MSK PROTOCOL COVER SHEET

Phase II of Neoadjuvant Olaparib in Combination with Pembrolizumab in Patients with Triple Negative Breast Cancer (TNBC) or Hormone Receptor-positive HER2-negative Breast Cancer and Germinline Mutations in DNA Damage Repair Genes

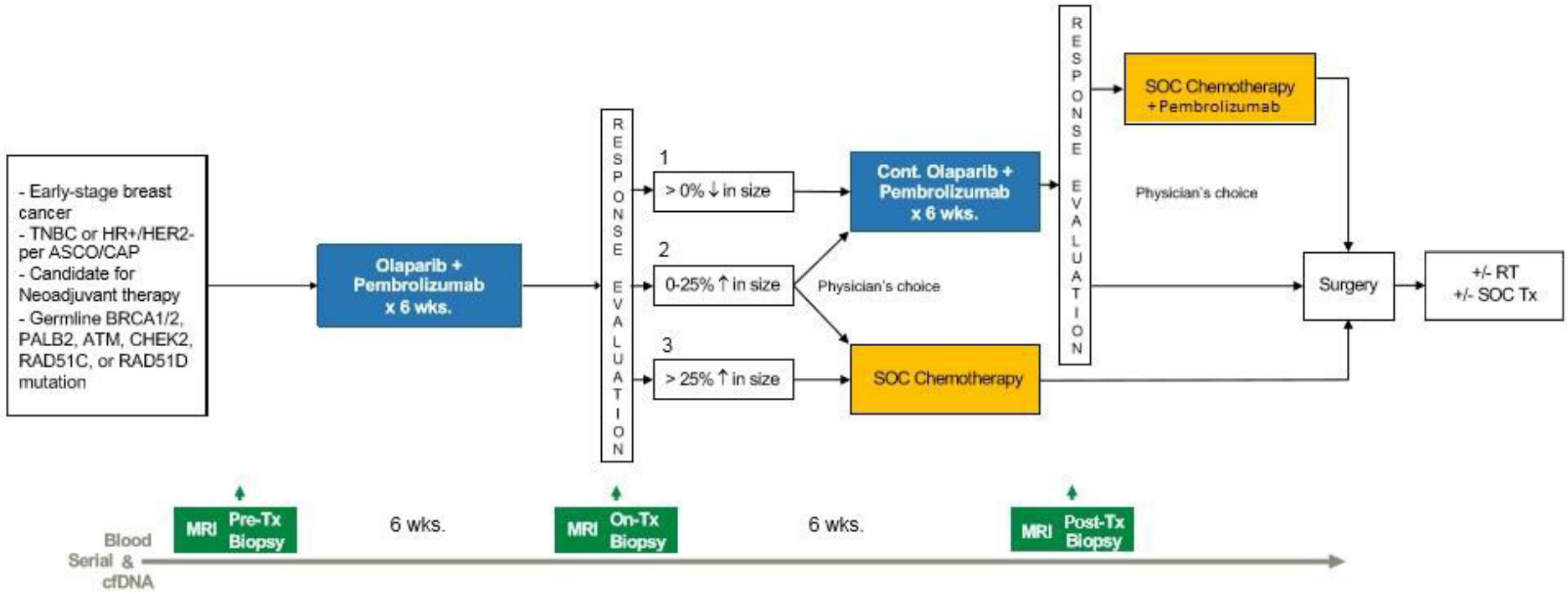
Principal Investigator/Department: Ayca Gucalp, MD/Medicine

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Abbreviated Title	Phase II of Neoadjuvant Olaparib in Combination with Pembrolizumab in Patients with Triple Negative Breast Cancer (TNBC) or Hormone Receptor-positive HER2-negative Breast Cancer And Germline Mutations in DNA Damage Repair Genes
Trial Phase	II
Clinical Indication	Neoadjuvant Breast Cancer/Germline mutations in DNA damage genes
Trial Type	Interventional
Type of control	Historical
Route of administration	Intravenous or oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Single arm study Olaparib 300 mg orally BID Pembrolizumab 400 mg intravenously q6weeks
Number of trial participants	23 patients will be enrolled.
Estimated enrollment period	~24 months
Estimated duration of trial	We estimate the trial will require approximately 32 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time he/she signs the Informed Consent Form (ICF) until withdrawing consent, becoming lost-to-follow-up, or end of study.
Estimated average length of treatment per patient	Subjects may be on study for ~6-36 weeks.

Trial Schema



Note: Patients in groups 1 and 2 will continue pembrolizumab every 6 weeks after surgery for up to 1 year total

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

- Determine the rate of pathologically negative MRI-guided biopsy after neoadjuvant combination olaparib-pembrolizumab therapy at 12 weeks, in the patient population

Secondary objectives:

- Determine the safety and tolerability of combination olaparib-pembrolizumab therapy in the neoadjuvant setting

- Determine the rate of pathologically negative MRI-guided biopsy after neoadjuvant combination olaparib-pembrolizumab therapy at 12 weeks, in the subpopulation of patients with PD-L1-positive disease

- Evaluate the association of pathologically negative MRI-guided biopsy and imaging complete response on MRI after neoadjuvant combination olaparib-pembrolizumab therapy at 12 weeks, in the patient population

- Evaluate the association of pathologically negative MRI-guided biopsy at 12 weeks and the rate of pathologic complete response at the time of surgery after neoadjuvant combination olaparib-pembrolizumab therapy +/- SOC chemotherapy, in the patient population

- Determine the rate of pathologic complete response after pre-operative treatment including neoadjuvant combination olaparib-pembrolizumab therapy +/- SOC chemotherapy, in the patient population

Exploratory objectives:

- To evaluate changes in tissue expression of selected immune markers at baseline, on-treatment and post-treatment from patients receiving neoadjuvant pembrolizumab/olaparib. Specifically, we will focus on CD3, CD4, CD8 to profile T-cells, CD11b/c, CD163, and CD68 for macrophages.

- To evaluate the potential effects of neoadjuvant pembrolizumab/olaparib on cGAS-STING pathway expression, by comparing tissues obtained at baseline, on-treatment and post-treatment period. Specifically, we will use validated antibodies that have been rigorously profiled in the Bakhoum Laboratory to stain for cGAS and assess its subcellular localization in micronuclei, STING, and ENPP1 – a negative regulator of cGAS-STING signaling.

- To perform high-throughput sequencing of the TCR-β CDR3 region in both tumor specimens and peripheral blood mononuclear cells (PBMCs) using the ImmunoSEQ immune profiling system to describe T-cell repertoire dynamics in patients receiving neoadjuvant pembrolizumab/olaparib.

- To characterize the genomic alterations and evolution of disease during neoadjuvant pembrolizumab/olparib in patient with germline mutations in DNA damage repair genes.

- To assess whether early circulating tumor DNA response can predict pathologic response

- To evaluate the potential effects of neoadjuvant pembrolizumab/olaparib on malignant and immune cell diversity, by comparing baseline, on-treatment and post-treatment tissues analyzed with ultra-high resolution single cell genomics and transcriptomics techniques.

- To evaluate a novel Echo-planar imaging (EPI) based Magnetic Resonance Fingerprinting (MRF) sequence for rapid measurements of quantitative susceptibility mapping, proton Density (PD), T1 and T2 relaxation maps, which would enable quantitative evaluation of the tumor over time and determine the ability of these parameters to predict breast cancer pathologic response.

- To evaluate a novel Chemical exchange saturation transfer Magnetic Resonance Fingerprinting (CEST-MRF) sequence, which is a multiparametric molecular imaging method for rapid simultaneous measurement of the water T1 and T2 relaxation maps, the pH-dependent amide exchange rate and volume fraction and the macromolecular exchange rate and volume fraction, and determine the ability of these parameters to predict breast cancer pathologic response.

3.0 BACKGROUND AND RATIONALE

3.1 Breast Cancer

Globally, breast cancer is the second most common invasive malignancy and the most common cause of cancer-related mortality in women. The majority of breast cancers in the Western world are diagnosed when the cancer is still confined to the breast, with or without locoregional lymph node spread (Sant et al. 2003; Jemal et al. 2011; Ferlay et al. 2013; Howlader et al. 2016). At these early stages (I-III, early breast cancer [EBC]), the largely asymptomatic disease is usually operable and can be treated with curative intent. And while breast cancer is potentially curable when detected at an early stage, it remains incurable in the metastatic setting. Thus, given its high prevalence, improved prevention of distant metastases remains a clinically meaningful unmet need.

3.1.1 BRCA mutation-associated breast cancer and homologous recombination (HR) defect (HRD)

Approximately 5% of breast cancers are associated with a mutation in the *BRCA1* and/or *BRCA2* gene (*BRCA1/2*) with ~3% associated with the *BRCA1* gene and ~2%

associated with the *BRCA2* gene (generally hormone receptor positive breast cancer). Approximately 70% of *BRCA1* mutated breast cancer present as triple negative breast cancer (TNBC). In contrast, breast cancer patients carrying mutations in the *BRCA2* gene are more likely to be positive for expression of the estrogen receptor (ER) and approximately 20% are triple negative (Mavaddat et al. 2012).

