the second leading cause of cancer-related death in women, with a yearly toll of more than 40,000 deaths in the United States in 2014[40]. TNBC represents 15-20% of all breast cancers[41] and is verlapping,

but not synonymous, with the basal-like subtype defined by gene expression, as about 70% of TNBCs have basal-like characteristics[42, 43], and is associated with poor prognosis[44]. Breast cancer–related deaths are mainly due to the "incurable" nature of metastatic breast cancer (MBC) at the current time. It is estimated that ~6% of patients have metastatic disease at the time of diagnosis and 20% to 50% patients first diagnosed with primary breast cancer will eventually develop metastatic disease. Even with the remarkable advances in research and clinical management, the current treatment strategies for breast cancer metastasis still largely rely on the use of systemic cytotoxic agents, which frequently deteriorate the patient's life quality due to severe side effects and, in many cases, have limited long-term success. The prognosis for MBC patients is poor, with an estimated 5-year survival of only 26%. Therefore, MBC remains the most challenging task facing both cancer researcher and oncologist. Distant metastasis remains the main cause of death in patients with breast cancer despite important medical advances[11].

Treatment of TNBC is challenging and represents an area of unmet medical need, as these tumors lack therapeutic targets, such as ER and HER2, and become rapidly resistant to chemotherapy upon local recurrence and/or metastasis (even though they are often sensitive to cytotoxic drugs at initial presentation)[45]. The majority of patients with metastatic TNBC (mTNBC) have experienced relapse after neoadjuvant or adjuvant therapy for early or locally advanced disease. In a frequently referenced study, the median OS of all (at any line of therapy) patients with mTNBC was 13.3 months; median duration of first line (1L) therapy for mTNBC was 11.9 weeks; 80% of patients received second line (2L) therapy with a median duration of 9 weeks, and about 50% received third line (3L) therapy with a median duration of 4 weeks[46].

Several studies have demonstrated that presence of tissue infiltrating lymphocytes (TILs) is the most consistent prognostic factor in breast cancer, thus implicating the immune system in the pathophysiology and potentially the treatment of such tumors. Greater lymphocytic infiltration confers better prognosis in breast cancer, independent of systemic therapy[48, 49]. In addition, unsupervised gene expression profiling of TNBCs has identified a gene signature enriched for cytotoxic CD8+ T cell genes and natural killer cell (NKC) activity, which is predictive of good clinical outcome[50]. These findings suggest that inhibition of immune checkpoints has the potential to improve breast cancer prognosis by increasing the efficacy of tumor-associated immune response in eliminating breast cancer cells[51].

The PD-1 ligand, PD-L1, is not detected in normal breast tissue, but has been reported to be expressed in about half of all breast cancers, particularly in hormone receptor (HR)-negative and high grade, proliferative tumors[52]. In addition, the presence of regulatory T cells, tumor PD-L1 expression, and PD-1–positive TILs has been associated with high histologic grade, ER negativity, and prominent tumor lymphocytic infiltration[53]. In an independent study, PD-L1 was found expressed in 23% of breast cancer specimens and it was again associated with age, tumor size, American Joint Committee on Cancer (AJCC) primary tumor classification, tumor grade, lymph node status, absence of ER expression, and high expression of the proliferation marker Ki-67[54]. A recent publication reported that PD-L1 messenger ribonucleic acid (mRNA) is expressed in nearly 60% of breast tumors, independently of HR status, and is positively correlated with PD-L1 protein expression and increased TILs[55].

Taken together, these data provide the rationale for using anti-PD-1 maintenance therapy to maintain disease control status. Chemotherapies can debulk the disease volume but cannot be used for maintenance. Therefore, using an anti PD-1 monoclonal antibody is a promising approach for these patients for whom no currently has available agents have been proven to maintain treatment response.

3.1.3 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[13] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. [14-18] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[19-20] PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. [19, 21-24] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. [25-26] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. [27-28] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.[29] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. [25,30-32] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL).[33] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Recently, our group evaluated PD-L1 expression in triple negative breast cancer (TNBC). Using the Cancer Genome Atlas (TCGA) RNA sequencing data, we showed significantly greater expression of the PD-L1 gene in TNBC (n=120) compared with non-TNBC (n=716; P<0.001). In

addition, using a tissue microarray of TNBC specimens, we showed PD-L1 expression in 20% suggesting PD-L1 as a therapeutic target in TNBC. [34]

