Phase II Study of Pembrolizumab and Capecitabine for Advanced Triple Negative and Hormone-Refractory Breast Cancer

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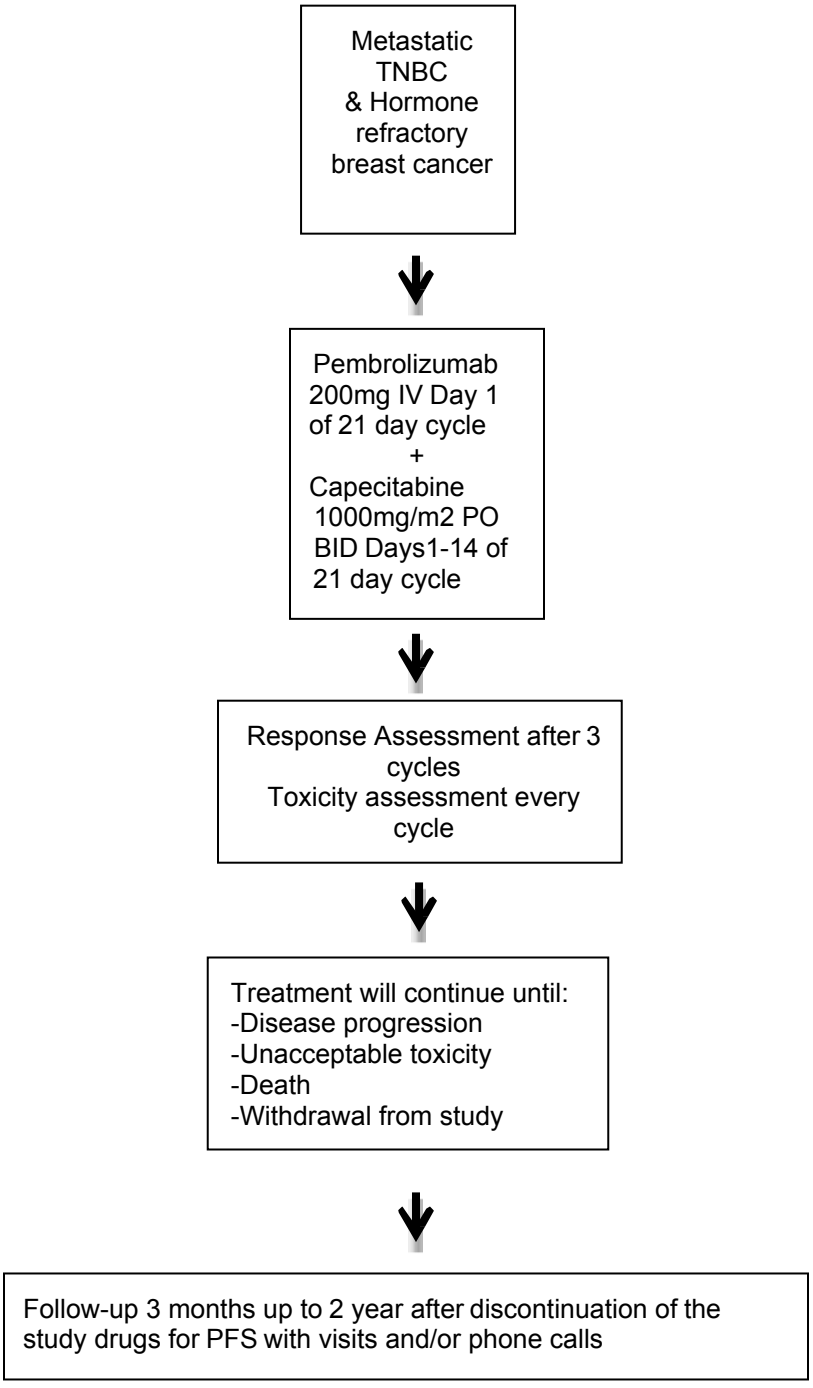
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CrCL	Creatinine Clearance
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
D_5W	Dextrose % in Water
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EMR	Electronic Medical Record
eCRF	Electronic Case report form
FOCBP	Females of Child-Bearing Potential
5-FU	5-Fluorouracil
HER2	Epidermal Growth Factor receptor 2
IV (or iv)	Intravenously
ITIM	Immunoreceptor Tyrosine –based Inhibition Motif
IHC	Immuno-Histochemical
INR	International Normalized ratio
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
LLN	Low Limit of Normal
MTD	Maximum Tolerated Dose
MBC	Metastatic Breast Cancer
MEL	Melanoma3
mAB	Monoclonal Antibody
NCI	National Cancer Institute
NS	Normal Saline
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PD-1	Programmed Death -1-Ligand
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response

PT	Prothrombin Time
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TNBC	Triple Negative Breast Cancer
TILs	Tumor Infiltrating Lymphocytes
Q2W	Every 2 weeks
Q3W	Every 3 weeks
ULN	Upper Limit of Normal
UPIRSO	Unanticipated problem involving risk to subjects or others
WBC	White Blood Cells

STUDY SCHEMA



NU Study Number: NU 16B08
Other Study Number: TBD

STUDY SUMMARY

Title	Phase II study of Pembrolizumab and Capecitabine for advanced triple negative and hormone-refractory breast cancer.
Study Design	This is an open-label, single arm, Phase II study of the combination of pembrolizumab and capecitabine in locally advanced or metastatic Triple Negative (TNBC) and hormone-refractory Breast Cancer.
Study Center(s)	Northwestern University – Robert H. Lurie Comprehensive Cancer Center.(RHLCCC)
Objectives	**Primary objective(s):** To evaluate the median progression-free survival (median PFS) for participants receiving pembrolizumab with capecitabine for the treatment of locally advanced or metastatic TNBC and hormone-refractory MBC. **Secondary Objectives:** -The objective response rate (ORR) for participants receiving pembrolizumab with capecitabine for the treatment of locally advanced or metastatic TNBC and hormone-refractory MBC. -To assess Safety and tolerability for the combination of pembrolizumab and capecitabine for the treatment of locally advanced or metastatic TNBC and hormone-refractory MBC.

Diagnosis & Key Eligibility Criteria	Key Inclusion criteria:
	
	1)The target population for this study is:
	• Patients(both female and male).with triple negative locally advanced or metastatic (stage IV) breast cancer
	• Patients with hormone refractory negative locally advanced or metastatic (stage IV) breast cancer.
	• Patients must be ≥18 years and have a life expectancy of ≥ 90 days.
	• Patients with central nervous system (CNS) involvement may participate if they meet all the following criteria:
	  • At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment,
	  • Clinically stable with respect to the CNS tumor at the time of screening
	
	Key Exclusion criteria:
	• Patients with documented HER2-positive metastatic disease are not eligible, even if their primary breast cancer was HER2-negative.
	• History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus
	• Patients who have evidence of active, noninfectious pneumonitis or have a history of severe pneumonitis that required treatment with steroids are not eligible for this study.
	• Patients with impaired GI function or GI disease that may significantly alter absorption of oral capecitabine.

Treatment Plan	This will be an open-label, single-arm, II study of the combination of pembrolizumab and capecitabine in locally advanced and metastatic triple negative and hormone-refractory breast cancer. Pembrolizumab will be administered at 200mg IV on Day 1 of each cycle (1 cycle=21 days). Capecitabine will be administered at 1000 mg/m2 BID D1-14 q21d. Patients will be instructed to take the morning dose of capecitabine before coming to clinic for pembrolizumab infusion. Patients will continue to receive treatment until disease progression or unacceptable toxicity. After discontinuation of study drugs, patients will be assessed every 3 months up to 1 year for PFS, with visits and/or phone calls.
Statistical Methodology	For PFS, assumptions are that the addition of pembrolizumab will increase PFS to 5 months compared to historical control of 3 months. Assuming exponential survival, with 27 evaluable patients, there is 80% power to detect this difference using a one-tailed z test at $p<0.05$. Recruitment will last approximately 30 months (2.5 years) and participants will be followed for a maximum of 2 years. The primary outcomes chosen is PFS based on mechanism of action. A total of 30 patients may be accrued in order to achieve 27 evaluable patients.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

1.1.1 Overview on Breast Cancer

Approximately 231,840 women will be diagnosed with breast cancer in the United States in 2015 making it the most frequently diagnosed cancer (excluding skin cancer) in women and ranking second as a cause of cancer death. Triple negative breast cancer (TNBC), defined as estrogen receptor negative, progesterone receptor negative and human epidermal growth factor receptor 2 (HER2) negative, accounts for 9-21% of newly diagnosed breast cancers[1, 2]. TNBC is associated with more aggressive disease both histologically and clinically. Patients with TNBC have a lower relapse free survival and decreased overall survival (OS) when compared to hormone receptor positive disease. In an observation study conducted by Pogoda(13), metastatic disease occurred in 35% of all TNBC patients within 6 years of diagnosis.

1.1.2 Treatment Options for Metastatic Triple Negative Breast Cancer and Hormone-Refractory Metastatic Breast Cancer

Current treatment options for metastatic breast cancer (MBC) are not curative and therapy aims to prolong survival while minimizing toxicity to preserve or improve quality of life for patients. In TNBC, there are no approved biologic or targeted agents and chemotherapy is the standard of care. While combination chemotherapy can provide higher rate of objective response and longer time to progression, it is associated with higher toxicity and minimal survival benefit[3]. Current recommendations for single agent therapies include anthracyclines, taxanes, anti- metabolites and microtubule inhibitors. Ultimately, patients will develop resistance to these therapies. Similarly, patients with hormone-positive metastatic breast cancer eventually become resistant to endocrine therapy, and chemotherapy is the standard of care.

1.1.3 The Immune System and Breast Cancer

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

The Programmed Death-1-Ligand (PD-1 receptor-ligand) interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T- cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an 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). The structure of murine PD-1 has been resolved. 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. 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. 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. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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. 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. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen- presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. 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). 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.

1.2 Intervention Background & Overview

1.2.1 Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab; MK-3475) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and a BRAF inhibitor, if BRAF V600 mutation positive.