BRCA1- and BRCA2-associated breast cancers share a defect in the homologous recombination (HR) DNA double strand break (DSB) repair pathway. As a result, *BRCA1*- or *BRCA2*-mutant tumor cells are sensitive to certain drugs that stall the normal progression of replication forks and cause them to collapse, frequently resulting in DSBs. In the absence of BRCA function and homologous recombination, cells either fail to repair the DNA damage caused by these agents and progress to cell death or attempt to repair the resultant DNA lesions using error-prone processes such as non-homologous end joining (NHEJ), which may cause significant genomic instability that is inconsistent with cell viability (Lord et al. 2012).

3.1.2 BRCAness: cancers with HRD in the absence of a germline BRCA1/2 mutation

BRCAness describes the situation in which an HRD exists in a tumor in the absence of a germline *BRCA1* or *BRCA2* mutation. Such HRDs may occur potentially from germline or somatic mutations in other genes in the HR pathway. Use of multi-gene panels for cancer susceptibility is now widespread, identifying breast cancer patients with germline mutations in DNA repair genes other than *BRCA1/2*. Cancers with these mutations are therefore candidates for displaying BRCAness**.** Approximately 4% of unselected patients with breast cancer have a germline mutation in a gene other than *BRCA1* or *BRCA2* involved in HR, as detected by commercially available NGS cancer susceptibility panels. The Cancer Genome Atlas (TCGA) identified 22 (4.3%) of 507 patients with breast cancer had a germline mutation in a DNA repair gene other than BRCA1/2 (Cancer Genoma Atlas. 2012).

It has been theorized that triple-negative breast cancers which are often characterized by altered BRCA function as well as impaired DNA damage repair may also demonstrate increased susceptibility to DNA damaging agents. Triple negative breast cancer (TNBC) is defined by the absence of immunostaining for ER, progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2). Overall, approximately 15%–20% of all breast cancers are classified as TNBC. Large-scale comprehensive genomic analyses have characterized the heterogeneous nature of TNBCs and their diverse gene expression patterns and underlying genomic changes, but these insights have not yet provided clear guidance for the identification of clinically effective targeted therapies currently under laboratory and clinical investigation. Unfortunately, TNBCs are more likely to have aggressive features, such as a high proliferative rate, and exhibit an invasive phenotype. Patients with TNBCs exhibit a poor clinical outcome, generally with rapid progression and a shorter time to local and distant relapse (Dent et al. 2007).

Early-stage TNBC comprises 10%-20% of all new diagnoses of EBC defined as Stages I-III (Lehmann et al. 2011; Howlader et al. 2016). Three-year event-free survival (EFS) rates between 74% and 76% have been reported for patients with TNBC who have received neoadjuvant anthracycline/taxane therapy (Sikov et al. 2015). Upon relapse, patients with metastatic TNBC have poor outcomes, with rapid progression and decreased overall survival (OS) (Kassam et al. 2009).

3.2 Treatment for Early Stage Breast Cancer

Multi-agent chemotherapy regimens have proven benefit as neoadjuvant/adjuvant therapy for early-stage TNBC, improving both disease-specific and OS outcomes (Berry et al. 2006; Senkus et al. 2015; NCCN 2016). Chemotherapy intended to reduce the risk of relapse may be given preoperatively (neoadjuvant) or postoperatively (adjuvant) to patients with EBC and is currently recommended for TNBC patients with Stage I-III disease. Globally, chemotherapy is most often administered as adjuvant therapy; however, rates of neoadjuvant treatment use are increasing.

The most effective chemotherapy combinations used for early-stage TNBC include anthracyclines, topoisomerase II inhibitors, platinum agents, cyclophosphamide, and/or taxanes (Early Breast Cancer Trialists' Collaborative Group 2005; Peto et al. 2012). Studies looking at optimizing the dose and schedule of EBC chemotherapy regimens (Citron et al. 2003; Sparano et al. 2008; Budd et al. 2015) have established one of the optimal regimens with respect to maximizing efficacy as doxorubicin 60 mg/m$_2$ and cyclophosphamide 600 mg/m$_2$ administered every 2 weeks (Q2W) for 4 cycles, followed by weekly (QW) paclitaxel 80 mg/m$_2$ for 12 weeks; the regimen is included as a preferred option in international guidelines (Senkus et al. 2015; NCCN 2016).

However, despite having received standard anthracycline-taxane-based therapy, approximately 30%-40% of patients with clinically localized disease at diagnosis develop metastatic disease and die of the cancer (Haffty et al. 2006; Tan et al. 2008; Budd et al. 2015). Thus, there is a substantial need to improve long-term treatment outcomes for patients with EBC.

3.3 PARP Inhibition

Polyadenosine 5'diphosphoribose [poly (ADPribose)] polymerisation (PARP) inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to DNA DSBs during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HRD, such as ovarian cancers in patients with *BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it

accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and *BRCA2* defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo (Rottenberg et al. 2008; Hay et al. 2009) and in the clinic (Fong et al. 2009). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday et al. 2011; Murai et al. 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by homologous repair. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic *BRCA* knockout models, either as a stand-alone treatment or in combination with established chemotherapies. Furthermore, pre-clinical data show that breast cancer cells with mutations in other HR genes demonstrate sensitivity to PARP inhibitors, including cells with mutations in NBN (NBS1), ATM, ATR, CHK1, CHK2 and RAD51D (McCabe et al. 2006; Loveday et al. 2011; Kunota et al. 2014). Early clinical data in other settings, specifically metastatic castrate-resistant prostate cancer (MCRPC) have called the response of ATM-associated cancers into question. On the other hand, incremental responses have been observed in patients with PALB2 mutation-associated breast cancer.

Several Phase 1 and 2 studies have shown that PARP inhibitors have single-agent activity in patients with metastatic breast cancer and a germline BRCA 1/2 mutation.

3.3.1 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

3.3.1.1 Olaparib monotherapy studies in breast cancer patients

Study D0810C00002

Study D0810C00002 was a Phase I open-label, dose escalation and cohort expansion study in 98 patients with solid tumors. Patients in the dose-escalation cohort received olaparib orally (PO) at doses ranging from 10 mg daily to 600 mg twice daily; whereas all patients in the dose expansion cohort received olaparib at 200 mg twice daily after the MTD was identified as 400 mg bid. The main tumors by type were ovarian (54 [55.1%]), breast, (13 [13.3%]); large intestine (5 [5.1%]), prostate (4 [4.1%]) and skin cancers (4 [4.1%]). Overall 23 patients were BRCA mutation carriers; of these, 19 patients had BRCA mutated ovarian, breast, or prostate cancer and were evaluable for response. Forty-seven percent (9/19) of the patients had a RECIST defined objective response and 63% (12/19) had stable disease for at least 4 months (Fong et al. 2009).

Study D0810C00008

Study D0810C00008 was a Phase II proof-of-concept study initiated as an open-label, single arm, international, multicenter study to assess the efficacy and safety of olaparib given orally bid in patients with advanced breast cancer. Patients had a median of 3 previous chemotherapy regimens. Approximately half of the patients had TNBC. The primary objective was to assess the efficacy of the capsule formulation at 2 different doses of olaparib in terms of ORR in patients with advanced breast cancer. Patients received olaparib at a dose of 400 mg PO bid or 100 mg bid continuously in 28-day cycles, for multiple cycles, until no further clinical benefit was apparent, or the patient was withdrawn from the study. The cohorts were conducted in sequence, the 400 mg bid group first (n=27) followed by the 100 mg bid group (n=27). In the ITT analysis set, the confirmed Response Evaluation Criteria in Solid Tumors (RECIST) objective response rate (ORR) overall was 11/27 (41%) at 400 mg bid and 6/27 (22%) at 100 mg bid. Responses were seen in both *gBRCA1* and *gBRCA2* carriers. Median time to progression was 5.3 months for the 400 mg bid group and 3.7 months for the 100 mg bid group (Tutt et al. 2010).

Study D0810C00020

Study D0810C00020 was a Phase II open-label, nonrandomized study of olaparib in patients with known *gBRCA* or high-grade serous/undifferentiated ovarian cancer and patients with known *gBRCA* or TNBC. All patients received olaparib 400 mg PO bid until disease progression or until the investigator believed it was in the best interest of the patient to stop treatment. Tumor response data was analyzed in 64 ovarian (*BRCA* or serous ovarian) and 26 breast (*BRCA* or triple negative) cancer patients who received olaparib 400 PO mg bid. Germline *BRCA* mutations were present in 11 out of the 26 breast cancer patients. Median number of prior chemotherapies in the breast cancer group was 3 (range: 1 to 7). Over 70% of the breast cancer patients had received more than 3 previous lines of chemotherapy, with a median of 35.3 months from diagnosis to start of treatment with olaparib. None of the breast cancer patients achieved a RECIST response. However, 63% of the patients with *BRCA* mutations had an overall best response of SD lasting 8 weeks or more. The median PFS in this group was 3.6 months (Gelmon et al. 2011).