3.1.4 Preclinical and Clinical Trial Data

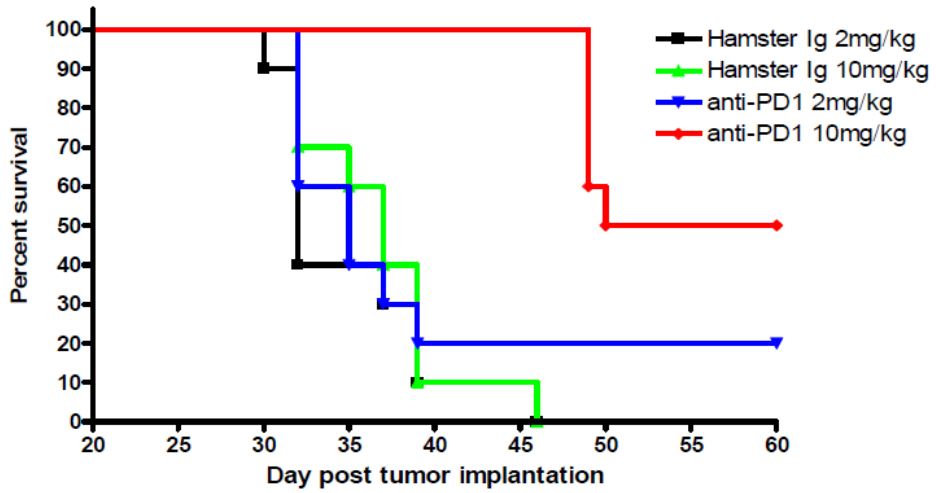
3.1.4.1 Preclinical Data (See Investigator's Boucher for details)

MK-3475 is a potent and highly selective humanized mAb designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 potently blocks binding to both ligands with half maximal inhibitory concentration (IC50) values below 1 nM. MK-3475 enhances T cell responses in human donor blood cell cultures with an EC50 of ~0.1 to 0.3 nM. MK-3475 binds to cynomolgus PD-1 with similar affinity, blocking activity, and demonstrates equivalent enhancement of cynomolgus T cell responses. It does not cross-react with rodent PD-1. MK-3475 strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T cells. Using an anti-mouse PD-1 analog antibody, PD-1 blockade is demonstrated to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-FU and combination therapy results in increased efficacy and increased complete regression rates in vivo.

Anti-mouse PD-1 (J43) was tested as a monotherapy in several syngeneic murine tumor models. In all monotherapy experiments, tumor cells were implanted subcutaneously in syngeneic hosts and were staged at 50-80 mm^3 before dosing was initiated. Anti-murine PD-1 or isotype control antibody was administered intraperitoneally (IP) every 3 to 4 days for a total of five treatments (the doses and schedule were determined based on experiments published in literature). Efficacy was determined by monitoring tumor volumes and long term survival for each experimental group.

The tumor growth curves in Figure 1 show that anti-mouse PD-1, administered at 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 10 mg/kg induced complete tumor regression in 50% of the animals resulting in long-term tumor free survival (Figure 1). 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 combined treatment of MC38 colon adenocarcinomas with gemcitabine and antimouse PD-1 showed a significant increase in anti-tumor efficacy over the individual monotherapies. 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 induced 20% complete regression in this experiment, whereas control antibody alone did not induce any regressions.

MK-3475 administered once every other week over 6-month duration to cynomolgus monkeys was well tolerated with systemic exposure (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 MK-3475 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). MK-3475

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 MK-3475 and the NOAEL 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 MK-3475 in clinical trials.

3.1.4.2 Clinical Data

Six clinical trials are currently evaluating MK-3475: PN001, PN002, PN006, PN010, PN011, and PN012.

PN001 is the Phase I first in human (FIH) study of MK-3475, a dose-escalation study in patients with progressive locally advanced or metastatic carcinomas, along with subject expansion cohorts in MEL and NSCLC. PN001 is an open-label study consisting of 5 primary aspects including the initial dose escalation and subsequent patient expansions. Part A examined 3 dose levels (1, 3, and 10 mg/kg) in patients with solid tumors. With no DLTs observed and no MTD reached, additional PK cohorts were examined at various doses (Parts A-1 and A-2). Subsequent cohorts were then initiated in patients with MEL [Part B (B1, B2, and B3) and D] and NSCLC (Parts C and F) at various dose levels and dose frequencies. Each of the two disease specific cohorts (MEL and NSCLC) are enrolled to confirm tolerability and to evaluate tumor response of MK-3475.

PN002 is a Phase II study designed to evaluate 2 doses of MK-3475 versus a chemotherapy control arm in patients with IPI-refractory metastatic melanoma. Patients are randomized in a 1:1:1 ratio to receive blinded MK-3475 2 mg/kg Q3W or MK-347510 mg/kg Q3W, or chemotherapy (according to current clinical practice) for the treatment of MEL. Patients assigned to the control chemotherapy arm may cross-over to the experimental MK-3475 arm once progression is confirmed (approximately ≥ Week 12).