In Oct. 2015, the U.S. Food and Drug Administration granted accelerated approval for Keytruda (pembrolizumab) to treat patients with advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express a protein called PD-L1. Keytruda was approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test, the first test designed to detect PD-L1 expression in non-small cell lung tumors.

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 every 3 weeks (Q3W) showed slow systemic clearance (0.22L/day), limited volume of distribution (7.7L), and a long half-life (26 days) (refer to Package Insert). 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 Q3W fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen were 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. 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.

The KEYNOTE-012 trial is a phase Ib study of patients with metastatic triple-negative breast cancer with tumors positive for the expression of PD-L1. 32 patients were treated with pembrolizumab at 10mg/kg Q2W until progression of disease. Preliminary analysis of the data demonstrated an overall response rate of 18.5% including one complete response (3.7%), four partial responses (14.8%) and seven patients with stable disease (25.9%).

Embryofetal Toxicity:
Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advice females of reproductive potential to use highly effective contraception during treatment with pembrolizumab and for 4 months after the last dose of pembrolizumab.

1.2.2 Capecitabine

Capecitabine is an oral fluoropyrimidine approved for treatment of metastatic breast cancer. Capecitabine is metabolized to 5-FU by an enzymatic process catalyzed by thymidine phosphorylase which has higher activity in tumor tissue compared to normal tissue[4]. A phase II trial by Blum et al demonstrated safety and efficacy of capecitabine in patients with paclitaxel refractory metastatic breast cancer with an overall response rate of 20% and a median duration of response of 8.1 months[5]. Another phase II study of capecitabine monotherapy in patients with both anthracycline and taxane pretreated metastatic breast cancer demonstrated an overall response rate of 28% and median time to progression of 4.9months[6]. Capecitabine has been associated with a favorable risk-benefit profile without having a negative impact on quality of life in patients with metastatic breast cancer[7]. Given the favorable safety profile and relative ease of administration, capecitabine is an ideal agent for consideration of combination therapy for palliative management of metastatic triple negative breast cancer. Currently, there is no randomized control data suggesting survival benefit to combined chemotherapy with capecitabine and the added chemotherapy comes with the risk of additional toxicity.

1.3 Rationale for the Current Study

Metastatic TNBC and hormone-refractory MBC are responsible for a disproportionate number of breast cancer deaths. Therefore, there is a significant unmet need to advance the management of MBC. Moreover, there have been fewer advances in the treatment of triple negative breast cancer than have been seen with other subtypes. Interestingly, triple negative breast cancers respond better to chemotherapy, but can become chemotherapy resistant and have a higher recurrence rate compared with other breast cancer subtypes. One mechanism of chemoresistance in TNBC may be the tumors ability to evade the innate immune system. It has been demonstrated that programmed death-1-ligand 1 (PD-L1) expression in cancer cells contributes to immunoresistance[8]. TNBC and basal subtypes of breast cancer are associated with increased expression of PD-L1[9] and this is associated with poor clinical prognosis[10]. Combining chemotherapy with immunotherapy may allow for a better response to chemotherapy and the innate immune system, leading to improved outcomes. Recent data show safety of pembrolizumab in metastatic TNBC*. Capecitabine is an FDA approved drug for metastatic breast cancer, which is effective in TNBC*. Combining pembrolizumab with standard of care chemotherapy capecitabine may improve upon survival outcomes for this patient population, whose median survival remains less than one year.

The standard dose used in clinical practice for capecitabine is 1000 mg/m2. Therefore it would not be necessary to repeat a dose finding phase I study. Furthermore, 2 studies have opened to date (one phase 2, one phase 3) that are evaluating this combination in gastrointestinal (GI) cancers. We do not feel it is necessary to repeat a phase I in only breast cancer patients.

Hence, we are proposing to do a Phase II study of the combination of pembrolizumab and capecitabine for Metastatic Triple Negative Breast Cancer (TNBC) and Hormone refractory breast cancer.

1.4 Exploratory Studies:

1. PD-L1 immunohistochemical (IHC) assessment, baseline tissue biopsy of a metastatic will be obtained for PD-L1 immunohistochemical (IHC) assessment. QualTek developed and validated a PD-L1 IHC assay using Merck's proprietary 22C3 antibody, and this will be used for the study. The study site's pathology core will be used to store, process, and ship samples to QualTek. The presence of PD-L1 expression will be correlated with response (PFS, RR) and other clinical-pathologic factors in an attempt to define a subset of patients that may benefit from pembrolizumab.
Note: The requirement for biopsy (fresh) may be omitted per treating physician's discretion, if the biopsy would cause undue morbidity to the patient and if enough tissue from a prior metastatic lesion (archival biopsy) is not available.

2. ORR and median-PFS assessment will be done using the irRECIST criteria, which is now applied to immunotherapeutic drugs.

2.0 OBJECTIVES

2.1 Primary objective(s):

- To evaluate the median progression-free survival (median PFS) for participants receiving pembrolizumab with capecitabine for the treatment of locally advanced or metastatic TNBC and hormone-refractory MBC. This will be assessed by using RECIST 1.1 criteria.

2.2 Secondary Objectives:

- To describe the objective response rate (ORR) for participants receiving pembrolizumab with capecitabine for the treatment of locally advanced or metastatic TNBC and hormone-refractory MBC. This will be assessed by using RECIST 1.1 criteria.
- To describe the safety and tolerability of the combination of pembrolizumab and capecitabine for the treatment of locally advanced or metastatic TNBC and hormone-refractory MBC. All adverse events will be assessed by NCI CTCAE 4.03 criteria

2.3 Exploratory Objectives

- Analysis of expression of Programmed Cell death 1 Ligand 1 (PD-L1) through immunohistochemical (IHC) analysis : A baseline tissue biopsy of a metastatic site will be obtained for PD-L1 immunohistochemical (IHC) assessment, from all patients. An archived specimen may be used (metastatic tissue only) if collected no more than 2 months of registration. Otherwise fresh biopsy of metastatic lesion is mandatory at baseline and should be performed no more than 2 months prior to registration.

  Note: The requirement for biopsy (fresh) may be omitted per treating physician's discretion, if the biopsy would cause undue morbidity to the patient and if enough tissue from a prior metastatic lesion (archival biopsy) is not available.

  Note: PD-L1 IHC assay from QualTek will be used for the study.
  Please refer to section 9.1 and laboratory manual for more details.

- To evaluate ORR and median-PFS using irRECIST:
  To evaluate efficacy endpoint median-Progression Free survival (PFS), assessment will be done up to 1 year after discontinuation of the study drugs. Assessment will be done using irRECIST (see Table 6)

ORR will be assessed every 3 cycles (every 9 weeks) with imaging (CT chest/abdomen/pelvis and bone scan[if indicated]). Assessment will be done using irRECIST.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with locally advanced and metastatic TNBC and hormone-refractory MBC. This will be a single-center trial conducted at Northwestern University. Patients will be recruited by the clinical team at Lynn Sage Comprehensive Breast Center of Northwestern University. The investigators may also utilize the services of the Cancer Trial Recruitment Nurse Coordinator as needed to assist with recruitment.

A total of 30 subjects will be needed to obtain 27 evaluable patients on this trial. Approximately 10 potentially eligible patients are seen per month, and it is anticipated that at least 1 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. William Gradishar, via the Clinical Research Office at (312) 695-1301.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically-confirmed unresectable, locally advanced or metastatic breast cancer that meets one of the following:

- Triple negative, defined as estrogen receptor (ER) negative, progesterone receptor (PR) negative, human epidermal growth factor receptor 2 (HER2) negative. HER2 negative defined as immunohistochemistry (IHC) 0 or 1+ or fluorescence in situ hybridization (FISH) negative.
- Her2- negative hormone-refractory breast cancer which denotes progression on one or more endocrine therapies (e.g., tamoxifen, aromatase inhibitors, fulvestrant) unless contraindicated.

3.1.2 Patients must be age 18 years or older and may be male or female.

3.1.3 Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2(see appendix 1).

3.1.4 Patients must have a life expectancy of ≥ 90 days.

3.1.5 Patients with central nervous system (CNS) involvement may participate if they meet all the following criteria:

- At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment.
- Clinically stable with respect to the CNS tumor at the time of screening

3.1.6 Patients must have baseline laboratory tests within the following parameters within 14 days prior to registration :

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency
Renal	

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

3.1.7 Females of child-bearing potential (FOCBP) must have a negative serum or urine pregnancy test within 7 days prior to registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Note: A FOCBP is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not undergone a hysterectomy or bilateral oophorectomy*
- *Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)*

3.1.8 Female subjects of childbearing potential (FOCBP) must be willing to use an adequate method of contraception as outlined in Appendix 2. Contraception must be used for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

3.1.9 Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Appendix 2. Contraception must be used starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: Male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition)

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

3.1.10 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.1.11 Patients must be willing and able to comply with scheduled visits, treatment plan and laboratory tests.

3.1.12 Patient must be able to swallow and retain oral medication.

3.2 Exclusion Criteria

3.2.1 Patients with documented HER2-positive metastatic disease are not eligible, even if their primary breast cancer was HER2-negative.

3.2.2 Patients who have received prior anti-cancer therapy (e.g., biologic or other targeted therapy, chemotherapy) within 2 weeks prior to registration. Hormone therapy is permitted until registration.
Note: patients who received prior anti-PD-1, PD-L1 or PD-L2 agents are still eligible. A wash-out period of 2 weeks prior to registration is required.

3.2.3 Patients who have received prior capecitabine therapy are not eligible.

3.2.4 Patients who have not recovered from adverse events to Grade 1 severity or lower due to agents administered more than 2 weeks earlier than registration, are not eligible, except for stable sensory neuropathy (≤ Grade 2) and alopecia.

3.2.5 Patients who have received radiotherapy ≤ 4 weeks prior to registration, with the exception of palliative radiotherapy, who have not recovered from side effects of such therapy to baseline or grade ≤ 1 are not eligible for participation.
Note: any lesions treated with radiation therapy cannot be used in disease assessment.