Study D0810C00042

Study D0810C00042 was a Phase II, open label, nonrandomized, noncomparative, multicenter study in patients with advanced cancers who had confirmed genetic *BRCA1* and/or *BRCA2* mutations. A total of 62 breast cancer patients were recruited, all of whom received at least 3 prior lines of therapy (with a median of 6 prior regimens). Eight (12.9%) of the breast cancer patients had an OR and the median duration of response was 204 days. At 16 weeks, disease control was observed in 23 (37.1%) patients. The median PFS was 3.68 months. The median OS was 11.01 months; the survival rate at 6 months was 74.6%, and at 1 year was 44.7% (Kaufmann et al. 2015).

The randomized, Phase 3 OlympiAD trial showed that, among patients with HER2-negative metastatic breast cancer and a germline BRCA 1/2 mutation, progression-free survival (PFS) was significantly longer with single-agent PARP inhibitor olaparib than with standard chemotherapy (capecitabine, eribulin mesylate, or vinorelbine)

(median PFS 7.0 months vs. 4.2 months; hazard ratio (HR) for PFS= 0.58; 95% CI: 0.43 - 0.80). The response rate in the olaparib group was approximately double the rate in the standard-therapy group (59.9% vs. 28.8%) (Robson et al. 2017).

3.4 Immune checkpoint inhibition

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis et al. 2010.) Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes (TILs) can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley et al. 2005; Hunder et al. 2008).

The programmed cell death protein 1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death ligand 1 (PD-L1) and/or programmed cell death ligand 2 (PD-L2)) (Greenwald et al. 2005; Okazaki et al. 2001).

The structure of murine PD-1 has been resolved (Zhang et al. 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki et al. 2001; Chemnitz et al. 2004; Sheppard et al. 2004; Riley et al. 2009). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry et al. 2005; Francisco et al. 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in breast cancer.

3.4.1 PD-1/PD-L1 Inhibitors as Monotherapy or in Combination with Chemotherapy for TNBC

Accumulating evidence shows a correlation between TILs in cancer tissue and prognosis in various malignancies (Bremens et al. 2011; Talmadge 2011; Mei et al. 2014). Greater lymphocytic infiltration confers better prognosis in TNBC, independent of systemic therapy (Mahmoud et al. 2011; Denkert et al. 2010). In addition, unsupervised gene expression profiling of TNBCs has identified a gene signature enriched for cytotoxic CD8+ T cell genes and natural killer (NK) cell activity, which is predictive of good clinical outcomes (Finak et al. 2008). These findings suggest that inhibition of immune checkpoints has the potential to improve TNBC prognosis by increasing the efficacy of tumor-associated immune response in eliminating breast cancer cells (Stagg et al. 2013).

The PD-1 ligand, PD-L1, is not detected in normal breast tissue, but has been reported to be expressed in about half of all breast cancers, particularly in hormone receptor (HR)-negative and high grade, proliferative tumors (Ghebeh et al. 2006). In addition, the presence of regulatory T cells, tumor PD-L1 expression, and PD-1–positive TILs have been associated with high histologic grade, ER negativity, and prominent tumor lymphocytic infiltration (Ghebeh et al. 2008). In an independent study, PDL1 was found expressed in 23% of breast cancer specimens and it was associated with age, tumor size/stage/grade, lymph node status, absence of ER expression, and high expression of the proliferation marker Ki-67 (Muenst et al. 2014).

A recent publication reported that PD-L1 messenger ribonucleic acid (mRNA) is expressed in nearly 60% of breast tumors, independent of HR status, and is positively correlated with PD-L1 protein expression and increased TILs (Schalper et al. 2014). Another study mining the Cancer Genome Atlas (TCGA) RNA sequencing data showed that PD-L1 gene expression is significantly higher in TNBCs compared to non-TNBCs and is associated with PTEN loss. In that same study, PD-L1 was found expressed in 20% of TNBCs [65]. Finally, PD-L1 protein levels are positively correlated with expression of other immune regulators, such as CTLA-4 and Indoleamine 2,3-DiOxygenase 1 (IDO1), and with androgen receptor (AR)-negative and BRCA1-mutant TNBC (Basu et al. 2014).

KEYNOTE-012 was a phase 1b trial of pembrolizumab in 32 women with PD-L1-“positive” metastatic triple negative breast cancer (mTNBC) (Nanda et al. 2016). In this study, PD-L1 positivity was defined as PD-L1 expression in the stroma or in ≥ 1% of tumor cells. The overall response rate was 18.5% in 27 evaluable patients, and the median time to response was 17.9 weeks (range, 7.3 to 32.4 weeks). Median OS was 10.2 months, and the 12-month OS rate was 41.1%. A total of 15.6% of the patients had at least one grade 3 to 5 AE, with the most common AE being arthralgia (18.8%) and fatigue (18.8%). Of the five responders, one had a complete response (CR), four had partial responses (PRs), and three have had long-lasting benefit from pembrolizumab.

The I-SPY2 trial has an adaptive randomization design that allows for expeditious evaluation of drugs in the pre-operative setting to determine whether they are likely to be successful in a randomized study. In a recent report from I-SPY2, paclitaxel was administered with or without pembrolizumab followed by four cycles of conventional doxorubicin with cyclophosphamide (AC) in women with early stage HER2-normal disease in the pre-operative setting (Nanda et al. 2017). When pembrolizumab was added to standard chemotherapy, the estimated pathologic complete response rate (pCR) was approximately 20% in the control arm versus 60% in the pembrolizumab-containing arm for the subset of women with TNBC.

KEYNOTE-522 enrolled 1,174 patients with newly diagnosed, operable, stage II or III triple-negative breast cancer. Patients were randomly assigned 2:1 to receive pembrolizumab at 200 mg every 3 weeks vs placebo, given together with chemotherapy in the neoadjuvant setting. All patients were administered carboplatin plus paclitaxel for 12 weeks followed by doxorubicin or epirubicin plus cyclophosphamide for an additional four cycles. After neoadjuvant therapy, patients underwent surgery and received definitive radiation therapy if indicated. Following surgery, patients received nine more cycles of adjuvant pembrolizumab or placebo.

Regardless of PD-L1 expression, more patients in the pembrolizumab arm achieved pathologic complete response: 64.8% vs 51.2% for placebo, representing an absolute difference of 13.6% (*P* = .00055). At the first planned interim analysis with just 15.5 months of follow-up, the second primary endpoint of event-free survival based on 1,174 patients was 91.3% in the pembrolizumab groups vs 85.3% in the placebo group at 18 months . Across disease stages, pembrolizumab achieved a consistent increase in pathologic complete response, with the greatest magnitude of benefit in patients with stage IIIB disease: 48.6% vs 23.1% for the placebo group, respectively, for an absolute difference of 25.6%. Lymph node–positive patients had a greater pathologic complete response benefit if they received pembrolizumab vs placebo: 64.8% and 44.1%, for an absolute difference of 20.6%. Node-negative patients also benefited from the addition of pembrolizumab, but the magnitude of benefit was smaller: 64.9% vs 58.6%, for an absolute difference of 6.3%. PD-L1 status was not associated with a tumor response. Regardless of exposure to chemotherapy, patients treated with pembrolizumab had an improved pathologic complete response compared with the chemotherapy/placebo group. [76]

3.4.2 PD-1/PD-L1 Inhibitors in Hormone Receptor-Positive, HER2-Negative Disease

KEYNOTE-028 was a phase 1b multicohort study of pembrolizumab for PD-L1-positive advanced tumors (Rugo et al. 2016). In this study, PD-L1 positivity was again defined as PD-L1 expression in the stroma or in ≥ 1% of tumor cells. Among the 25 patients with estrogen-positive/HER2-negative metastatic breast cancer treated on study, an ORR of 12% was reported with three PRs with only 16% of patients experiencing a grade 3 or grade 4 AE. In the I-SPY2 study, wherein pre-operative chemotherapy was administered with or without pembrolizumab in a curative-intent population, the

estimated pCR rate was 34 versus 13%, respectively, in women with hormone receptor-positive/HER2-normal breast cancer (Nanda et al. 2017). Thus, although hormone receptor-positive disease may not be innately sensitive to checkpoint blockade monotherapy, chemotherapy combinations—particularly when administered earlier in the course of disease—may be particularly effective.

3.4.3 Pembrolizumab

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

3.4.3.1 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

3.4.3.2 Justification for Dose

The planned dose of pembrolizumab for this study is 400 mg intravenously (IV) every 6 weeks (Q6W).