PN006 is a randomized, controlled, open-label, three-arm pivotal study of two dosing regimens of MK-3475 versus IPI in patients with unresectable or metastatic MEL who have not received IPI treatment. Patients are randomized in a 1:1:1 ratio to receive 10 mg/kg Q2W, 10 mg/kg Q3W, or ipilimumab.

PN010 is multi-center, worldwide, randomized, adaptively designed Phase II/III trial of MK-3475 at two dosing schedules versus docetaxel in patients with NSCLC with PD-L1 positive tumors who have experienced disease progression after platinum-containing systemic therapy. Patients are randomized to receive 10 mg/kg Q3W, 2 mg/kg Q3W, or docetaxel 75 mg/m2 Q3W.

PN011 is an open-label, non-randomized, multi-center Phase I study of MK-3475 alone in Japanese patients with advanced solid tumors, and in combination with cisplatin/pemetrexed and carboplatin/paclitaxel in patients with advanced NSCLC. In Part A (monotherapy 3+3 design), patients with advanced solid tumors are receiving escalating doses of MK-3475 2 mg/kg (Dose level 1) or 10 mg/kg (Dose level 2) Q2W. In Part B (combination, 3+6 design), patients with

advanced NSCLC will receive MK-3475 10 mg/kg Q3W in combination with cisplatin/ pemetrexed (Cohort 1), or carboplatin/paclitaxel (Cohort 2).

PN012 is a multicenter, nonrandomized, multi-cohort trial of MK-3475 in patients with PD-L1 positive advanced solid tumors. All patients will receive MK-3475 10 mg/kg Q2W. Cohort A is enrolling patients with triple negative breast cancer, Cohort B is enrolling patients with squamous cell carcinoma of the head and neck, Cohort C is enrolling patients with urothelial tract cancer of the renal pelvis, ureter, bladder, or urethra, and Cohort D is enrolling patients with adenocarcinoma of the stomach or gastroesophageal junction.

In addition, Phase I studies in combination with various standard-of-care agents may be initiated, and single-agent efficacy of MK-3475 may be evaluated in additional solid tumors.

3.1.5 Rationale for the Trial and Selected Subject Population

The prognosis for metastatic breast cancer (MBC) patients is poor, with an estimated 5-year survival of only 26%. Distant metastasis remains the main cause of death in patients with breast cancer despite important medical advances[11]. Therefore, MBC remains the most challenging task facing both cancer researcher and oncologist.

Triple negative breast cancer (TNBC) and inflammatory breast cancer (IBC) are associated with younger age at diagnosis, premenopausal status, African American race, more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer, Breast Cancer 1 (BRCA1) mutations, and more aggressive behavior than other breast cancer subtypes[4, 41.]

To date, no IBC-specific targeted therapeutic options exist for the treatment of metastatic IBC. Unfortunately, the median survival is only 2.3 years indicating that all patients will not maintain disease control after achieving a clinical response to systemic chemotherapy or endocrine therapy. Indeed, hormone receptor (HR) positive disease is not favorable prognostic biomarkers in IBC [35] despite of endocrine therapy. Further, our recent publication suggests that IBC has been suggested to have immune dysfunction (section 3.1.1).

As reported in a seminal study on TNBC, 34% of all patients with TNBC experience distant recurrence with a median distant recurrence-free survival (DRFS) of 2.6 years, compared to a distant recurrence rate of 20% and a median DRFS of 5 years in other breast cancer subtypes[47]. The median survival is only 2.3 years for IBC indicating that all patients will not maintain disease control after achieving a clinical response to systemic chemotherapy or endocrine therapy. Indeed, hormone receptor (HR) positive disease is not favorable prognostic biomarkers in IBC[35] despite of endocrine therapy. Further, our recent publication suggests that IBC has been suggested to have immune dysfunction (section 3.1.1). To date, no specific targeted therapeutic options exist for the treatment of metastatic IBC and TNBC[3.47].

Therefore, we will enroll patients with HER2 negative metastatic IBC and non-IBC TNBC, which include both ER+ and triple negative receptor status metastatic IBC and non-IBC TNBC. HER2 positive MBC is excluded because there are numerous anti-HER2 therapies prescribed among patients with HER2+ MBC.

Taken together, these data provide the rationale for using anti-PD-1 antibody to maintain disease control status of HER2 negative metastatic IBC and non-IBC TNBC. Chemotherapies can debulk the disease volume but cannot be used for maintenance due to their toxicities. Using an anti PD-1 monoclonal antibody is a promising approach for these patients for whom no currently available agents have been proven to maintain treatment response.

3.1.6 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.

Currently the FDA has approved a new dosage for pembrolizumab (Keytruda) of 400 mg administered every 6 weeks across all adult indications, whether the PD-1 inhibitor is used as monotherapy or in a combination regimen. This approval is especially important in light of reduced clinic visits to protect patients with cancer due to the coronavirus disease 2019 (COVID-19) pandemic. The prior dosage for pembrolizumab, 200 mg every 3 weeks, will also still be a dosage option.