3.2.6 Patients who have undergone major surgery ≤ 4 weeks prior to registration or have not recovered from side effects of such procedure are not eligible for participation.

3.2.7 Patients may not be receiving any other investigational agents.
Note: A wash-out period of 2 weeks prior to registration is required for any patient to be enrolled in the study.

3.2.8 Patients who have a history of allergic reactions or hypersensitivity reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab and/or humanized antibodies are not eligible.

3.2.9 Known hypersensitivity to capecitabine, fluorouracil, or any component of the formulation.

3.2.10 History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis or glomerulonephritis.

- Patients with history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
- Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen for more than a month may be eligible for this study.

- Patients with auto immune disease that does not recur unless patient is exposed to an external trigger (i.e. gluten and celiac disease) may also be eligible.

3.2.11 Patients who have evidence of active, noninfectious pneumonitis or have a history of severe pneumonitis that required treatment with steroids are not eligible for this study.
(Note: Replacement physiologic dose of steroids (prednisone 10 mg daily or equivalent) are allowed)

3.2.12 Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible:

- Hypertension that is not controlled on medication (defined as ≥140/100 at rest, average of 3 consecutive readings)
- Ongoing or active infection requiring systemic treatment
- Symptomatic congestive heart failure
- Unstable angina pectoris
- Cardiac arrhythmia
- Psychiatric illness/social situations that would limit compliance with study requirements
- Known positive test for HIV
- Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- Active tuberculosis
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Administration of a live, attenuated vaccine within 4 weeks before starting the study treatment or anticipation that a live attenuated vaccine will be required during the study.
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

3.2.13 Female patients who are pregnant or nursing (lactating) are not eligible.

3.2.14 Patients exhibiting any other condition that would, in the Investigator's judgment, preclude patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures are not eligible for participation. This might include, but is not limited to, infection/inflammation, intestinal obstruction, and/or social/psychological complications.

3.2.15 Patients with impaired GI function or GI disease that may significantly alter absorption of oral capecitabine (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection) are not eligible for participation.

3.2.16 Patients with a history of another malignancy that progressed or required treatment within the past year prior to registration are not eligible for participation. Note: the exceptions to this include non-melanoma skin cancer or excised carcinoma in situ of the cervix.

4.0 TREATMENT PLAN

4.1 Overview

This will be an open-label, single-arm, phase II study of the combination of pembrolizumab and capecitabine in locally advanced and metastatic triple negative and hormone-refractory breast cancer.

Pembrolizumab will be administered at 200mg IV on Day 1 of each cycle (1 cycle=21 days).Capecitabine will be administered at 1000 mg/m2 BID D1-14q21d. Patients will be instructed to take the morning dose of capecitabine before coming to clinic for pembrolizumab infusion. (Refer to section 8.2.5 for details about drug intake). Patients will continue to receive treatment until disease progression or unacceptable toxicity. After discontinuation of study drugs, patients will be assessed every 3 months up to 1 year for PFS, with visits and/or phone calls.

4.2 Treatment Administration

Agent	Pre-medications	Dose	Route	Schedule	Cycle Length
Pembrolizumab	n/a	200 mg	IV	Day1 of a 21 day cycle	21 days
Capecitabine	n/a	1000 mg/m2	oral	BID on Days 1-14 every 21 days	

4.2.1 Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab; MK-3475) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

In this trial, pembrolizumab will be given at a dose of 200 mg IV every 21 days (Day 1 of a 21-day cycle, can be administered +/- 3 days of Day 1) in a 30 minute IV infusion (-5 min/+10 min).

No pre-medications are required as part of this study.
See Section 4.9 for supportive care guidelines for pembrolizumab, including use of corticosteroids.

4.2.2 Capecitabine

Capecitabine is to be self-administered by patient, 1000 mg/m2 PO BID Days 1-14 every 21 days. It is to be taken preferably 12 hours apart (with minimum 8 hours between doses).It is to be ingested with food or within 30 minutes of eating with 8 oz glass of water (not fruit juices). Tablets are to be swallow whole and not crushed or cut. No supportive medications are required as part of this study.

If dose is missed and next dose would normally be in less than 8 hours, then dose should be skipped entirely and marked accordingly on the medication diary (available as stand-alone document).

Patients will also record doses taken, missed, or skipped, as well as any

occurrence of vomiting, diarrhea, increased stool frequency, or rashes on the Medication Diary. This Diary will be reviewed by a member of the study team at every study visit, and any issues with compliance will be addressed. Along with the diary, patients should bring the medication bottle and any remaining tablets with them on each study visit. The Coordinator and PI will monitor for compliance. If a patient misses more than 7 consecutive doses of capecitabine due to poor adherence, the patient will be removed from study treatment. If capecitabine doses are missed, and it is < 7 doses, they may be made up within the same cycle. Patients will be given 14 days of supply at the start of study treatment. Additional capecitabine tablets will be dispensed every 3 weeks. The consent form will also ask that patients agree to keep the capecitabine pills out of reach from children and other individuals in their home.

4.2.3 Continuation of Investigational Therapy after Radiographic Progression (Pseudoprogression)

Treatment may be continued in the setting of pseudoprogression (radiographic increase or new lesions felt to be due to inflammation/immune response) as long as all of the following criteria are met:

- Absence of clinical symptoms or signs indicating clinically significant PD.
- No significant decline in Eastern Cooperative Oncology Group (ECOG) performance status.
- Absence of rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention
- Patients are made aware of the potential benefits and risks of continuing study therapy in the setting of Pseudo-Progression.

These patients will continue to be monitored for safety parameters. Patients continuing therapy in the setting of suspected pseudoprogression should continue with treatment according to protocol as long as the above criteria are met and clearly documented in the patient's medical record.

4.3 Dose Modifications

4.3.1 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 1 below. Dose reductions for pembrolizumab are not permitted.

Capecitabine should be withheld/dose reduced for drug-related toxicities and AEs as per Table 2, 3, 4.
See Section 4.9 for supportive care guidelines for pembrolizumab, including use of corticosteroids.

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the

development of toxicity according to the timeframe referenced in the Schedule of Events table). Toxicity will be assessed according to NCI's CTCAE, version 4.03.

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 of capecitabine and 12 weeks of interruption of pembrolizumab, unless otherwise discussed with the Principal Investigator and QAM. The reason for interruption should be documented in the patient's study record.

If pembrolizumab is held for toxicity, participants are permitted to continue on protocol therapy with capecitabine alone. If capecitabine is held for toxicity, participants are permitted to continue on therapy with pembrolizumab alone.

If capecitabine doses are missed,and it is < 7 doses, they may be made up within the same cycle.

If one drug is permanently withdrawn for toxicity (i.e. the patient cannot dose reduce any further on capecitabine), then the patient should come off study completely.

Capecitabine Dose Reduction Table

Dose Level	Dose
1	1000 mg/m2
-1	800 mg/m2
-2	640 mg/m2
Stop	N/A

Table 1 –Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with 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.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Capecitabine Dose Modifications:

Table 2: Hematologic Toxicities

ANC(/mm^3)		Platelets (/mm^3)	Modification
<1000/mm^3	AND/OR	<100,000/mm^3	Hold until ANC>=1000/mm^3 and PLt >=100,000 ^{3} resume at 20% dose reduction
>=1000/mm^3	AND	>=100,000/mm^3	No dose modification

Table 3: Mucositis, Diarrhea or Esophagitis

Grade	Toxicities/Symptoms	Modification
1	Mucositis, esophagitis, or diarrhea	No dose modification
2	Diarrhea	No dose modification
2	Mucositis, or esophagitis	Hold until <=grade1 and resume at 20% dose reduction
3	Diarrhea	Hold until <=grade 1; resume at 20% dose reduction
3/4	Mucositis or esophagitis	Hold until <=grade 1; resume at 20% dose reduction

Table 4: Palmar-Plantar Erythrodysesia Syndrome (Hand and Foot Rash)

Grade	Modification
1	No dose modification
2	Hold until symptoms resolve to grade 0 or 1 Resume a 20% dose reduction *(per treating physician's discretion)*
>=3	Hold until symptoms resolve to Grade 1 or lower. Resume with dose reduction of 1 level (20% dose reduction).

Non-hematologic Toxicity
For other non-hematologic toxicities, dose reductions of capecitabine will be at the discretion of the investigator. A 20% dose reduction must be performed with each subsequent reduction. A maximum of 2 dose reductions will be performed.

4.4 Concomitant Medications/Treatments

Premedication: National Comprehensive Cancer Network (NCCN) approved prophylactic antiemetics may be given as appropriate

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial,

discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with PI. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

Acceptable concomitant medications:

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2 and 7.3.3.3

Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Radiation therapy to symptomatic lesions or to the brain may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest 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.

Concomitant Medications/treatments to be taken with precaution

Capecitabine is a strong CYP2C9 inhibitor. Caution should be exercised when capecitabine is co - administered with CYP2C9 substrates (see Section 8.2).Capecitabine may increase the serum concentration of vitamin K antagonists (warfarin). Patients receiving concomitant capecitabine and oral warfarin-

derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly.

Pembrolizumab may be associated with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Risk factors for SJS and TEN include certain medications such as anticonvulsants, sulfonamides, aminopenicillins, allopurinol, and NSAIDs. These should be taken after consultation with the treating physician. Non-medication triggers include infection, contrast media, and vaccinations. Malignancy is associated with an increased mortality rate in patients with SJS and TEN

Certain medications such as anthracyclines, alkylating agents and checkpoint inhibitors as well as radiation may be risk factors for immune-mediated myocarditis. These should be taken after consultation with the treating physician.

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

4.5 Duration of Therapy

Patients may continue to receive cycles of treatment until any of the following occur:

- Disease progression
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from either study treatment or the whole study
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)

4.6 Duration of Follow Up

- End of treatment visit is required approximately 30 days after the last dose of pembrolizumab for the purposes of adverse event assessment.
- Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.
- Patients will be assessed every 3 months up to 2 year after discontinuation of the study drugs for PFS with visits and/or phone calls.