The current approved dosing regimens of pembrolizumab for IV administration are 200 mg Q3W and 400 mg Q6W for adults.

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on M&S analyses, given the following rationale:

PK simulations demonstrating that in terms of pembrolizumab exposures:

- Cavg (or AUC) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
- Trough concentrations (Cmin) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
- Peak concentrations (Cmax) at 400 mg Q6W are well below the Cmax for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab

- Exposure Response (E-R) for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, use of 400 mg Q6W is not expected to alter efficacy across indications

3.5 Rationale for Combination Therapy with Checkpoint Blockade and PARP Inhibition

Based on the mechanisms of action discussed in sections 3.3 and 3.4, olaparib and pembrolizumab have the potential to produce additive or synergistic anti-tumor activity, with olaparib functioning to promote immune priming and tumor immunogenicity and pembrolizumab functioning to overcome PD-1-mediated inhibition of any resulting anti-tumor immune response.

Specifically, the activity of pembrolizumab depends on generation of a productive immune response, composed of effective antigen presentation, T-cell priming, infiltration of tumors, and recognition and killing of tumor cells (Chen at al. 2013). Olaparib, via its ability to promote increased DNA damage, has the potential to promote several of these key stages of the immune response.

Firstly, olaparib-mediated cell death, via either PARP trapping or via increased DNA damage, has the potential to release antigens into the tumor microenvironment, promoting effective antigen presentation; this has been described for other therapies that lead to increased tumor cell death (Galluzzi et al. 2017). Secondly, DNA damage promotes inflammation via two alternative pathways, the first being activation of the NF-κB pathway (Ioannidou et al. 2016), and the second being activation of the stimulator of interferon genes (STING) signaling pathway via generation and detection of cytosolic DNA (Hartlova et al. 2015; Parkes et al. 2017). Activation of these pathways leads to increased pro-inflammatory signaling that enhances effective recognition and infiltration of tumors by immune cells and has recently been shown to be critical to the response to checkpoint inhibition in mice (Wang et al. 2017). Finally, DNA damage has been shown to increase the intrinsic immunogenicity of tumor cells and enhance their recognition and killing by T cells and NK cells via up-regulation of major histocompatibility complex (MHC), natural killer group 2 member D Ligand (NKG2DL), and inducible costimulator ligand (ICOSL) (Soriani et al. 2009; Tang et al. 2014).

PARP inhibition has been shown to increase CD8+ T-cells and increased IFN-gamma and TNF-α in *BRCA1*-deficient murine ovarian cancer (Huang et al. 2015), and PARP inhibition has also been shown to upregulate PD-L1.

The MEDIOLA study with the combination of olaparib and PD-L1 inhibitor durvalumab demonstrated a disease control rate of 80% (90% CI 62-92%) and ORR of 52% (95% CI, 31%-72%) in 25 pretreated BRCA-mutant metastatic breast cancer patients; no enhanced toxicity was observed with olaparib and no change was seen from the

expected toxicity of durvalumab (Domchek et al. 2017). Furthermore, patients treated in first or second line setting for metastatic disease appeared to have a greater likelihood of response (12/18 vs 1/7 treated in >2nd line), suggesting that benefit from combination PARP inhibition and checkpoint blockade is more likely earlier in the disease trajectory.

Given the interplay of DNA damage repair pathways and the immune system, combination therapy with PARP inhibitors and immune checkpoint inhibitors is a rational therapeutic strategy for investigation. Thus, we hypothesize that the addition of olaparib and pembrolizumab to conventional pre-operative chemotherapy will increase the rate of pCR observed and will not compromise the ability to deliver conventional preoperative chemotherapy.

3.6 Rational for imaging endpoints

MRI is standard practice pre- and post-neoadjuvant chemotherapy (NAC) to evaluate treatment response and is recommended by the National Comprehensive Care Network.[8] Multiparametric MRI (mpMRI), which combines the functional knowledge of different sequences, is the most accurate imaging modality for monitoring treatment response when compared with a clinical breast exam, mammography, and ultrasound.[2, 25-28] MRI has a reported accuracy of 83% for identifying pCR.[72] Although accurate, MRI is not yet sufficient to obviate the need for pathologic confirmation of pCR. This is in part because there is no standard definition regarding what constitutes an imaging complete response (iCR) on breast MRI post-NAC. Currently, surgery is required to diagnose a pCR post NAC because no imaging method is sensitive enough.

There is a clinical need for quantitative MR sequences that improve the accuracy of MRI in evaluating breast cancer treatment response in the neoadjuvant setting. Magnetic Resonance Fingerprinting (MRF) enables fast multiparametric quantitative imaging with a single acquisition and can obtain a unique temporal signal evolution for each set of tissue and system parameters (i.e. T1, T2, Proton density, diffusion, B0 and B1). MRF has shown promise for measuring tissue changes in pathologies such as cancer. MRF has been shown to improve cancer diagnosis and has been used to evaluate longitudinal treatment response in prostate. Early reduction in relaxometry parameters (T1, T2 and PD) of breast cancer were an early prediction of pathologic response to naeoadjuvant chemotherapy in breast cancer. Native relaxation parameters are acquired without the use of intravenous contrast and represents quantitative intrinsic and fundamental tissue properties. As part of the exploratory aims we want to incorporate: (1) a novel Echo-planar imaging (EPI) based Magnetic Resonance Fingerprinting (MRF) sequence for rapid measurements of quantitative susceptibility mapping, proton Density (PD), T1 and T2 relaxation maps and (2) a novel Chemical exchange saturation transfer Magnetic Resonance Fingerprinting (CEST-MRF) sequence, which is a multiparametric molecular imaging method for rapid simultaneous measurement of the water T1 and T2 maps, the pH-dependent amide exchange rate and volume fractions and the macromolecular exchange rate and volume fraction. We hypothesize that these rapid sequences have

the ability to predict pathologic complete response of breast cancer in the neoadjuvant setting.

Preliminary data pertinent to the below described study design is the proof-of-concept clinical trial (NCT03289195) lead by co-investigator Dr. Sutton that evaluated the accuracy of MRI-guided biopsy for diagnosing a post-NAC pCR compared with reference-standard surgical resection. This was single-arm, single-institution, phase 1 study from September 2017–July 2019. The median follow-up was 1.26 years (interquartile range, 0.85–1.59). Data analysis was performed in November 2019. Patients had stage 1A–3C biopsy-proven operable invasive breast cancer; standard-of-care NAC; pre- and post-NAC MRI with imaging complete response defined as no residual enhancement on post-NAC MRI; and definitive surgery. Post-NAC MRI-guided biopsy without the use of intravenous contrast of the tumor bed prior to definitive surgery. The primary endpoint was the negative predictive value (NPV) of MRI-guided biopsy, with true negative defined as a negative biopsy (i.e. no residual cancer) that corresponded with a surgical pCR. Accuracy, sensitivity, positive predictive value (PPV) and specificity were also calculated. 20 patients were evaluable (100% female; median age, 51.5 years); 19/20 (95%) had invasive ductal carcinoma; 15/20 (75%) had stage 2 cancer; 11/20 (55%) had HER2 positive cancer; and 6/20 (30%) had triple negative cancer. Surgical pathology demonstrated a pCR in 13/20 (65%) patients and no-pCR in 7/20 (35%) patients, with pCR was defined as no residual invasive cancer. MRI-guided biopsy had an NPV of 92.8%, with accuracy, sensitivity, PPV, and specificity of 95%, 85.8%, 100%, and 100%, respectively. Only 1 patient had a false negative MRI-guided biopsy for which surgical pathology demonstrated less than 0.02 cm of residual invasive cancer. The accuracy of MRI-guided biopsy to diagnose a post-NAC pCR approaches that of reference-standard surgical resection. MRI-guided biopsy may be a viable alternative to surgical resection for this population following NAC.

While Heil et al.,[23] Rauch et al.,[24] and Kuerer et al.[20-22] have all previously shown the potential utility of image-guided biopsies as an alternative to surgery in exceptional responders to NAC, none required a complete imaging response as a measure of outcome or investigated the utility of MRI or MRI-guided biopsy. Heil et al.[23] investigated the utility of minimally-invasive biopsy (MIB), which was either a core-cut or vacuum-assisted biopsy. The positive predictive value (PPV) of an MIB in diagnosing a pCR was 71.3% and thus the overall accuracy was insufficient to change clinical practice; however, they had a broad inclusion criteria and did not require imaging, which is more sensitive than clinical breast exam which has an accuracy of pCR post-NAC of 54%.[65] Rauch et al.[24] investigated the utility of mammography, ultrasonography, and image-guided biopsy (either ultrasound or stereotactic-guided biopsy) for predicting a pCR and found that the PPV for pCR was 60% for ultrasound-guided biopsy. Kuerer et al.,[20-22] working with Rauch et al., reported a false negative rate of 10% for pCR for ultrasound and stereotactic-guided biopsy but did not report the PPV for pCR. The results from our above-described novel method are more accurate than the majority of published data and support the need for a larger study

comparing MRI-guided biopsy to reference standard surgical resection in diagnosing a pathologic complete response post-neoadjuvant chemotherapy. These results are the basis for the below described study design. Further, this proof-of-concept clinical trial (NCT03289195) is currently being expanded at MSK.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This trial is designed as a single-arm, open-label, non-randomized study with sample size calculated using the Simon two-stage minimax design. The primary endpoint is pathologically negative MRI-guided biopsy after neoadjuvant combination olaparib-pembrolizumab therapy at 12 weeks. Patients are eligible if they have newly diagnosed cT1c-3N0-3M0 invasive breast cancer, either triple negative according to ASCO/CAP guidelines or hormone receptor positive breast cancer with a germline mutation in BRCA1, BRCA2, PALB2, RAD51C, or RAD51D and have undergone a pre-neoadjuvant chemotherapy MRI.