3.1.7 Study Endpoint

Most patients with metastatic IBC who achieved a maximum tumor response by standard chemotherapies will eventually have disease progression within 4 months. The goal of this clinical trial is to observe clinical activity signals of MK-3475 for disease stabilization or control as a maintenance therapy after achieving a maximum tumor response by standard chemotherapy. The efficacy endpoint is to evaluate the rate of patients who remain progression free at the end of 4 months from the maximum tumor response after receiving MK-3475[36].

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 HER2 normal breast carcinoma with a clinical diagnosis of IBC based on presence of inflammatory changes in the involved breast, including diffuse erythema and edema (peau d'orange), with or without an underlying palpable mass involving the majority of the skin of the breast. Pathological evidence of dermal lymphatic invasion should be noted but is not required for diagnosis of inflammatory breast cancer regardless of ER/PR status

   OR

   Has histological confirmation of triple negative breast carcinoma (HER2 normal, ER/PR < 10%) without clinical diagnosis of IBC

4. Has stage IV or recurrent disease that has been treated.

5. Has clinical response or stable disease for minimum of two months (three cycle of every three week chemo or 8 weeks of weekly regimen, etc.) after receiving any prior chemotherapy for metastatic/recurrent disease. A minimum of two cycles (6-8 weeks) of chemotherapy is required to determine clinical response.

   Per RECIST criteria 1.1, Clinical response for *measurable disease* is defined as complete response (CR) or partial response (PR); for *non-measurable disease only* (i.e. bone metastasis, ascites, pleural effusion, and pathological lymph nodes >/= 10 to <15 mm short axis) is defined as persistence of one or more non-target lesion(s) and no increase in overall tumor burden.

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

8. Has adequate organ function as determined by the following laboratory values:

   ANC >/= 1000 /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 or </=5 x ULN for subjects with liver metastases.

9. Subjects of childbearing potential should be willing to use effective methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through at least 4 months after the last dose of study drug. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Effective methods of birth control include 1). Use of hormonal birth control methods: pills, shots/injections, implants (placed under the skin by a health care provider), or patches (placed on the skin); 2).Intrauterine devices (IUDs); 3).Using 2 barrier methods (each partner must use 1 barrier method) with a spermicide. Males must use the male condom (latex or other synthetic material) with spermicide. Females must choose either a Diaphragm with spermicide, or Cervical cap with spermicide, or a sponge (spermicide is already in the contraceptive sponge).

10. Has negative serum or urine pregnancy test for subjects of childbearing potential.

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 is receiving systemic steroid therapy 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 malignancy (other than breast cancer) except basal cell carcinoma or squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

5. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate if they are stable, and have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

6. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids 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 or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study.

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

8. Has an active infection requiring systemic therapy.

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

10. 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).

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

12. Has a known active Hepatitis B or Hepatitis C

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

14. Is receiving concurrent anti-cancer therapy for metastatic disease.

4.2 Treatment Plan

The treatment to be used in this trial is outlined in Table 1 below. This plan was adjusted based on current FDA approval for the new dosage for pembrolizumab (Keytruda) of 400 mg administered every 6 weeks across all adult indications, whether the PD-1 inhibitor is used as monotherapy or in a combination regimen.

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475	200 mg	Every 3 weeks	IV infusion	Cycle 1 to 8 or until meet drug discontinuation criteria (See 4.5)	Experimental
MK-3475	400 mg	Every 6 weeks	IV infusion	Cycle 9 to up to 24 months or until meet drug discontinuation criteria (See 4.5)	Experimental
The MK-3475 dosing interval may be increased due to toxicity described in 4.2.2.					

4.2.1 Dose Selection

For cycle 1 to 8, each cycle is defined as 3 weeks interval. MK-3475 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). For cycle 9 and beyond, each cycle is defined as 6 weeks interval. MK-3475 400 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). MK-3475 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 MK-3475 dose calculation, reconstitution, preparation of the infusion fluid, and administration.

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 2 below. See Section 4.4 and Events of Clinical Interest Guidance Document for supportive care guidelines (Appendix C), including use of corticosteroids.

Table 2 Dose Modification Guidelines for Drug-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 (see exception below)[1]	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.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Infusion Reaction	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.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	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.
[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[2] 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 MK-3475 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.

- Any anti-cancer agents.
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain will be allowed.
- 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 and in greater detail in the ECI guidance document (Appendix C in PDOL). 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 is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 4.2.2 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. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document (Appendix C in PDOL).

- **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 3 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475.