4.7 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate electronic case report form (eCRF) and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant

- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

4.8 Patient Replacement

If a patient is withdrawn from the study prior to completing 21 days of therapy, for reasons other than adverse event or progression of disease, an additional patient may be added. If a patient discontinues treatment due to early progression prior to completing 3 cycles of therapy, the patient will be evaluable for toxicity but not for efficacy endpoints; in this case an additional patient may be added. *(Note: any patient receiving 1 dose of pembrolizumab is evaluable for toxicity but not for primary objective of PFS).*

Patients missing 14 or more doses of capecitabine due to toxicity will not be replaced.

4.9 Supportive Care Guidelines & Toxicity Management

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. Toxicity will be attributed to either or both drugs per physician's clinical judgement, and dose modifications/delays will be made accordingly.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the treatment guidance (as outlined below)

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Refer section 4.3 for dose modification.

4.9.1 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.

4.9.2 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.

4.9.3 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.

4.9.4 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.

4.9.5 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) (see section 5.0) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

4.9.6 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.

4.9.7 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.

4.9.8 Stevens-Johnson Syndrome(SJS) and Toxic Epidermal Necrolysis(TEN)

- For signs or symptoms of SJS or TEN, withhold pembrolizumab and refer the patient for specialized care for assessment and treatment.
- If SJS or TEN is confirmed, permanently discontinue pembrolizumab.

4.9.9 Immune-mediated myocarditis

- For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies, and administer corticosteroids as appropriate.

4.9.10 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** 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg 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.		

4.10 Restrictions during pregnancy and lactation

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman.

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Northwestern University and within 2

working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).
The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Northwestern University. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Northwestern University and to Merck and followed as described above and in Section 7.0
It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.0 STUDY PROCEDURES

	Screening (-28 days)	On Treatment [10]		Off Treatment	
Time Period	Baseline	Cycle 1+ (+/- 3days)	After Every 3 cycles	End of Treatment	Follow-up[11]
Assessment or Activity					
Informed Consent	X				
Medical history (H)	X			X	
Concomitant Medications[12]	X	X		X	X[12]
Vitals, Physical exam[1] (PE)[1]	X	X		X	
ECOG status	X	X		X	
Toxicity assessment[14]		X		X	X[15]
Tumor Measurements[2]	X		X[2]	X	
Biopsy/archival tissue[3]	X				
CBC with diff [4]	X	X		X	
Chemistry panel [5]	X	X[5]		X	
PT/PTT/INR [6]	X				
Thyroid function tests[13]	X		X[13]		
Pregnancy test[7]	X				
Pembrolizumab[8]		X			
Capecitabine[9]		X			
Survival status					X

[1] Every physical exam will be a full physical exam and is standard of care. It will include vital signs (pulse, temperature, and blood pressure) and height (baseline only) and weight.

[2] CT c/a/p AND bone scan. In place of bone scan, a PET/CT may be used. If CT is contraindicated, MRI may be used. Any additional imaging such as MRI can be completed at the physician's discretion. The same modality should be used throughout the study. The baseline procedure is to be performed within 28 days prior to registration. Subsequently, it will be done prior to the start of the next treatment cycle e.g 4, 7, 10 etc. For patients who are unable to obtain scans at the designated time points, a window of 7-10 days is allowed. This exception is not applicable to the screening period. Bone scans are to be repeated at each time point ONLY if the patient has bone metastasis or if it is clinically indicated. If the original bone scan during screening is negative, then bone scans are not required in subsequent visits.

[3] A baseline tissue biopsy of a metastatic site will be obtained for PD-L1 immunohistochemical (IHC) assessment, from all patients. An archived specimen may be used (metastatic tissue only) if collected no more than 2 months prior to registration. Otherwise fresh biopsy of metastatic lesion is mandatory at baseline and should be performed no more than 2 months prior to registration. The requirement for biopsy (fresh) may be omitted per treating physician's discretion, if the biopsy would cause undue morbidity to the patient and if enough tissue from a prior metastatic lesion (archival biopsy) is not available.

PD-L1 IHC assay from QualTek will be used for the study.
Please refer to section 9.1 and laboratory manual for more details

[4] Hematology will include white blood cells (WBC) with differential, platelet count, hematocrit, and hemoglobin. To be performed within 14 days before Day1

[5] Serum Chemistry will include calcium, chloride, creatinine, sodium, potassium, blood urea nitrogen, bicarbonate, glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, and total protein. To be performed within 14 days prior to registration. Patients with liver metastatis will have additional liver function testing done on C1D7 and C1D14, which can be done locally and sent to NU for review.

[6] This is to be done if the patient is required to have a biopsy (in order to test for bleeding parameters before biopsy). It is to be performed and resulted before the biopsy. (Also refer to footnote 14)

[7] Serum or urine test for females of child-bearing potential.

[8] Pembrolizumab will be administered IV at the assigned dose, at Day 1 of every cycle (1cycle =21 days)

[9] Capecitabine will be self-administered orally by patients at a fixed dose daily on Days 1-14 twice daily, of each cycle.

[10] A cycle is defined as 21 days (+/- 3 days).

[11] Patients will be assessed every 3 months up to 2 year after discontinuation of the study drugs for PFS with visits and/or phone calls.

[12] concomitant medications to be recorded during screening, at the beginning of each cycle and for 30 days after end of treatment

[13]Thyroid function will be evaluated at baseline (performed within 14 days of Day1) and prior to the start of the next treatment cycle e.g. 4, 7, 10 etc. The tests included are TSH, freeT3, and freeT4.

[14] Toxicity assessment to be done at the beginning of each cycle, at the end of treatment visit and for 30 days after end of treatment.

6.0 ENDPOINT ASSESSMENT

6.1 Disease Definitions

Patients with non-measurable and measurable disease are eligible for this study. Response to treatment will be assessed using RECIST1.1 guidelines (Appendix 3). Response and progression will be assessed in this study via physical exam and imaging. Lesions are defined as either measurable or non-measurable using the criteria provided below.

6.1.1 Measureable Disease

Measurable disease per RECIST 1.1 is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. For irRC, measurable lesions are defined as as those that can be accurately measured in at least two dimensions as 10x10mm with CT scan. All tumor measurements must be recorded in millimeters.

6.1.2 Non-Measurable Disease

For both RECIST 1.1 and irRC, all other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Evaluation of Overall Timepoint Response for Patients without Measurable disease at baseline

Non-target	New	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal Progression	Yes or No	PD
Any	Yes	PD

CR=Complete Response, PD=Progressive disease, NE=Inevaluable

6.1.3 Target Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and

will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated at baseline and used as the reference by which to characterize the objective tumor response.

6.1.4 Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required.

6.2 Guidelines for Evaluation of Measureable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed within the timeframe noted in section 5.0. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

6.2.1 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

6.3 Endpoints

6.3.1 Primary Endpoint(s):

To evaluate the median progression-free survival (median PFS) for participants receiving pembrolizumab with capecitabine for the treatment of locally advanced or metastatic TNBC and hormone-refractory MBC. This will be assessed by using RECIST 1.1 criteria.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target 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).
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Please note patients with PD may stay on study with PD if they meet the critiera in section 4.2.3.

*Any patient who has completed **at least 3 cycles** of pembrolizumab and capecitabine will be evaluable for this endpoint*.
Note: the first set of scans is required to establish that the patient is evaluable for this endpoint.

6.3.2 Secondary Endpoints:
To describe the objective response rate (ORR) for participants receiving pembrolizumab with capecitabine for the treatment of locally advanced or metastatic TNBC and hormone-refractory MBC.
This will be assessed by using RECIST 1.1 criteria (appendix 3).

*Any patient who has completed **at least 3 cycles** of this combination therapy are evaluable for this endpoint. Note: the first set of scans is required to establish that the patient is evaluable for this endpoint.*

To describe the safety and tolerability of the combination of pembrolizumab and capecitabine for the treatment of locally advanced or metastatic TNBC and hormone-refractory MBC. All adverse events will be assessed by NCT CTCAE 4.03 criteria.

*Any patient who has completed **at least one dose** of either pembrolizumab or capecitabine will be evaluable for this endpoint*.

***(**NOTE: If a patient discontinues treatment due to early progression prior to completing 3 cycles of therapy, the patient will be evaluable for toxicity but not for efficacy endpoints; in this case an additional patient may be added).*

6.3.3 Exploratory Endpoint: <u>PD-L1 assessment</u>

A baseline tissue biopsy of a metastatic site will be obtained for PD-L1 immunohistochemical (IHC) assessment, from all patients. An archived specimen may be used (metastatic tissue only) if collected no more than 2 months prior to registration. Otherwise fresh biopsy of metastatic lesion is mandatory at baseline and should be performed no more than 2 months prior to registration.
Note: The requirement for biopsy (fresh) may be omitted per treating physician's discretion, if the biopsy would cause undue morbidity to the patient and if enough tissue from a prior metastatic lesion (archival biopsy) is not available.

Note: PD-L1 IHC assay from QualTek will be used for the study.
Please refer to section 9.1 and laboratory manual for more details

QualTek developed and validated a PD-L1 IHC assay using Merck's proprietary

22C3 antibody, and this will be used for the study. The study site's pathology core will be used to store, process, and ship samples to QualTek. The presence of PD-L1 expression will be correlated with response (PFS, RR) and other clinical-pathologic factors in an attempt to define a subset of patients that may benefit from pembrolizumab.