At baseline, consented patients will undergo a research tumor biopsy and the index tumor volume will be quantified on the standard of care breast MRI. Patients will then receive olaparib and pembrolizumab for 6-12 weeks, followed by SOC chemotherapy +/- pembrolizumab and surgery. Depending on response to study therapy, the sequence of cytotoxic chemotherapy +/- pembroliziumab vs surgery will be determined by the primary clinical team. At the 6-week timepoint, all patients will undergo MRI for tumor assessment of interval response, which will be immediately followed by a concurrent MRI-guided biopsy. Similarly, at the 12-week timepoint, all patients who remain on olaparib/pembrolizumab for > 6 weeks will undergo another MRI for tumor assessment of interval response, which will be immediately followed by a concurrent MRI-guided biopsy.

At 6 weeks of treatment, the first study MRI will be performed, and treatment response will be assessed by comparing difference in tumor volume on this MRI to that measured on the pre-neoadjuvant chemotherapy MRI. Patients will be categorized as follows:

Group 1: Decrease in tumor volume
- 1a) Decrease in tumor volume of at least 50% (≥50%D)
- 1b) Decrease in tumor volume of 0 to 50% (<50%D)

Group 2: Enlargement in tumor volume of 0 to 25% (<25%E)

Group 3: Enlargement in tumor volume of 25% or greater

All evaluable patients across the 4 categories will be included for the primary endpoint.

Patients who are responding (any decrease in tumor size, groups 1a and 1b above) will continue the study therapy for 6 additional weeks after the initial tumor

assessment (12 weeks total). Due to the mechanism of action, patients may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of olaparib and pembrolizumab. Patients who have increases in tumor size of 0-25% (group 2) and are tolerating study therapy at the 6-week timepoint can continue study therapy for another 6 weeks or elect SoC chemotherapy, at the discretion of their primary clinical team. The treating physician may consult with the Principal Investigator for help with assessing the patient. To ensure safety, patients who have a >25% increase in tumor size at the initial assessment (group 3) will immediately move to SoC chemotherapy. Patients should also discontinue study therapy upon further evidence of progression.

At the time of 6-week MRI, all patients will undergo concurrent MRI-guided biopsy.

At 12 weeks, all patients that continued olaparib/pembrolizumab for 6 additional weeks will undergo a second study MRI followed by a concurrent MRI-guided biopsy. Again, MRI treatment response will be assessed by comparing difference in tumor volume on this MRI to that measured on the pre-neoadjuvant chemotherapy and first study MRI.

pCR will be assessed at the time of surgery.

After completion of the olaparib/pembrolizumab portion of the treatment, patients will receive SoC systemic therapy in conjunction with pembrolizumab and undergo surgery. The sequence of cytotoxic chemotherapy +/- pembroliziumab vs surgery will be determined by the primary clinical team. Patients on study will receive pembrolizumab in conjunction with olaparib during the initial 12 weeks of the study and then with cytotoxic chemotherapy (after the completion of olaparib) if administered prior to surgery and the patient was not deemed to have tumor growth at the 6 week assessment requiring transition to SOC therapy. Patients will undergo a 2 week washout period after the completion of olaparib prior to the initiation of neoadjuvant cytotoxic chemotherapy. Postoperatively patients will then continue pembrolizumab therapy in the adjuvant setting to complete 1 year of treatment. If appropriate, patients will receive radiation and any additional standard of care systemic therapy by breast cancer subtype as per their primary clinical team.

4.2 Intervention

Patients will start both olaparib 300 mg PO BID and pembrolizumab 400 mg IV Q6W and continue BID dosing of olaparib with further infusions of pembrolizumab every 6 weeks. Patients will receive olaparib and pembrolizumab for 6-12 weeks, followed by SOC chemotherapy/pembroliziumab and surgery. The sequence of cytotoxic chemotherapy +/- pembroliziumab vs surgery after study treatment will be determined by the primary clinical team. Patients will undergo baseline and then 6-week volumetric radiographic tumor assessment with MRI. At the 6-week timepoint, all patients will undergo a biopsy at the time of radiographic tumor assessment with MRI. Radiographic

tumor assessment with MRI and biopsy will be repeated at 12 weeks (for those patients who remain on olaparib/pembrolizumab for > 6 weeks). The pre, 6-week and 12-week diagnostic MRI with incorporate the (1) EPI-MRF and (2) CEST-MRF sequences. The EPI-MRF sequence has been optimized for rapid measurements of quantitative susceptibility mapping, proton Density (PD), T1 and T2 relaxation maps. The sequence works by variable excitations and delays which simultaneously sensitizes the signal to the PD, T1 and T2 tissue parameters. Imaging time is approximately 6 seconds per slice with no intravenous contrast is needed. The CEST-MRF sequence is a multiparametric molecular imaging method for rapid simultaneous measurement of the water T1 and T2 relaxation maps, the pH-dependent amide exchange rate and volume fraction and the macromolecular exchange rate and volume fraction. The sequence is fast (acquisition time=2 minutes), requires no intravenous contrast. Both sequences are implemented on 3T GE scanners (Signa Premier). The acquisition time for both the EPI-MRF and CEST-MRF sequences together will take less than 10 minutes, which will ensure all MRI examination will be successfully completed within the allocated time slot.

At 6 weeks patients will be categorized as follows: 1a) Decrease in tumor size at 6-weeks of at least 50% (≥50%D) 1b) Decrease in tumor size at 6-weeks of 0 to 50% (<50%D) 2) Enlargement in tumor size of 0 to 25% (<25%E) 3) Enlargement in tumor size of 25% or greater at 6 weeks (>25%E). Patients who clinically progress before the 6 week assessment will be taken off study and undergo SOC treatment. Patients with a decrease in the size of the tumor at the 6-week study assessment will continue olaparib and pembrolizumab for an additional 6 weeks for a total of 12 weeks and then proceed with SoC chemotherapy or definitive surgery, at the discretion of the primary clinical team. Patients with enlargement in tumor size of 0-25% at the 6-week study assessment will either continue olaparib and pembrolizumab for an additional 6 weeks for a total of 12 weeks and then proceed SoC chemotherapy/pembrolizumab and surgery or immediately change to SoC chemotherapy or proceed with definitive surgery at the discretion of the primary clinical team. Patients with > 25% enlargement in tumor size at the 6 week study assessment will proceed with SoC chemotherapy or definitive surgery at the discretion of the primary clinical team. The sequence of cytotoxic chemotherapy vs surgery in the scenarios above will be determined through multidisciplinary coordination of care by the primary clinical team (breast medical oncology/breast surgery/radiation oncology).

BREAST MRI- MRI Guided biopsies:

The MRI-guided biopsies will be performed by investigators from the Breast Radiology Service. The research MRI guided percutaneous biopsy technique will be similar to that performed for clinical diagnosis except intravenous contrast will have already been administered for the preceding breast MRI and will not be given again. All MR guided biopsies will be performed with either a 1.5-T or 3.0T whole-body MRI GE unit equipped with a dedicated 8- or 16-channel surface breast coil. On the day of the procedure, the site of biopsy proven enhancing cancer and/or tumor bed will first be localized with MRI using tumor enhancement, the accurately positioned pre-NAC

biopsy marker as well as anatomic landmarks to define the treated tumor bed. Our biopsy protocol will include a localizing sequence followed by a sagittal T1-weighted fat-suppressed images. The pre, 6-week and 12-week MRI biopsies with incorporate the (1) EPI-MRF sequence and (2) CEST-MRF. The EPI-MRF sequence has been optimized for rapid measurements of quantitative susceptibility mapping, proton Density (PD), T1 and T2 relaxation maps. The sequence works by variable excitations and delays which simultaneously sensitizes the signal to the PD, T1 and T2 tissue parameters. Imaging time is approximately 6 seconds per slice with no intravenous contrast is needed. The CEST-MRF sequence is a multiparametric molecular imaging method for rapid simultaneous measurement of the water T1 and T2 relaxation maps, the pH-dependent amide exchange rate and volume fraction and the macromolecular exchange rate and volume fraction. The sequence is fast (acquisition time=2 minutes), requires no intravenous contrast. Both sequences are implemented on 3T GE scanners (Signa Premier). The acquisition time for both the EPI-MRF and CEST-MRF sequences together will take less than 10 minutes, which will ensure all MRI examination will be successfully completed within the allocated time slot. Acquiring the sequences at the time of MRI biopsies will ensure direct radiologic-pathologic correlation.