Table 3 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1		None

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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.	
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: 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, MK-3475 administration will continue until one of the following conditions is observed.

4.5.1. Disease progression [iRECIST Criteria]

Disease progression is defined as rapid growth of multiple measurable, non-measurable or new lesions, or at least a 20% increase in the sum of diameters of target (measurable) lesions, taking as

reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

4.5.2 Noncompliance:

If the patient is not able to 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.

4.6 Criteria for Disease Control

The purpose of this study is to maintain disease control status of patients with metastatic IBC who have achieved clinical response from prior systemic therapy for metastatic disease. PI will be responsible to monitor disease control status. Date of disease progression will be documented and recorded in the study specific database.

4.6.1. Definition of Treatment Response

We will use iRECIST criteria to evaluate and define the treatment response by following the guideline which released in the Lancet Oncology on March 2017[56].

iRECIST was developed by the RECIST working group for the use of modified Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) in cancer immunotherapy trials, to ensure consistent design and data collection, facilitate the ongoing collection of trial data, and ultimate validation of the guideline. This guideline describes a standard approach to solid tumour measurements and definitions for objective change in tumour size for use in trials in which an immunotherapy is used. Additionally, it defines the minimum datapoints required from future trials and those currently in development to facilitate the compilation of a data warehouse to use

to later validate iRECIST.

Terminology of iRECIST

iRECIST is based on RECIST 1.1. Responses assigned using iRECIST have a prefix of "i" (ie, immune)—eg, "immune" complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for stable disease (iSD), New lesions are assessed and subcategorised into those that qualify as target lesions (new lesion, target) or non-target lesions (new lesion, non-target).

iRECIST Criteria

iRECIST criteria are listed in below tables. Table 4 Shows the comparison of RECIST 1.1 and iRECIST. Table 5 shows the assignment of timepoint response using iRECIST. More details about this guideline is available in Appendix J in PDOL or http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30074-8/fulltext

Table 4: Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

Table 5: Assignment of timepoint response using iRECIST

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)

Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

* non-iCR/non-iUPD = criteria for neither CR nor PD have been met.

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

4.6.2.1. 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.

4.6.2.2. 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.

4.6.2.3. 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. .

5.0 STUDY FLOW CHART

Trial Period:	**Screening Phase**	**Treatment Cycles**[j]									**End of Treatment**	**Post-Treatment**		**Survival Follow Up**[k]
Treatment Cycle/Title:	Screening /Baseline	1	2	3	4	5	6	7	8	Cycle 9 and beyond	If pt returns for follow up	Safety F/U [f]	Follow-Up[g,]	
Scheduling Window (Days):	Within 28 days	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3			1 month after last dose	3 months after last dose	Annually for at least 5 years
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	x	x	x	x	x			
Adverse Events [b]	x	x	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	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	x			
EKG, ECHO or MUGA as SOC[d]	x													
TSH, Free T4 and Totalcortisol[i]	x			x		x		x		x	x			
Radiological Evaluation as clinically indicated and as SOC [d]	x			x		x		x		x	x			
Archived biopsy or surgical specimens (block or unstained slides) obtained at any time prior to treatment.	x													
Correlative Studies Blood Collection [e]	x			x			x			x				
MK-3475 Administration		x	x	x	x	x	x	x	x	x				
Survival Status													x	x
Optional biopsy at disease progression [h]											x			

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

b. Complete physical exam during the screening period. This will not be repeated if done within 8 (+/- 3 days) days before the start of treatment. During treatment, Physical Exam as clinically indicated prior to trial treatment administration. Adverse events and ECOG performance status assessment can be done within 8 (+/- 3 days) days before the start of treatment. Adverse events and ECOG will be assessed every 3 weeks either in the clinic visit or by calling through the end of treatment.

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 8 (+/- 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 abdomen, Ultrasound, bone Scan and X-Rays, brain MRI 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. During treatment, an earlier evaluation will be performed if clinically indicated. The same method of evaluation, specific to the subject's condition, will be performed according to the time points.

e. Peripheral blood and serum for correlative studies. Approximately 50cc of blood will be drawn at baseline, cycle 3rd, 6th, 9th, then every 2 cycles (i.e.11th, 13th, 15th, etc.) and at disease progression.

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. 3 months follow up can be performed in the clinic, or by phone if patient is not willing to come to the clinic for follow up.

h. Optional biopsy at disease progression.

i. TSH, Free T4 and Total cortisol will be monitored at baseline, every other cycle during Cycle 1-8 and every cycle for Cycle 9 and beyond as standard of care.

j. Cycle 1-8 are defined as 3 weeks per cycle, Cycle 9 and beyond are defined as 6 weeks per cycle, pembrolizumab (200mg or 400mg) will be given on Day 1 of each cycle as section 4.2.

k. registration

6.0 OTHER STUDY PROCEDURES

6.1 Informed Consent/Patient Registration

The study will be discussed with the patient, and any patient wishing to participate must give informed consent. A signed, Institutional Review Board (IRB) approved, informed consent must be obtained from patients before any study specific procedures or registration for study treatment can occur. All patients will be registered in the OnCore system.