PFS and ORR assessment (using irRECIST)

To evaluate efficacy endpoint median-Progression Free survival (PFS), assessment will be done up to 1 year after discontinuation of the study drugs. Assessment will be done using irRECIST (see table below)

ORR will be assessed every 3 cycles (every 9 weeks) with imaging (CT chest/abdomen/pelvis and bone scan [if indicated]). Assessment will be done using irRECIST (see table below)

Table No: 6 Tumor Response Evaluation: Comparison between RECIST 1.1 and irRECIST

Criteria	RECIST 1.1	irRECIST
New measurable lesions (≥10 mm)	Always represents PD	Incorporated into tumor burden
New non-measurable lesions (< 10 mm)	Always represents PD	Does not define progression but precludes irCR
Non-Target lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥ 30% decrease in the sum of the longest diameter of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions	≥ 30% decrease in tumor burden compared with baseline
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study	Neither a 30% decrease in tumor burden compared with baseline nor a 20% increase compared with nadir can be established
PD	At least 20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions is also considered progression.	At least 20% increase in tumor burden compared with nadir (at any single time point)*

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University

(http://cancer.northwestern.edu/cro/data/DataandSafetyMonitoringPlanMay2014.pdf). The level of risk attributed to this study requires high intensity monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations and as required by the NCI AdEERS Reporting Guidelines.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for timepoints). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.
Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.
Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-

specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.3. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

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

7.2.2 Severity of AEs

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through **90** days after last dose of study medication (SM) or until start of new anticancer regimen, but for at least 30 days post last SM dose, whichever occurs first.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is *life-threatening*.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- **Results in *persistent or significant disability or incapacity*.**
- **Is a *congenital anomaly/birth defect.***
- **Is an *important medical event*.**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
  - Is a new cancer (that is not a condition of the study);
  - Is associated with an overdose.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form is required (refer to NU template SAE Form available in NOTIS)

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 10 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.3.3 Reporting to FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.3.4 Reporting to Merck

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.5 for additional details) that occurs to any subject must be reported within 24 hours to the NU QA and/or IRB (see section 7.3.3.1 and 7.3.3..2)r and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.5 for additional details whether or not related to the Merck product, must be reported within 24 hours to the S and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought

to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).
For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the NU QA /IRB (refer section 7.3.3.1 and 7.3.3.2) and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:
1. An overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of

abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.3.3.5 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3(expedited reporting), unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

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

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

7.3.3.6 Reporting of Overdose to Merck

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
If a dose of Merck's product meeting the protocol definition of overdose (refer section 7.2.1) is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."
All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

(*Note: This does not apply to Northwestern University, because, as per NU IRB regulations, any amount of overdose will be reported as a reportable New Information [RNI])(Refer Section 11.7.2).*

7.3.3. 7 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

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

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

8.0 DRUG INFORMATION

8.1 Pembrolizumab

8.1.1 Other Names

Keytruda (Pembrolizumab; MK-3475 [Anti-PD-1 Antibody MK-3475])

8.1.2 Classification

Humanized X PD-1_mAb (H409A11) IgG4

8.1.3 Mode of action

Highly selective anti-PD-1 humanized monoclonal antibody which inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding. Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling (Hamid, 2013). Anti-PD-1 antibodies (including pembrolizumab) reverse T-cell suppression and induce antitumor responses.

8.1.4 Storage and Stability

Please refer to pharmacy manual for detailed instructions

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

Store Pembrolizumab vials under refrigeration at 2 to 8 degrees Celsius (^{0}C) or 36 to 46 degrees Fahrenheit (^{0}F). Do not freeze; do not shake.
Prior to reconstitution, the vials of lyophilized powder can be out of refrigeration (temperatures at or below 25°C (77°F)) for up to 24 hours.

Storage following reconstitution and dilution: Store at room temperature for a cumulative time up to 4 hours (this includes room temperature storage of the diluted infusion solution and the duration of infusion). IV bags and/or reconstituted vials can be also stored refrigerated at 2—8 degrees ^{0}C (36—46 degrees ^{0}F) for up to 20 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use. Do not freeze.

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.

8.1.5 Protocol dose specifics

200mg IV once every 3 weeks until disease progression or unacceptable toxicity. Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 21 days. A window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

8.1.6 Preparation

Please refer to pharmacy manual for detailed instructions.

Pembrolizumab is provided as a white to off-white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only. Pembrolizumab is formulated with L-histidine as buffering agent, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment (if necessary).
Pembrolizumab Powder for Solution for Infusion is reconstituted with 2.3 mL sterile water for injection (SWFI) to yield a 2.4 mL solution containing 25 mg/mL of pembrolizumab prior to further dilution. Pembrolizumab vial contains an excess fill of 10 mg (equivalent to 0.4 mL of reconstituted solution) to ensure the recovery of label claim of 50 mg/2 ml pembrolizumab per vial.

The product after ***reconstitution with sterile water for injection*** and the liquid drug product is a clear to opalescent solution, which may contain extraneous and proteinaceous particulates. The reconstituted drug product solution and liquid drug product are to be further diluted with normal saline in polyvinyl chloride (PVC) or non-PVC IV bags to achieve final concentration between 1 mg/mL and 10 mg/mL.
Reconstituted vials and infusion solutions should be immediately administered after preparation. If not used immediately, reconstituted vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution and liquid drug product in vials, storage of infusion solution in the IV bag and the duration of infusion.

8.1.7 Route of administration for this study

Intravenous (IV)

8.1.8 Incompatibilities

None known
Refer to pharmacy manual for list of infusion set materials compatible with pembrolizumab.

8.1.9 Availability & Supply

Merck will supply pembrolizumab (investigational / clinical supply) directly to the NU Investigational Pharmacy at no charge to subjects participating in this clinical trial. The contact for drug ordering will be Sloan Stribling

(sloan_stribling@merk.com) or Tammy Moll (tammy.moll@merck.com). The Merck Drug Request Form, provided by Merck, should be completed and emailed to these contacts.

The treating 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.

8.1.10 Side effects

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, thyroid disorders (hypothyroidism/hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitus, uveitis, and nephritis. After a recent review of data, events newly characterized as identified risks also include pancreatitis, myositis, and severe skin reaction; these are included in the reference safety information in the current IB. The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy.

In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

Most common (seen in >10% of patients):

- *Fatigue*
- *Headache*
- *Chills*
- *Difficulty sleeping*
- *Dizziness*
- *Leg swelling*
- *Itching and/or rash*
- *Elevated blood sugar level*
- *High triglycerides (type of cholesterol)*
- *Lower levels of calcium or sodium in the blood*
- *Nausea and/or vomiting*
- *Decreased appetite*
- *Diarrhea or constipation*
- *Pain in the abdomen*
- *Cough*
- *Shortness of breath*
- *Fever*

Less common (seen in 1 to 10% of patients):

- *Skin infection*
- *Abnormal thyroid function (decreased or increased)*
- *Colitis (inflammation or infection of the colon [large intestine]*
- *Sepsis (infection in the bloodstream)*
- *Kidney failure*

- *Pneumonitis (inflammation of the lung) or pneumonia (infection in the lung)*

Rare but serious or life-threatening (seen in <1% of patients)

- *Immune system attacking adrenal gland (adrenocortical insufficiency), joints (arthritis), liver (hepatitis), kidneys (nephritis), skin (dermatitis) muscles (myositis), eyes (optic neuritis or uveitis), pancreas (pancreatitis), brain (partial epilepsy), heart (immune-mediated myocarditis) or other organs causing possibly irreversible damage to these organs.*
- *Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have also been identified as rare but serious life-threatening side-effects.*
- *Sarcoidosis is a clinically significant, immune-mediated adverse reaction that was reported in less than 1% of patients*
- *Encephalitis is a clinically significant, immune-mediated adverse reaction that was reported in less than 1% of patients*

Please refer to the current version of the Investigator's Brochure for a complete list of adverse events.

8.1.11 Nursing implications

Pembrolizumab will be administered at 200mg IV on Day 1 of each cycle (1 cycle=21 days).Capecitabine will be administered at 1000 mg/m2 BID D1-14 q21d. Patients will be instructed to take the morning dose of capecitabine before coming to clinic for pembrolizumab infusion (Refer to section 4.0 for details)

Pembrolizumab will be administered as an IV infusion ((section 8.1.6) over approximately 30 minutes Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration.

When an IV bag is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered

Since the compatibility of pembrolizumab with other IV medications and solutions, other than normal saline (0.9% [w/v] sodium chloride for injection) and D5W , is not known, the Pembrolizumab solution should not be infused through an IV line in which other solutions or medications are being administered. The date, start time, interruption, and completion time of Pembrolizumab administration must be recorded in the source documents. Any unused solution for injection should not be used for another infusion of the same or different subject.

8.1.12 Return and Retention of Study Drug

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 pembrolizumab vial(s) shall be returned to the designated facility for destruction.

Please refer to pharmacy manual for the address of the designated facility.

All used 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.

8.2 Capecitabine

8.2.1 Other Names

Xeloda

8.2.2 Classification – Type of Agent

Antineoplastic Agent, Antimetabolite (Pyrimidine Analog)

8.2.3 Mode of action

Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle.

8.2.4 Storage and stability

Capecitabine is commercially available as 150 mg or 500 mg tablets. Physician may prescribe either 150mg or 500mg tablets based on calculation of patient's BMI

Capecitabine tablets should be stored at room temperature (15° to 30°C) in the container in which they are provided.
Patient will keep medication in a cool, dry place out of reach of children and other individuals.

8.2.5 Protocol dose specifics

Patient to take capecitabine 1000mg/ /m2 BID D1-14 of a 21 day cycle. Capecitabine will be taken orally. It is self-administered by patient. Patients will be instructed to take the morning dose of capecitabine before coming to clinic for pembrolizumab infusion.

Capecitabine is to be taken preferably 12 hours apart (with minimum 8 hours between doses).
It is to be ingested with food or within 30 minutes of eating with 8 oz glass of water (not fruit juices). Tablets are to be swallow whole and not crushed or cut.
If dose is missed and next dose would normally be in less than 8 hours, then dose should be skipped entirely and marked accordingly on the medication diary (available as stand-alone document).

8.2.6 Preparation

Film coated tablets

8.2.7 Route of administration for this study

Oral. Self-administered by patient.