Biopsies will be performed with a 9-guage vacuum-assisted MRI compatible biopsy system (ATEC Breast Biopsy System, Suros Surgical Systems, Indianapolis, IN). The skin will be cleansed with Betadine and 3 cc of 1% lidocaine will be used for superficial anesthesia. 10 cc of 1% lidocaine with epinephrine (1:200,000; 5mcg/ml) will be used for deep anesthesia. A skin nick will be made. The 9-gauge vacuum-assisted MRI compatible biopsy device will be inserted when target confirmed through the single skin nick and directed to the region of biopsy proven cancer. 12 core biopsy specimens will then be obtained at the same time through a vacuum. After MRI guided biopsy is complete, a titanium marker will be placed at the site of the MRI guided biopsy. The specimens will be dropped off to pathology for analysis.
Following the procedure, pressure will be held on the site(s) until bleeding ceases. The area(s) will be cleansed, and Steri-Strips applied. Post biopsy instructions will be given verbally and in writing. Risks of the procedure include pain, bleeding and infection. The non-therapeutic intervention will not impact treatment.

A post-biopsy mammogram will be performed to document adequate position of the titanium marker within the MRI guided biopsy cavity.
The research percutaneous biopsy specimens will undergo pathology analysis. At the time of breast surgery, pathologic complete response will be determined by standard department of pathology methods and the amount of residual cancer burden will be estimated by a pathologist, who will be blinded to the pathology of the percutaneous MRI biopsy.

If a patient experiences side effects from intervention resulting in a delay of their planned treatment, this will be considered a complication. The planned intervention is to perform MR guided biopsy in the region of the index tumor.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

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

Supplies will be labeled in accordance with regulatory requirements.

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

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

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

Clinical supplies may not be used for any purpose other than that stated in the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

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

The treatment to be used in this trial is outlined in the table below.

Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	400 mg	Q6W	IV infusion	Day 1 of each 6 week cycle	Experimental
Olaparib	300mg	BID	PO	BID	Experimental

5.1 Pembrolizumab

Structure:
Chemical Name: Humanized X PD-1-mAb (H409A11) IgG4
Pembrolizumab DS is an aqueous solution stored frozen at –40 ± 5°C at a concentration of 22.5 to 27.5 mg/mL in 10 mM histidine buffer, pH 5.2 to 5.8, containing 7% sucrose and 0.02% polysorbate 80. The DS at room temperature is a clear to opalescent liquid. The color of the solution is colorless to slightly yellow.

Pembrolizumab DP (solution for infusion, 100 mg/vial) is a sterile-filtered liquid and is aseptically filled into single-use vials. The vials contain 4 mL of sterile solution for IV infusion, 25 mg/mL pembrolizumab, and a total of 100 mg protein/vial. The pembrolizumab DP liquid is diluted with normal saline (0.9% sodium chloride injection, USP) or 5% dextrose (5% dextrose injection, USP) prior to IV administration.

Storage
All study drugs should be kept in a secure place under appropriate storage conditions. Please refer to the Pharmacy manual for details.

Source of Supply
Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD) will supply pembrolizumab.

Dosing/Timing of Dose Administration
Trial treatment should be administered on Day 1 of each cycle after all procedures/ assessments have been completed as detailed on the Study Calendar (Section 10.1). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 400 mg will be administered as a 30 minute IV infusion every 6 weeks in conjunction with olaparib during the initial 12 weeks of the study and then with cytotoxic chemotherapy (after the completion of olaparib) if administered prior to surgery and the patient was not deemed to have tumor growth at the 6 week assessment requiring transition to SOC therapy. Patients will undergo a 2 week washout period after the completion of olaparib prior to the initiation of neoadjuvant cytotoxic chemotherapy. Postoperatively patients will then continue pembrolizumab therapy in the adjuvant setting to complete 1 year of treatment. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2 Olaparib

Structure:
Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one

Chemical Formula: $C_{24}H_{23}FN_4O_3$

Molecular Weight: 434.46

Half-life: 11.9 hours

Olaparib is a crystalline solid, is non-chiral and shows pH-independent solubility of approximately 0.1 mg/mL across the physiological range

Storage
All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the Olaparib bottle specifies the appropriate storage.

Source of Supply
Merck is in collaboration with AstraZeneca and will supply Olaparib. Study treatment is available as a green film-coated tablet containing 150 mg or 100 mg of olaparib. Olaparib will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures.

Dosing/Timing of Dose Administration
The planned dose of 300 mg PO BID will be made up of two (2) x 150 mg tablets BID with 100 mg tablets used to manage dose reductions. Tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

It is prohibited to consume grapefruit juice while on olaparib therapy.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g. as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Once patients have been discontinued from study treatment or completed study treatment, further treatment options will be at the discretion of the investigator/primary clinical team.

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

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

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

Treatment with bisphosphonates or denosumab for the prevention of bone disease is permitted. GnRH agonists for the prevention of chemotherapy-associated amenorrhea are permitted.

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.

Specifically, the following agents are permitted:
- Antiallergic measures such as corticosteroids and antihistamines
- Antiemetics in accordance with ASCO guidance or local standard of care
- Antidiarrheal therapy in accordance with ASCO guidance or local standard of care
- Aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulants are permissible but should be used with caution. However, they should be stopped appropriately prior to biopsy procedures due to risk of bleeding.

Prohibited Concomitant Medications
Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (combined olaparib and pembrolizumab therapy):
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- PARPi not specified in this protocol
- Investigational agents other than pembrolizumab and olaparib

- Radiation therapy
- Live vaccines within 30 days prior to the first dose of study treatment, while participating in the study, and during the 30-day follow up period. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than for supportive care in the setting of chemotherapy administration as per local guidelines or modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.

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

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the Principal Investigator, the treating physician and the participant. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

Rescue Medications & Supportive Care

Pembrolizumab
Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 11.1. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to the tables in Section 11.1 for guidelines regarding dose modification and supportive care. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Olaparib
CYP3A restrictions patients on olaparib
The use of any natural/herbal products should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded.

In vitro data have also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4/5 and in vivo data have shown that co-administration with itraconazole (a known CYP3A inhibitor) increases olaparib AUC by an average of 2.7- fold. Consequently, strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib. If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF (or patient's notes) with the reason documented as concomitant CYP3A inhibitor use.

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg twice daily for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards.
- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards.
- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

In addition, in vivo data have shown that co-administration with rifampicin (a known CYP inducer) reduces olaparib AUC by an average of 87%. Therefore, strong CYP3A inducers (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg, bosentan, efavirenz, modafinil) should not be taken with olaparib.

If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib.

If a patient requires use of a strong or moderate CYP3A inducer, then they must be monitored carefully for any change in efficacy of olaparib.

Effect of olaparib on other drugs
Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4 (eg, hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine), OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (eg. , metformin), OCT2 (eg, serum creatinine), OAT3 (eg, furosemide and methotrexate) , MATE1 (eg, metformin) and MATE2K (eg, metformin).Based on limited in vitro data, olaparib may reduce the exposure to substrates of 2B6 (eg, bupropion, efavirenz) .Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Signed Informed Consent Form

2. Ability to comply with protocol, in the investigator's judgment

3. Women or men aged ≥ 18 years

4. Newly diagnosed histologically confirmed Stage T1c-3N0-3:
    a. TNBC (ER/PgR negativity will be defined using IHC per ASCO/CAP criteria/HER2-negativity will be defined using ISH or IHC assays per ASCO/CAP criteria)
    OR
    b. Hormone receptor-positive, HER2-negative breast cancer defined as per ASCO/CAP criteria

5. Measurable disease per RECIST v1.1

6. Minimum tumor size of 1.5 cm

7. All patients must have a germline mutation in BRCA1, BRCA2, PALB2, RAD51C, or RAD51D.

8. ECOG Performance Status of 0 or 1 (see Appendix A)

9. Patient agreement to undergo appropriate surgical management including, if indicated, axillary lymph node surgery and partial or total mastectomy after

completion of neoadjuvant treatment. *Note: consideration of neoadjuvant treatment will be determined by disease management team based on the subtypes and minimum size the tumor has to be.*

10. Baseline LVEF ≥ 53% measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans

11. Have adequate organ function as defined by the following laboratory results obtained within 14 days prior to the first study treatment (see table below):

    Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN Patients with known Gilbert syndrome who have serum bilirubin level ≤ 3 X ULN may be enrolled.
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase);
AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase);
GFR=glomerular filtration rate; ULN=upper limit of normal.
[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.
[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

12. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    a.) Not a woman of childbearing potential (WOCBP) as defined by institutional guidelines
    OR
    b.) A WOCBP who agrees to follow the contraceptive guidance starting at the time of informed consent, during the treatment period and for at least 120 days after the last

dose of study treatment (pembrolizumab, olaparib) according to local standard of care.