6.2 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.

6.2.1 Tumor Samples

Collection

Archived biopsy 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 with disease progression and accessible lesions.

Evaluation

- Characterization of tumor infiltrating lymphocytes (TIL).
- 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. These IHC analyses will include but not necessarily be limited to: CD4, CD8, FOXP3, PD-1, and PD-L1. PD-L1 IHC will be performed by both MD Anderson and QualTek.
- Genetics profiling performed by Insight Genetics (only done for the prior biopsy and/or surgery tumor samples).

6.2.2 Blood samples

Collection and processing

Multiple blood draws will be required for this trial. All blood tubes will be labeled only with the patients' unique study number. Approximately 100cc will be drawn for each immunologic assessment (at baseline; prior to dosing of study drug with every third cycle i.e. cycle 3, 6, 9, 12 etc , or every other cycle after for patients who start Pembrolizumab 400mg at C9 and beyond; 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. 70cc 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. Plasma will be collected from CPT Cell Preparation tubes and stored. 20cc blood will be collected in heparin 10ml green top tubes for FACS assay.

6.2.3 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.

Plasma

• Exosomal RNA-sequencing will be performed with RNA extracted from plasma by Insight Genetics, Inc along with the tumor sample listed in section 6.2.1. There is only one time point plasma sample needed, and plasma samples at baseline will be preferred, but samples collected at other time points can be substitute if the baseline sample is unavailable.

• Plasma will be stored for future research purpose.

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.

6.3 Safety Monitoring and Reporting

6.3.1 Adverse Event

Adverse events will be assessed according to the CTCAE version 4.0. All study patients who have received any dose of MK-3475 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.

AEs (>/=2 non-hematological and >/=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 in the medical record and recorded in REDCap database. Abnormal laboratory values will not be reported as AEs; however, any clinical consequences of the abnormality should be reported as AEs.

6.3.2 Serious Adverse Event Reporting (SAE)

6.3.2.1 Internal SAE 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 INDIND 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.**

6.3.2.2 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.

6.3.2.3 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), and reporting timeline is as below:

Type of Event	**Reporting Time Period:** **Consent to Randomization/ Allocation**	**Reporting Time Period:** **Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period:** **After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Merck:**
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 2 business days but no longer than 3 calendar days of receipt of information
Pregnancy/Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of receipt of information
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of receipt of information

Events of clinical interest (ECI) for this trial include:

1. An overdose of MK-3475that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of MK-3475 will be defined as any dose of 1,000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
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.

6.3.4 Evaluating Adverse Events

An investigator or a designee will evaluate and record adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0 as standard practice per institution guidelines.

7.0 STATISTICAL ANALYSIS PLAN

The primary objective of this phase II trial is to assess the efficacy of MK-3475 as a single agent in metastatic IBC and non-IBC TNBC patients. The primary endpoint is the rate of disease control measured at the end of 4 months from the start of therapy.

The disease control rate is defined as the percentage of patients either 1) with measurable disease that achieve iCR, iPR, iSD, or 2) with non-measurable disease that achieve iCR or iSD, , by 4 months or more in all evaluable patients. We will also perform secondary analysis on intent-to-treat patient population where those patients who drop out early will be considered as progression.

The trial will be conducted using Simon's optimal two-stage design and the rate of disease control will be estimated accordingly. It is assumed that the MK-3475 single agent will have a disease control rate of 30%. A disease control rate of 10% or lower will be considered treatment failure and the regimen will be rejected under this circumstance. When the probability of accepting a "bad" regimen (i.e. disease control rate 10% or lower) is 0.10 and the probability of rejecting a "good" regimen (i.e. disease control rate 30% or higher) is also 0.10, Simon's optimal 2-stage design requires 12 patients enter in the first stage. The study accrual will be delayed until all 12 patients are evaluable for disease control status. If 1 or no patients maintain disease control on treatment, the trial will be stopped and the regimen will be declared as ineffective. If 2 or more patients maintain disease control, 23 more patients will be enrolled to the study to reach a total of 35 treated patients. By the end of the study, the new regimen will be rejected if rate of disease control is less than or equal to 5/35 and will be considered worthy of further investigation otherwise.