8.2.8 Incompatibilities

Potential drug interactions: Capecitabine is a strong inhibitor of CYP2C9 and concomitant administration of CYP2C9 substrates should be avoided (ex: bosentan, cannabis, carvedilol, diclofenac, dronabinol, fosphenytoin, lacosamide, metronidazole, ospemifene, parecoxib, phenytoin, ramelteon, warfarin).

Warfarin: [US Boxed Warning]: Capecitabine may increase the anticoagulant

effects of warfarin; bleeding events, including death, have occurred with concomitant use. Clinically significant increases in prothrombin time (PT) and INR have occurred within several days to months after capecitabine initiation (in patients previously stabilized on anticoagulants), and may continue up to 1 month after capecitabine discontinuation. May occur in patients with or without liver metastases. Monitor PT and INR frequently and adjust anticoagulation dosing accordingly. An increased risk of coagulopathy is correlated with a cancer diagnosis and age >60 years.

Leucovorin Calcium-Levoleucovorin: May enhance the adverse/toxic effect of Capecitabine. *Risk C: Therapy to be monitored.*

Capecitabine may enhance the immunosuppressive effect of Immunosuppressants (ex: Leflunomide, Tacrolimus, etc.) concomitant administration is prohibited.

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants.

Cimetidine: Since cimetidine can decrease the clearance of 5-FU, co-administration should be avoided. Ranitidine or a drug from another anti-ulcer class can be substituted for cimetidine if necessary.

For a complete and detailed list, please refer to FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

8.2.9 Availability & Supply

Capecitabine is standard of care treatment for metastatic breast cancer and will be provided through patient's insurance. Patients will be given a 14 days supply of tablets at the start of study treatment (patients will collect the tablets from their respective pharmacies). Additional capecitabine tablets will be dispensed every 3 weeks. The consent form will also ask that patients agree to keep the capecitabine pills out of reach from children and other individuals in their home.

8.2.10 Side effects

Frequency listed derived from monotherapy trials. Incidence reported for all indications and usage, unless otherwise noted. Frequency not always defined.

Most common (seen in >10% of patients):

- Fatigue
- Diarrhea
- Nausea and/or vomiting
- Decreased appetite
- Numbness or tingling
- Weakness
- Rash on the palms or soles
- Leg swelling
- Lowering of the white blood cell count or platelet count
- Anemia
- Higher levels of bilirubin in the blood
- Eye irritation
- Fever

- *Less common (seen in 1 to 10% of patients):*
- Blood clot in the veins
- Chest pain
- Irregular heart rhythms
- Fluid around the heart
- Heart stopping
- Heart attack
- Headache
- Dizziness
- Depressed mood or mood changes
- Difficulty swallowing
- Feeling sleepy
- Skin rash
- Hair loss
- Itching
- Increased thirst
- Hot flashes
- Lowering of the potassium or magnesium levels in the blood
- Weight gain
- Pain in your belly/indigestion
- Bleeding in the GI tract
- Feeling bloated
- Abnormal liver tests in the blood
- Hypersensitivity (allergic) reaction
- Back pain
- Muscle and/or joint aches
- Cough
- Shortness of breath
- Flu-like symptoms
- Coughing up blood
- Hoarse voice
- Nose bleeds

Rare but serious or life-threatening (seen in <1% of patients)

- Kidney failure (usually reversible)
- Fluid buildup in the abdomen
- Bronchitis and/or pneumonia
- Stroke
- Confusion
- Passing out
- Blood clots
- Sepsis (infection in the bloodstream)
- Stevens-Johnson syndrome (allergic reaction)

9.0 CORRELATIVES/SPECIAL STUDIES

9.1 PD-L1 testing

A baseline tissue biopsy of a metastatic will be obtained for PD-L1 immunohistochemical (ICH) assessment from all patients no more than 2 months prior to registration. An archived specimen may be used (metastatic tissue only) if collected no more than 2 monthsprior to registration. Otherwise fresh biopsy of metastatic lesion is mandatory at baseline and should be performed no more than 2 months prior to registration . The requirement for biopsy (fresh) may be

omitted per treating physician's discretion, if the biopsy would cause undue morbidity to the patient and if enough tissue from a prior metastaic lesion (archival biopsy) is not available.

QualTek developed and validated a PD-L1 IHC assay using Merck's proprietary 22C3 antibody, and will be used for this study[11-12].

The study site's pathology core will be used to store, process, and ship samples to QualTek.

For patient samples, positively charged ProbeOn Plus slides **(Fisher ProbeOn Plus Catalog Number 22-230-900)** must be used for tissue sections. Slide measurements should strictly be 75mm x 25mm x 1mm. Other standard-sized positively-charged slides (75mm x 25 mm x 1mm) are acceptable as a last resort, however QualTek must be notified as there is a risk that outside slides cannot be stained. The slides must be sized as described above or the sample **cannot be tested and will be returned.**

Tumor tissue for biomarker analysis must be provided as **five (5) freshly cut, serially sectioned, unstained slides** cut at 4 microns per patient for PD-L1 testing.

Storage and Shipping: Samples may be held as blocks indefinitely at the site and then cut in batches. Slides must be shipped to QualTek immediately after sectioning to comply with the protocol's testing requirements. Patient slides must be shipped within seven (7) days of sectioning. Slides must be shipped cold (2-8°C) and in the dark.

See *QualTek MISP Sample Handling Manual* (available as stand-alone document) for detailed information regarding the processing, labelling and shipping of tissue samples prior to shipment.

Samples are to be shipped to:
QualTek Molecular Laboratories
MISP Receiving
300 Pheasant Run
Newtown, PA USA 18940
Phone: 215.504.7402
Email: MISPsamples@qmlabs.com

10.0 STATISTICAL CONSIDERATIONS

For PFS, assumptions are that the addition of pembrolizumab will increase PFS to 5 months compared to historical control of 3 months. Assuming exponential survival, with 27 evaluable patients, there is 80% power to detect this difference using a one-tailed z test at $p<0.05$.

Recruitment of 30 participants to accrue 27 evaluable will last approximately 30 months (2.5 years) and participants will be followed for a maximum of 2 years from enrollment of the last patient. The primary outcomes chosen is PFS based on mechanism of action..

PFS will be analyzed using a Kaplan-Meier curve. A confidence interval for the median PFS will be calculated (Brookmeyer, R. and Crowley, J. (1982), "A Confidence Interval for the Median Survival Time," *Biometrics*, 38, 29–41.), and if the confidence interval is totally above 3 months, then it may be concluded that the PFS exceeds 3 months.

Objective response rate will be summarized using a proportion and an exact 95% binomial confidence interval. Anti-tumor activity will be reported as a percentage change in the sum of the dimensions of all measurable lesions as defined by RECIST 1.1 criteria. The baseline imaging before treatment will be compared to each subsequent imaging assessment. The maximum anti-tumor activity will be reported using the assessment with the smallest sum of dimensions (maximum response).

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Janssen Scientific Affairs. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office at Northwestern University before enrollment to study.

Registering a Patient to a Phase II Study

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Eligibility eCRF (complete in NOTIS)
- Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)
- Signed and dated informed consent document (upload in NOTIS)
- Pathology Report (upload in NOTIS)

The QAM will review the registration, register the patient, assign an identification number, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment. The QAM can be contacted at croqualityassurance@northwestern.edu.

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document). Generally, for all phase II patients, data are due at the end of every cycle.

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires high level monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the Appendices for additional data submission instructions.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it: Has harmed or increased the risk of harm to one or more research participants.

- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

  Any deviation that would constitute an instance of Reportable New Information must be reported to the Northwestern IRB within 5 business days of knowledge or notification.

11.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. The assigned QAM will prepare a preliminary data summary (to be approved by the DMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

12.0 REFERENCES

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Katarzyna Pogoda, Anna Niwińska, Magdalena Murawska, Tadeusz Pieńkowski
Med Oncol. 2013 March; 30(1): 388. Published online 2013 January 5. doi: 10.1007/s12032-012-0388-4 PMCID: PMC3586394

13.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, bu ambulatory and able to carry out work of a light or sedentary nature (e.g., ligh housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: CONTRACEPTION (specifications for Pembrolizumab)

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.
For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).
Female subjects will be considered of non-reproductive potential if they are either:
(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
OR
(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
OR
(3) has a congenital or acquired condition that prevents childbearing.
Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:
(1) practice abstinence† from heterosexual activity;
OR
(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Appendix 3: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

Appendix 4: AE Assessment Guidelines for Reporting to Merck

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

14.0 HISTORY OF PROTOCOL AMENDMENTS

Amendment 1–October 24th, 2016			
Sections(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Protocol cover page	IND number: exempt	Updated to: Pre-IND Number is132860	***Study deemed non-exempt by sponsor and will be submitted to FDA.***
Section 7.3.3.3 Reporting to FDA	N/A	New section added to state details about FDA reporting	***Study deemed non-exempt by sponsor and will be submitted to FDA***
Section 11.5 Data Management and monitoring/Auditing	The level of risk attributed to this study requires [high], as outlined in the DSMP	Modified to : The level of risk attributed to this study requires high level monitoring, as outlined in the DSMP	***For clarity***