13. Male participants must agree to use contraception starting at the time of informed consent, during the treatment period and for at least 120 days after the last dose of study treatment (pembrolizumab, olaparib) and refrain from donating sperm during this period.

6.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Prior history of invasive breast cancer

2. Stage IV (metastatic) breast cancer

3. Prior systemic therapy for treatment and prevention of breast cancer

4. Contraindication to MRI scan and/or allergy to intravenous contrast-gadolinium (See appendix D)

5. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

6. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks.
   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.
   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

7. Has received prior radiotherapy within 2 weeks of start of study treatment.
   Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.

8. Has received a live vaccine within 30 days prior to the first dose of study drug.
   Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

9. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

10. Has a known additional malignancy that is progressing or has required active treatment within the past X 3 years prior to screening. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or cervical carcinoma in situ are not excluded. Patients with prior ductal/lobular carcinoma in situ are not excluded if they were treated exclusively with mastectomy > 3 years prior to diagnosis of current breast cancer.

11. Has severe hypersensitivity (≥Grade 3) to pembrolizumab or olaparib and/or any of its excipients.

12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

14. Severe infections within 4 weeks prior to initiation of study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

15. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment.
    a. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible for the study.

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

17. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

18. Has a known history of active TB Bacillus Tuberculosis.

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

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

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

22. A WOCBP who has a positive urine pregnancy test within 72 hours prior to study start. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
    - Note: If 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.
    - Patients who have undergone hCG-stimulation for egg harvest as part of fertility preservation within 7 days before treatment initiation are permitted to receive treatment despite a positive pregnancy test.

7.0 RECRUITMENT PLAN

The clinical trial will be listed on the clinicaltrials.gov website. Patients will be identified through internal referrals and external referrals by Medical and Surgical Oncologists, nationally and internationally. Patients will be recruited through the Breast Disease Management Team. The Breast Medicine Service, Breast Service, and the Breast Disease Management Team each hold weekly interdepartmental meetings to identify study participants for open clinical trials. We will also discuss the trial and patient recruitment with several patient support groups. Potential subjects identified will be referred to the investigator/research staff of the study. The principal investigator will be available to all patients for further questions and information through a contact number, which will be provided on the consent form.

All eligible patients, regardless of sex and race, will be approached for participation. The investigators are aware of the NIH policy concerning inclusion of women and minorities in clinical research populations.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with

the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable). Participation in the study is completely voluntary. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. Patients will not receive payment for their participation on this study. Patients are free to withdraw from the study without consequence at any time.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

8.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research

specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form. Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

Screening

All aspects of the screening evaluation must be completed prior to entering the study, unless otherwise noted:

The following must be completed within **28 days** of starting treatment:

- Confirmation of disease: documented presence of Stage T1c-T3N0-N3 invasive breast cancer
- Signed informed consent for study participation
- Full medical history including all active conditions
- Review of concomitant medications including any prior medications taken
- Physical exam (including height and weight)
- Vital signs (pulse, blood pressure, temperature, respiratory rate, and oxygen saturation). Note: height may be documented at any time prior to registration
- ECOG performance status
- Complete blood count with differential, including lymphocyte and eosinophil count
- Comprehensive metabolic panel (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium), phosphorus, magnesium, amylase, lipase, CK, and LDH
- PT (or INR) and aPTT (for screening only)
- Hepatitis B and C testing as per institutional policy
- Serum β-HCG or urine pregnancy test for women with child-bearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Urinalysis
- Cortisol
- 12-lead electrocardiogram (ECG)
- Echocardiogram or MUGA scan
- Research blood tests
- Volumetric assessment of tumor based upon MRI
- Pre-treatment research biopsy
    - Research breast core biopsies of the target lesion will be obtained from all participants prior to initiating protocol chemotherapy unless there is sufficient archival material available from the diagnostic biopsy. These research biopsies are mandatory and will be obtained at the time of MRI

volumetric assessment. It is strongly recommended that core biopsies be image-guided. If a clip was not placed at the time of diagnostic biopsy one should be placed at the time of the pre-chemotherapy research biopsy.

- Computed tomography scan, bone scans, liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease; these assessments should be performed within a timeline as per current local standard of practice.

10.0 TREATMENT/INTERVENTION PLAN

Study drugs

The treatment to be used in this trial is outlined in the table below.

Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	400 mg	Q6W	IV infusion	Day 1 of each 6 week cycle	Experimental
Olaparib	300mg	BID	PO	BID	Experimental

10.1.1 Pembrolizumab

Dosing/Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/ assessments have been completed as detailed on the Study Calendar (Section 10.1). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 400 mg will be administered as a 30 minute IV infusion every 6 weeks in conjunction with olaparib (for the first 12 weeks) and cytotoxic chemotherapy (after olaparib has been completed) if administered prior to surgery and if the patient is not deemed to have tumor growth. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

10.1.2 Olaparib

Dosing/Timing of Dose Administration
Study treatment is available as a green film-coated tablet containing 150 mg or 100 mg of olaparib. Olaparib will be packed in high-density polyethylene (HDPE) bottles with
child-resistant closures. Each dosing container will contain sufficient medication for at least each treatment period plus overage. The planned dose of 300 mg BID will be made up of two (2) x 150 mg tablets BID with 100 mg tablets used to manage dose reductions. Tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

It is prohibited to consume grapefruit juice while on olaparib therapy.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g. as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

10.2 Duration of therapy

Patients will start both olaparib 300 mg PO BID and pembrolizumab 400 mg IV Q6W and continue BID dosing of olaparib with further infusions of pembrolizumab every 6 weeks. Patients will receive olaparib and pembrolizumab for 6-12 weeks, followed by SOC chemotherapy/pembrolizumab and surgery. Depending on response to study therapy, the sequence of cytotoxic chemotherapy +/- pembrolizumab vs surgery will be determined by the primary clinical team. Pembrolizumab will only be administered prior to surgery. Patients will undergo baseline and then 6-week volumetric radiographic tumor assessment with MRI. At the 6-week timepoint, all patients will undergo a biopsy at the time of radiographic tumor assessment with MRI. Radiographic tumor assessment with MRI and biopsy will be repeated at 12 weeks (for those patients who remain on olaparib/pembrolizumab for > 6 weeks).

At 6 weeks patients will be categorized as follows: 1a) Decrease in tumor size at 6-weeks of at least 50% (>50%D) 1b) Decrease in tumor size at 6-weeks of 0 to 50% (<50%D) 2) Enlargement in tumor size of 0 to 25% (<25%E) 3) Enlargement in tumor size of 25% or more at any time during the first 6-weeks (>25%E). Patients with a decrease in the size of the tumor at the 6-week study assessment will continue olaparib and pembrolizumab for an additional 6 weeks for a total of 12 weeks and then proceed with SoC chemotherapy/pembrolizumab or definitive surgery at the discretion of the clinical team. Patients with enlargement in tumor size of 0-25% at the 6-week study assessment will either continue olaparib and pembrolizumab for an additional 6 weeks

for a total of 12 weeks and then proceed SoC chemotherapy/pembrolizumab and surgery or change to SoC chemotherapy or proceed with definitive surgery at the discretion of the clinical team. Patients with > 25% enlargement in tumor size at the 6 week study assessment will proceed with SoC chemotherapy or definitive surgery. The sequence of cytotoxic chemotherapy +/- pembrolizumab vs surgery in the scenarios above will be determined through multidisciplinary coordination of care by the primary clinical team (breast medical oncology/breast surgery/radiation oncology).