However, with a larger sample size, we will be able to detect a smaller target disease control rate of 0.25. It is assumed that the MK-3475 single agent will have a disease control rate of 25%. A disease control rate of 10% or lower will be considered treatment failure and the regimen will be rejected under this circumstance. When the probability of accepting a "bad" regimen (i.e. disease control rate 10% or lower) is 0.10 and the probability of rejecting a "good" regimen (i.e. disease control rate 25% or higher) is also 0.10, Simon's optimal 2-stage design requires 21 patients enter in the first stage. The study accrual will be delayed until all 21 patients are evaluable for disease control status. If 2 or less patients maintain disease control on treatment, the trial will be stopped

and the regimen will be declared as ineffective. If 3 or more patients maintain disease control, 29 more patients will be enrolled to the study to reach a total of 50 treated patients. By the end of the study, the new regimen will be rejected if rate of disease control is less than or equal to 7/50 and will be considered worthy of further investigation otherwise. But, that will not happen based on the current disease control rate.

At any time after first 5 patients are treated, if >=30% patients experience serious adverse events (SAE) within 2 cycles of treatment, we will stop the trial and claim that the regimen is too toxic. SAE is defined as an adverse event is serious, unexpected, and related to the study drug.

Patients' characteristics will be summarized at the end of the study. For discrete or categorical data, descriptive statistics will be generated including tabulations of frequencies. For continuous data, summary statistics including sample size, mean, standard deviation, median, minimum and maximum will be computed. A 95% exact binomial confidence interval on disease control rate will be computed.

Various biomarker endpoints will be measured in various specimens. Correlation among biomarkers at baseline in each specimen and between different specimens will be assessed. The association among various continuous and discrete biomarkers or disease status groups will be assessed by the exploratory data analysis using scatter plot matrix, box plots, BLiP plot [37] and trellis plot, etc, and may be tested by t-test/ANOVA/Wilcoxon rank sun test/Kruskal-Wallis test, whichever is appropriate. Correlation between continuous biomarkers will be examined by Pearson or Spearman rank correlation coefficients. The association between discrete biomarkers will be tested by chi-square or Fisher's exact test. Paired t-test/Wilcoxon rank sum test and McNemar's test may be used to test the change of a single continuous biomarker and discrete biomarker, respectively, over time within each treatment group. Repeated measures analysis including mixed effects model will be performed to analyze the correlation between disease control and biomarkers change over time. [38] Disease control survival and overall survival time from the registration date will be estimated using Kaplan-Meier method.

All statistical tests will be performed at a two-sided significance level of 5% using SAS or S-Plus, as appropriate.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 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
MK-3475 100 mg/ 4mL	Solution for Injection

8.2 Packaging and Labeling Information

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

8.3 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.

8.4 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.

8.5 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.

9.0 DATA MANAGEMENT

Data collected from the study will be entered in REDCap database. 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. Deidentified data will be shared with University of Hawaii Cancer Center (UHCC) for review and analysis.

9.1 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;

3) history of breast cancer surgery, and radiation therapy, if applicable;

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 clinic database, and will not be recorded in the study database.

9.2. 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.

10.0 REFERENCES

1. Edge S, Byrd D, Compton C: AJCC Cancer Staging Handbook (ed 7th ed.). New York, American Joint Committee on Cancer, Springer, 2010 pp. 417-60.

2. Dawood S, Merajver SD, Viens P, et al: International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 22:515-23, 2011

3. Anderson WF, Schairer C, Chen BE, et al: Epidemiology of inflammatory breast cancer (IBC). Breast Dis 22:9-23, 2005

4. Hance KW, Anderson WF, Devesa SS, et al: Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. J Natl Cancer Inst 97:966-75, 2005

5. Jaiyesimi IA, Buzdar AU, Hortobagyi G: Inflammatory breast cancer: a review. J Clin Oncol 10:1014-24, 1992

6. Wingo PA, Jamison PM, Young JL, et al: Population-based statistics for women diagnosed with inflammatory breast cancer (United States). Cancer Causes Control 15:321-8, 2004

7. Elias EG, Vachon DA, Didolkar MS, et al: Long-term results of a combined modality approach in treating inflammatory carcinoma of the breast. Am J Surg 162:231-5, 1991

8. Curcio LD, Rupp E, Williams WL, et al: Beyond palliative mastectomy in inflammatory breast cancer--a reassessment of margin status. Ann Surg Oncol 6:249-54, 1999

9. Miller KD, Sledge GW, Jr.: The role of chemotherapy for metastatic breast cancer. Hematol Oncol Clin North Am 13:415-34, 1999

10. O'Shaughnessy J: Extending survival with chemotherapy in metastatic breast cancer. Oncologist 10 Suppl 3:20-9, 2005

11. Lu J, Steeg PS, Price JE, et al: Breast cancer metastasis: challenges and opportunities. Cancer Res 69:4951-3, 2009

12. Gao H et al (2009) Immune profile of inflammatory breast cancer patients. In: Proc 32nd Annual San Antonio Breast Cancer Symposium, 2009, San Antonio, TX, Abstract # 4129.

13. Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28(29):4531-8.

14. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

15. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

16. Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170:1257-66.

17. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

18. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

19. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26:373-400.

20. Usubütün A, Ayhan A, Uygur MC, zen H, klu C, acan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

21. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal symphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

22. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen p, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

23. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18:689-94.

24. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.

25. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15:544-51.

26. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94:426-30.

27. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

28. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet 2009;10(840):841.

29. Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57:97-106.

30. Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

31. Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58:449-59.

32. Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-7.

33. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010;107:1500-6.

34. Mittendorf E, Philips A, Meric-Berstam F, et al. PD-L1 Expression in Triple Negative Breast Cancer. Cancer Immunol Res 2014; January 10.

35. Masuda, H., Brewer, T. M., Liu, D. D., Iwamoto, T., Shen, Y., Hsu, L., Ueno, N. T.,. (2013). Long-term treatment efficacy in primary inflammatory breast cancer by hormonal receptor- and HER2-defined subtypes. Annals of Oncology. doi:10.1093/annonc/mdt525

36. Ueno, N. T., Bertucci, F., Finetti, P., Vermeulen, P., Lucci, A., Robertson, F. M., et al. (2013). Gene expression profiles of inflammatory breast cancer: correlation with response to neoadjuvant chemotherapy and metastasis-free survival. Annals of Oncology. doi:10.1093/annonc/mdt496

37. Lee, J. J. and Tu Z.N. (1997) A versitile one-dimentional distribution plot: the BLiP plot. The American Statistician, 51: 63-70.

38. Liang, K.Y and Zeger, S.L. (1986) Longitudinal data analysis using generalized linear models. Biometrika, 73: 13-22.

39. Tamer M. Fouad, Takahiro Kogawa, et al. Comparison of long-term outcome of breast cancer metastasis with history of Inflammatory Breast Cancer Patients and Non-Inflammatory Breast Cancer. 36th SABCS, Santonio, TX, 12/2013.

40. Siegel, R., et al., Cancer statistics, 2014. CA Cancer J Clin, 2014. **64**(1): p. 9-29.

41. Bauer, K.R., et al., Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer, 2007. 109(9): p. 1721-8.

42. Sorlie, T., et al., Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A, 2001. **98**(19): p. 10869-74.

43. Rakha, E.A. and I.O. Ellis, Triple-negative/basal-like breast cancer: review. Pathology, 2009. **41**(1): p. 40-7.

44. Perou, C.M., Molecular stratification of triple-negative breast cancers. Oncologist, 2011. **16** Suppl 1: p. 61-70.

45. Arnedos, M., et al., Triple-negative breast cancer: are we making headway at least? Ther Adv Med Oncol, 2012. 4(4): p. 195-210

46. Kassam, F., et al., Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer, 2009. **9**(1): p. 29-33.

47. Dent, R., et al., Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res, 2007. 13(15 Pt 1): p. 4429-34.

48. Mahmoud, S.M., et al., Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. J Clin Oncol, 2011. 29(15): p. 1949-55.

49. Denkert, C., et al., Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol, 2010. 28(1): p. 105-13.

50. Finak, G., et al., Stromal gene expression predicts clinical outcome in breast cancer. Nat Med, 2008. 14(5): p. 518-27.

51. Stagg, J. and B. Allard, Immunotherapeutic approaches in triple-negative breast cancer: latest research and clinical prospects. Ther Adv Med Oncol, 2013. 5(3): p. 169-81.

52. Ghebeh, H., et al., The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressedin breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors. Neoplasia, 2006. 8(3): p. 190-8.

53. Ghebeh, H., et al., FOXP3+ Tregs and B7-H1+/PD-1+ T lymphocytes co-infiltrate the tumor tissues of high-risk breast cancer patients: Implication for immunotherapy. BMC Cancer, 2008. 8: p. 57.

54. Muenst, S., et al., Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. Breast Cancer Res Treat, 2014. 146(1): p. 15-24.

55. Schalper, K., et al., In Situ Tumor PD-L1 mRNA Expression Is Associated with Increased TILs and Better Outcome in Breast Carcinomas Clin Cancer Res, 2014. 20: p. 2773

56. Lesley Seymour, Jan Bogaerts, Andrea Perrone, Robert Ford, Lawrence H Schwartz, Sumithra Mandrekar, Nancy U Lin, Saskia Litière, Janet Dancey, Alice Chen, F Stephen Hodi, Patrick Therasse, Otto S Hoekstra, Lalitha K Shankar, Jedd D Wolchok, Marcus Ballinger, Caroline Caramella, Elisabeth G E de Vries, on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics The Lancet Oncology, Volume 18, No. 3, e143–e152, March 2017