Amendment 2–January 30th , 2017			
Sections(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Title page	Pre-IND number listed	Converted to IND number	***IND application accepted by FDA and IND number granted.***
Study summary and section 3.1.5 and 3.2.5(eligibility criteria)	Criteria regarding patients with CNS involvement was listed as an exclusion criteria	This criteria has been moved to the inclusion criteria	***The language used to describe it makes it more applicable as an inclusion criteria***
Section 2.1 Primary objective	Primary objective stated	Added language to indicate that the RECIST 1.1 criteria will be used to assess the primary objective.	***For clarity***
Section 3.1.1 Inclusion criteria	Statement that patients must have hormone refractory breasts cancer	Added: Her2-negative to the statement .Also, added " on one or more endocrine therapies" .	***For clarity and to denote that the patient does NOT have to have received all 3 hormone agents before calling them hormone refractory. They should have received at least 1 of the agents, and determined to be hormone refractory per treating physician (based***

			on clinical judgement)
Section 3.1.6. Inclusion criteria	Baseline laboratory tests to be done within 4 weeks(28 days)	modified to: baseline lab tests to be done within 2 weeks(14 days)	***For safety and convenience***
Section 3.1.7 Inclusion criteria	Pregnancy test within 7 days prior to registration AND must be at least within 3 days prior to first dose of study drug.	Modified to state only: "within 7 days prior to registration"	***For convenience***
Section 3.2.2 Exclusion criteria	A caveat stating that patients receiving PD-1, PD-L1 or2 agents are eligible even though prior anti-cancer therapy is not permitted (with some exceptions).	Language added to clarify that a wash-out period of 2 weeks prior to registration is required for these agents.	***For safety and clarity***
Section 3.2.4 Exclusion criteria	Criteria about patients treated with radiotherapy not being eligible for the study(with some exception)	Note added to state that "any lesions treated with radiation therapy cannot be used in disease assessment."	***For clarity***
Section 3.2.6 Exclusion criteria	Statement that patients receiving any other investigational agent will not be eligible for the study.	Language added to clarify that a wash-out period of 2 weeks prior to registration is required for such patients to be eligible.	***For safety and clarity***
Section 3.2.8 Exclusion criteria	Criteria stating that patients with known hypersensitivity to capecitabine is not eligible. But patients with prior treatment with capecitabine is eligible.	Language inserted to clarify that a wash-out period of 2 weeks is required for any patient with history of prior treatment with capecitabine to be eligible for this study.	***For safety and clarity***
Section 3.2.9 Exclusion criteria	Criteria stating exclusion of autoimmune disease patients with some caveats for exceptions.	One more caveat added stating that "Patients with auto immune disease that does not recur unless patient is exposed to an external trigger (i.e. gluten and	***For flexibility and clarity***

		celiac disease) may also be eligible".	
Section 3.2.11 Exclusion criteria	List of uncontrolled intercurrent illness that made patient ineligible, included ECG abnormality	ECG abnormality removed from this list	***For flexibility***
Section 4.2.3 sub-section of treatment administration	N/A	New sub-section added to state details about **"**Continuation of Investigational Therapy after Radiographic Progression (Pseudoprogression)"	***For safety and clarity to state that treatment can be continued in the setting of pseudoprogression***
Section 4.3.1 Dose modifications	Details about dose modifications for pembrolizumab and capecitabine	Added language: 1. Dose reductions for pembrolizumab are not permitted. 2. Capeciatbine should be withheld/dose reduced for drug –related toxicities. 3. Capecitabine dose reduction table inserted. 4. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption of capecitabine and 12 weeks of interruption of pembrolizumab, unless otherwise discussed with the Principal Investigator and QAM. 5.If pembrolizumab is held for toxicity, participants are permitted to continue on protocol therapy with capecitabine alone. If capecitabine is held for toxicity, participants are permitted to continue on therapy with pembrolizumab alone. 6. If one drug is permanently withdrawn for toxicity (i.e. the	***For safety and clarity***

		patient cannot dose reduce any further on capecitabine), then the patient should come off study completely.	
Section 4.4 subsection Concomitant medications/treatments to be taken with precaution	Previous details	Language added regarding medication and non-medication risk factors for Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Immune-mediated myocarditis.	***Based on pembrolizumab action letter received from Merck, dated 2.10.17***
Section 4.9 Supportive Care guidelines and Toxicity Management	Previous details	Language added to state that toxicity will be attributed to either or both drugs per physician's clinical judgement, and dose modifications/delays will be made accordingly. In addition, two new subsections 4.9.8 and 4.9.9 have been added to state the management of Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Immune-mediated myocarditis	***For clarity*** ***Based on pembrolizumab action letter received from Merck, dated 2.10.17***
Section 5.0 Study procedures	Study procedures table with footnotes	Modifications made: 1. Added -28 days to screening column to clarify duration 2. Column stating "every 3 cycles" renamed as "After every 3 cycles" 3. Footnote 1 modified to state that a 'full physical exam 'will be done every time. Also, respiration has been removed from vitals. 4. In footnote 2 and 13 the language has been modified for clarity. Thyroid test have been elaborated. Time points for measurement clearly stated. 5. Tumor measurement during follow-up has been removed from the table. 6. Footnote 12 has been modified to clearly state the time points for concomitant medication	***For clarity and consistency***

		monitoring. The 'x' for con-meds in the 'after 3 cycles' column has been removed' from the table. 7. New footnote 15 added to describe toxicity assessment. The 'X' in the follow-up column for this has been removed.	
Section 6.1.1 Endpoint assessment description of measurable disease	Description of measurable disease was taken from outdated RECIST version	Description of measurable disease updated to RECIST 1.1	***Correction of error and for consistency with rest of the protocol***
Section 6.1.2 Endpoint assessment description of Non-Measurable Disease	Description of non-measurable disease was taken from outdated RECIST version	Description of non-measurable disease updated to RECIST 1.1 Table inserted for "Evaluation of Overall Timepoint Response for Patients without Measurable disease at baseline".	***Correction of error , consistency with rest of the protocol and increased clarity***
Section 6.1.3 Endpoint assessment description of Target lesions	Description of target lesions was taken from outdated RECIST version	Description of target lesion updated to RECIST 1.1	***Correction of error and for consistency with rest of the protocol***
Section 6.2.1 Endpoint assessment description of Clinical lesions	Description of clinical lesion was taken from outdated RECIST version	Description of clinical lesion updated to RECIST 1.1	***Correction of error and for consistency with rest of the protocol***
Section 6.2.2 Endpoint assessment description of Cytology, Histology	Language describing cytology and histology in relation to PR and CR	This section removed	***This section is not applicable to this protocol***
Section 6.3.1 Primary endpoint	Description of primary endpoint.	Language added: 1. RECIST 1.1 will be used to assess primary endpoint. 2. Description of CR,PR,PD and SD inserted 3. Note inserted stating that the first set of scans is required to establish that patient is	***For clarity***

		evaluable for primary endpoint.	
Section 6.3.2 Secondary endpoint	Description of secondary endpoint	Note inserted stating that the first set of scans is required to establish that patient is evaluable for secondary endpoint.	***For clarity***
Section 8.1.10	Side effects of pembrolizumab listed	Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Immune-mediated myocarditis added to the category of 'rare but serious life-threatening side-effects of pembrolizumab.	***Based on pembrolizumab action letter received from Merck, dated 2.10.17***
Section 8.2.9 Capecitabine availability and supply	Statement that patients will be given 14 days' supply of tablets at the start of study treatment.	Language added to state that patients will collect the tablets from their respective pharmacies.	***For clarity***
Amendment 2–March 15, 2017 (additional changes made after initial SRC approval of amendment 2 dated 1.30.17)			
Sections(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Section 1.4 background: exploratory studies	Language describing the evaluation of ct-DNA(circulating tumor DNA)	Removed all language referring to ct-DNA as exploratory studies	***Removal of ct-DNA evaluation as exploratory objective due to issues with Guardant 360 commercial processing laboratory.***
Section 2.3 and Section 6.3.3 Exploratory Objectives and Endpoints	One of the exploratory objectives was the assessment of ct-DNA in peripheral blood samples at baseline and at time of progression, using kits provided by Guardant 360 and processed at Guardant.	Removed all language referring to Guardant 360 and ct-DNA assessment as exploratory objective.	***Removal of ct-DNA evaluation as exploratory objective due to issues with Guardant 360 commercial processing laboratory.***

Section 3.2.15	Patients with a history of another malignancy that progressed or required treatment within 5 years prior to registration are not eligible for participation. Note: the exceptions to this include non-melanoma skin cancer or excised carcinoma in situ of the cervix.	Updated the window for past malignancy from 5 years to 1 year. .	***To increase flexibility for enrollment***
Section 5.0 Study procedures table	Footnote 14 and the corresponding row in the table stated the research blood sample collection(ct-DNA with Guardant 360 kits) at screening and end of treatment.	Removed the footnote 14 that detailed ct-DNA collection with Guardant kits and also removed the corresponding row in the table. Replaced footnote 14 with details about optional baseline biopsy for PD-L1 assessment and tagged it to the appropriate row in the table for clarity	***Removal of ct-DNA evaluation as exploratory objective due to issues with Guardant 360 commercial processing laboratory.*** ***For added clarity***
Section 9.2 Correlatives/Special studies	Details about ct-DNA assessment as an exploratory study	Removed all language related to ct-DNA and Guardant 360.	***Removal of ct-DNA evaluation as exploratory objective due to issues with Guardant 360 commercial processing laboratory.***
Amendment 3–June 1st , 2017 SRC-approved June 26, 2017			
Sections(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Title page and Section 3.0	PI: Sarika Jain, MD	Changed PI to: William Gradishar, MD. All contact information inserted.	***Dr.Jain leaving NU and handing over study to Dr.Gradishar***

Section 2.3 –Exploratory Objectives and Section 6.3.3 Exploratory Endpoint and Section 9.1 PD-L1 testing (correlative studies)	Baseline tissue biopsy of metastatic site for PD-L1 assessment, was optional and if patient did not consent, then archived tissue may be used subject to patient consent.	Modified to state: "A baseline tissue biopsy of a metastatic site will be obtained for PD-L1 immunohistochemical (IHC) assessment, from all patients. An archived specimen may be used (metastatic tissue only) if collected within 2 months of registration. Otherwise fresh biopsy of metastatic lesion is mandatory at baseline and should be performed within 28 days prior to Day 1."	***For increased convenience***
Section 3.0 Eligibility criteria introduction and Section 10.0 statistics	A total of 33-39 subjects will be needed for this trial	A total of 30 subjects will be needed to obtain 27 evaluable patients this trial. Similar updates made in statistics section to state this clearly.	***Correction of error.*** ***For clarity***
Section 3.1.6 Inclusion criteria	Baseline laboratory tests were to be done *at least* 2 weeks prior to registration. Coagulation parameters required to be tested for all patients as an eligibility criteria	Modified to state that baseline laboratory tests are to be done *within* 14 days prior to registration. Note inserted to state that coagulation parameters are required only for patients needing biopsy.	***Correction of error*** ***For safety and flexibility***
Section 3.1.9 Inclusion criteria	Details about male contraception requirements for eligibility	"Added note: "Male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition)."	***For increased clarity***

Section 3.2.3 and Section 3.2.9	Section 3.2.9 stated that prior capecitabine was permitted and no wash-out period was required for enrollment.	New eligibility criteria 3.2.3 added stating: "Patients who have received prior capecitabine are not eligible." Section 3.2.9 modified to remove the 'capecitabine permitted without wash-out' language. Now, it only contains language regarding ineligibility due to hypersensitivity to capecitabine, fluorouracil or its components.	***In order to streamline enrollment.***
Section 4.3.1 Dose modification and Section 4.2.2 Capecitabine treatment administration	Language regarding dose modification of Capecitabine	Added language: "If capecitabine doses are missed, and it is < 7 doses, they may be made up within the same cycle."	***For increased clarity and safety***
Section 5.0 Study Procedures	Footnote 2: Tumor measurements by CT c/a/p bone scan(per treating physician's discretion). Footnote6: PT/PTT/INR was optional. To be done only if patient consented for ***optional*** biopsy.	Footnote2: Updated to: "CT c/a/p AND bone scan. In place of bone scan, a PET/CT may be used. If CT is contraindicated, MRI may be used. Any additional imaging such as MRI can be completed at the physician's discretion." Footnote 6 updated to state that PT/PTT/INR is to be done if the patient is required to have a biopsy (in order to test for bleeding parameters before biopsy). It is to be performed and resulted before the biopsy.	***Correction of error. And to increase flexibility regarding permitted imaging modalities.*** ***To align with updates made to biopsy requirements as stated in footnote 14 and sections 2.3, 3.1.6, 6.3.3 and 9.1***

	Footnote 14 Baseline tissue biopsy of metastatic site for PD-L1 assessment, was optional and if patient did not consent, then archived tissue may be used subject to patient consent.	Footnote 14 modified to state : "A baseline tissue biopsy of a metastatic site will be obtained for PD-L1 immunohistochemical (IHC) assessment, from all patients. An archived specimen may be used (metastatic tissue only) *if collected within 2 months of registration*. *Otherwise fresh biopsy of metastatic lesion is mandatory at baseline and should be performed within 28 days prior to Day 1."*	***To align with updates made to biopsy requirements as stated in sections 2.3, 6.3.3 and 9.1***
Amendment 4– August 22nd , 2017 SRC-Approved August 23, 2017 and October 4, 2017			
Sections(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Title page	Cesar Santa-Maria, MD as Sub-Investigator	Removed Dr. Santa-Maria as Sub-Investigator	Dr.Santa-Maria has left Northwestern University
Section 1.4 and 2.3 Exploratory studies/objectives; Section 6.3.3 exploratory endpoint for PD-L1 assessment	A fresh baseline tissue biopsy of a metastatic site was mandatory and was to be performed within 28 days prior to day 1 . An archived specimen of metastatic tissue could be used if collected within 2 months of registration.	Language modified to state that: The fresh biopsy should be obtained no more than 2 months prior to registration. An archival tissue of a metastatic lesion can be used if collected no more than 2 months prior to registration. Otherwise fresh biopsy of metastatic lesion is mandatory at baseline and should be performed no more than 2 months prior to registration. *A note has been added by which this requirement can be omitted: "The requirement for biopsy (fresh) may be omitted per treating physician's discretion, if the biopsy would cause undue morbidity to the patient and if enough tissue from a prior metastatic lesion (archival biopsy) is not available."*	For increased flexibility, which will facilitate enrollment.

Section 5.0 Study procedures table	Footnote 3 and 14 contained previous specifications regarding biopsy	Footnote 14 moved to footnote 3 and reworded to state that The fresh biopsy should be obtained no more than 2 months prior to registration. An archival tissue of a metastatic lesion can be used if collected no more than 2 months prior to registration. Otherwise fresh biopsy of metastatic lesion is mandatory at baseline and should be performed no more than 2 months prior to registration. *A note has been added by which this requirement can be omitted: "The requirement for biopsy (fresh) may be omitted per treating physician's discretion, if the biopsy would cause undue morbidity to the patient and if enough tissue from a prior metastatic lesion (archival biopsy) is not available."* *Other footnotes renumbered as needed.*	For increased flexibility, which will facilitate enrollment.
Section 4.2.2 and Section 8.2.5 Capecitabine drug administration	Tablets are to be taken morning and evening but at least 8 hours apart.	Language modified to state: " Capecitabine is to be taken preferably 12 hours apart (with minimum 8 hours between doses)	For increased clarity
Section 4.3.1 Dose modification for Capecitabine	If capecitabine doses are missed and it is <7 days of doses, they may be made up within the same cycle.	Corrected "< 7 days of doses" to "< 7 doses."	Correction of error. To be consistent with the rest of the protocol.
Section 8.1.10 Side Effects	N/A	Added risks of sarcoidosis and encephalitis with pembrolizumab	Requested by the IRB during CR001

Amendment 5 , November 8th ,2017			
Sections(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Section 4.2.2 Capecitabine dose reduction table	The dose reduction level (-2) is stated as 600mg/m2	The dose reduction level (-2) modified to 640mg/m2	*Correction of error. The dose reductions are a 20% reduction, which makes the second reduction 640mg/m2,It was earlier stated as 600mg/m2 in error.*
Section 4.3 capecitabine dose modifications Table 2:Hematologic toxicities	For ANC <1500mm^3 and/or Platelets< 100,000/mm^3 Hold until ANC>=1500/mm^3 and PLt >=100,000 ^{3} resume at 20% dose reduction For ANC >=1500/mm3 and platelets >=100,000/mm3=no dose modifications	Modified to : For ANC <1000mm^3 and/or Platelets< 100,000/mm^3 Hold until ANC>=1000/mm^3 and PLt >=100,000 ^{3} resume at 20% dose reduction Modified to: For ANC >=1000/mm3 and platelets >=100,000/mm3=no dose modification	*For convenience and flexibility*
Section 4.9.10 Management of Infusion reactions	Language: " Error! Reference source not found"	Replaced by: " Table 5" (referring to table 5 below)	*Correction of error*

Amendment 6 , February 14th 2018			
Sections(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***

Section 3.1.6 Eligibility criteria	Baseline laboratory test acceptable values included AST and ALT ≤2.5XULN OR ≤5XULN for subjects with liver metastasis	The language pertaining to liver metastasis "≤5XULN for subjects with liver metastasis" has been removed.	***For safety. All patients are now required to have AST and ALT ≤2.5XULN to be enrolled into the study. (refer to related update in section 5.0, footnote 5)***
Section 4.3.1 Table 1 Pembrolizumab Dose modifications	Previous table (as sent by Merck)	Replaced by new table sent by Merck titled **"**Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab**".**	***Per Merck*** *(sponsor of pembrolizumab)*
Section 4.3 Table 4 Capecitabine dose modification (Palmar-plantar erythrodynesia syndrome	For Grade >=3, direction was to hold until symptoms resolve	Added language " Hold until symptoms resolve to Grade 1 or lower. Resume with dose reduction of 1 level (20% dose reduction).	***For increased clarity***
Section 4.4 Concomitant medications	The prohibited medications section contained direction that "The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor"	The requirement of consulting with sponsor (PI) has been removed.	***This requirement is no longer needed, since the new pembrolizumab dose modification table clearly states that "For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid."***

Section 5.0 Study procedures table Footnote 2(containing details regarding CT and bone scan)	Details about CT/MRI and bone scan.	Added language "For patients who are unable to obtain scans at the designated time points, a window of 7-10 days is allowed. This exception is not applicable to the screening period. Bone scans are to be repeated at each time point ONLY if the patient has bone metastasis or if it is clinically indicated. If the original bone scan during screening is negative, then bone scans are not required in subsequent visits. "	***To increase flexibility of protocol and putting bone scans in line with standard of care practices while minimizing exposure***
Section 5.0 Study procedures table Footnote 5 (details about serum chemistry)	Description of tests included in serum chemistry panel. Serum chemistry is to be performed within 14 days of Day 1	Added language "Patients with liver metastatic will have additional liver function testing done on C1D7 and C1D14, which can be done locally and sent to NU for review." Updated to " Serum chemistry to be performed within 14 days prior to registration"	***For safety.*** ***Correction of error. To maintain consistency with rest of the protocol.***
Section 6.3.3 and section 2.3 Exploratory endpoint: PFS and ORR assessment (using irRECIST)	Endpoint stated as: "ORR will be assessed every 3 cycles (every 9 weeks) with imaging (CT chest/abdomen/pelvis and bone scan."	Updated to : "ORR will be assessed every 3 cycles (every 9 weeks) with imaging (CT chest/abdomen/pelvis and bone scan **[if indicated]**)."	***Added "if indicated" provision for bone scan, in order to minimize exposure and discomfort of patients, if a test is not required."*** ***(Refer to related update in section 5.0, footnote 2)***

Amendment 7 , September 13th 2018			
Sections(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***
Section 4.3 Capecitabine Dose Modifications (Table 4: Palmar-Plantar Erythrodysesia syndrome)	Dose modifications for Grade 2 stated: "Hold until symptoms resolve to grade 0 or 1. Resume a 20% dose reduction."	The 20% dose reduction is now per treating physician's discretion. Language has been added to state this clearly.	***For safety, flexibility and to align better with current clinical practices***
Section 4.4 Concomitant Medications/Treatments	Radiation therapy was included as a prohibited treatment with a caveat that "radiation therapy to *a symptomatic solitary lesion* or to the brain may be allowed at the investigator's discretion"	The caveat has been modified to state that radiation therapy to *symptomatic lesions* (more than one lesion) or to the brain may be allowed at the investigator's discretion.	***For increased flexibility and to align better with current clinical practices***