Study Calendar

	Screening[a]	Treatment				Completion of Study Therapy/Early Termination[c]
		Neoadjuvant Treatment		Pre-Surgery Visit/Surgery[b]	Adjuvant Treatment	
		Olaparib/ pembrolizumab			+/- SoC chemotherapy/ pembroluzumab	
	Days -28 to -1	42-Day Cycles Cycles 1-2 (Weeks 0-12) (+/- 3 days)		Post olaparib/pembro vs Post SoC chemotherapy/ pembrolizumab	42-Day Cycles[y] (+/- 3 days)	30 days (+/- 5 days) from last dose of pembrolizumab
		C1D1	C2D1		Day 1 of Every Cycle	
Informed Consent[d]	X					
Baseline tumor tissue sample for exploratory biomarkers (mandatory)[e]	X					
Medical history and baseline conditions	X					
Disease status assessments[f]	X	X		X		
Tumor staging[g]	X					
Vital signs[h]	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Height	X					
Physical examination[i]	X	X	X	X	X	X
ECOG performance status[j]	X	X	X	X	X	X
ECG (12-lead)[k]	X	As clinically indicated				
ECHO or MUGA scan[l]	X	As clinically indicated				
Routine labs (CBC, CMP)[m]	X	X	X	X	X	X
Pregnancy test[n]	X			X		
TSH, free T3 (or total T3), free T4[o]	X	Every 12 weeks				X
Viral serology[p]	X					
Urinalysis[q]	X	As clinically indicated				
Cortisol	X	As clinically indicated		X	As clinically indicated	
Blood and plasma samples for biomarkers[r]	X	X (Weeks 3, 6, and 12)			X (post-op)	X

Tumor tissue (fresh sample preferred) at screening, on-study, and the time of surgery[s]	X	X (Week 6; Week 12 for those continuing)				
Mammogram[t]	X			X (as indicated)		
US[t]	X (as indicated)			X (as indicated)		
MRI[u]	X	X (Week 6, Week 12 for those continuing)		X		
Systemic Radiographic assessments (e.g., CT scan, MRI, PET scan)[g]	As clinically indicated					
Concomitant medications[v]	X	X	X	X	X	X
Adverse events[w]	X	X	X	X	X	X
Olaparib (PO) administration		X				
Pembrolizumab (IV) administration[z]		X	X		X	
SOC therapy administration[x]			X	X	X	

a: Results of standard-of-care tests or examination performed prior to obtaining informed consent and within 30 days prior to Day 1 may be used; such tests do not need to be repeated for screening.
b: Pre-surgical visit and associated assessments should occur within 14 days of surgery. Surgery should be conducted no earlier than 14 days and no later than 6 weeks after last dose of neoadjuvant therapy as long as it is deemed clinically safe by the treating investigator.
c: Patients who discontinue study treatment will return to clinic for a treatment discontinuation visit no more than 30 days (+/-5 days) after the last dose of pembrolizumab or surgery (for patients in group 3 who do not continue pembrolizumab/olaparib).
d: Informed consent must be documented before any study-specific screening procedure is performed. Informed consents are valid for 45 days from the day the participant signed prior to treatment. After 45 days, re-consent is required prior to treatment.
e: After signing of the Informed Consent Form, retrieval and submission of tumor tissue sample is required. Tumor tissue should be of good quality based on total and viable tumor content. An FFPE block or at least 20 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for screening and on-study evaluation. Retrieval of baseline tumor sample can occur outside the 28-day screening period.
f: Assessment of primary tumor and regional lymph nodes should be done by physical examination at baseline and prior to administration of each cycle of study treatment during neoadjuvant therapy. Pre-operative imaging should be conducted according to local standard of care. Physical examination is mandatory within 28 days prior to treatment and within 14 days pre-surgery. Disease status based on all available clinical assessments should be documented every 3 months during adjuvant treatment. In addition, liver function tests, bone scans, chest X-ray/diagnostic CT scan, liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease; these assessments should be performed within a timeline as per current local standard of practice. Whenever possible, disease recurrence should be confirmed pathologically. If disease recurrence is diagnosed at any time during the study, patients will discontinue scheduled study assessments.

g: Baseline distant sites tumor staging procedures should be performed in alignment with National Comprehensive Cancer Network (NCCN) or national guidelines, within 28 days prior to treatment. In addition, liver function tests, bone scans, chest X-ray/diagnostic CT scan, liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease.
h: Includes respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline. At subsequent visits, record new or worsened clinically significant abnormalities. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (+/- 5) minutes during and 30 (+/- 10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (+/- 10) minutes after the infusion.
i: Includes evaluation of the head, eyes, ears, nose, throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record abnormalities observed at baseline. At subsequent visits, record new or worsened clinically significant abnormalities. At subsequent visits perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities.
j: See Appendix A.
k: ECG recordings will be obtained during screening and as clinically indicated. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.
l: Cardiac monitoring (ECHO or MUGA scan) will be performed on all patients enrolled in the study at baseline. ECHO is the preferred method. The same method used for a given patient a screening should be used throughout the study if clinically indicated.
m: Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate or total CO2, glucose, BUN or urea, creatinine, total protein, albumin, calcium, total bilirubin, alkaline phosphatase, ALT, AST. Magnesium and phosphorus should be included at screening and as clinically indicated during study treatment. Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment. CBC/CMP will also be taken at week 3 during Cycle 1.
n: All women of childbearing potential will have a serum pregnancy test at screening and within 72 hours prior to study treatment start. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
o: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessedevery 12 weeks during treatment.
p: At screening, patients will be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed to rule out active HBV infection prior to initiation of study treatment. If a patient has a positive HCV antibody test at screening, an HCV RNA test should be performed to rule out active HCV infection prior to initiation of study treatment.
q: Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted
r: See sections 11.0 and 11.1 for additional details.
s: Tumor tissue should be of good quality based on total and viable tumor content. For core-needle biopsy specimens, at least three cores should be submitted for screening and on-study evaluation. Retrieval of baseline tumor sample can occur outside the 28-day screening period.
t: Mammogram and/or ultrasound evaluation bilaterally should occur prior to study start. The unaffected breast should be imaged within 60 days prior to study start and the affected breast should be imaged within 28 days prior to study start. Imaging modality may include ultrasound, mammogram, or MRI, at the discretion of the treating team. Imaging should be repeated at conclusion of study therapy, 2-4 weeks after the last chemotherapy dose, to assess tumor response. The same imaging modality should be used for tumor measurements at each timepoint.
u: Bilateral breast MRI will be required at baseline and on study at 6 +/- at 12 weeks for volumetric assessment of the tumor.

v: Includes any medication (e.g., prescription drugs, over -the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 28 days prior to initiation of study treatment (for the purposes of screening) until the treatment discontinuation visit. Record all prior anti-cancer therapies.
w: After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol -mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment.
x: All Patients will receive olaparib and pembrolizumab for 6-12 weeks, followed by SOC chemotherapy/pembrolizumab and surgery. Depending on response to study therapy at the post treatment wk 12 biopsy, the sequence of chemotherapy +/- pembrolizumab vs surgery will be determined by the primary clinical team. During SOC chemotherapy/pembrolizumab therapy, up to 2 visits are required to coincide with a CTN visit to assess toxicity and conmedication review and may be completed as telehealth visits.
y: The cycle length is based on pembrolizumab administration. Patients will be seen as per standard of care for assessments during chemotherapy.
z: Pembrolizumab may be administered within a +/- 2 week window depending on surgery scheduling.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Study Evaluations

Signed informed consent will be obtained from the patient or patient's legally acceptable representative before any study-specific procedures are performed or any prohibited medications are withheld for purposes of study participation. The schedule of activities to be performed during the study is provided in Study Calendar (Section 10.1). All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that would preclude the visit, the visit should be scheduled on the nearest following feasible date. Any delay visits should be reverted to the original schedule within the next few subsequent visits. For example, no study drug infusion should be skipped due to a visit delay. Assessments scheduled on the day of study drug administration should be performed prior to study drug infusion, unless otherwise noted. Test results or examinations that are performed as standard of care prior to obtaining informed consent and appropriately within 30 days prior to study start be used to satisfy screening requirements rather than repeating required tests; such tests do not need to be repeated for screening.

Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Please see Study Calendar (Section 10.1). for the schedule of screening assessments.

Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline.

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. At the time of each follow-up

physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

Physical Examinations
A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Bilateral breast examination, including evaluation of locoregional lymphatics, should be conducted. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Limited, symptom-directed physical examinations should be performed at post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Vital Signs
Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. At every clinic visit where study treatment is administered, vital signs should be measured within 60 minutes prior to the first infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the Study Calendar (Section 10.1) and at unplanned clinic visits while patient is on study. Vital signs are not required to be entered into the eCRF unless abnormal and clinically significant, in which case they are to be reported as adverse events.

Locoregional Tumor Status

Physical Examination
Assessment of primary tumor and regional lymph nodes must be done by physical examination during the baseline evaluation, within 3 days prior to each 4-week cycle of study treatment during the neoadjuvant phase, and within 14 days prior to surgery. The tumor site must be marked with a radiopaque marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy. Clinical assessment of tumor measurement in the breast and/or lymph nodes should be conducted in a consistent manner at each evaluation. Clinical measurements of tumor in the breast should be performed, preferentially using calipers or a ruler/tape measure. The tumor should be accurately measured in at least one dimension (longest diameter to be recorded) with conventional techniques (positron emission tomography [PET] scan, CT scan, magnetic resonance imaging (MRI), ultrasound, or X-ray). If possible, these measurements should be conducted

by the same assessor at baseline and throughout the neoadjuvant phase. Tumor measurements at baseline and within 14 days prior to surgery are to be recorded in the eCRF. The main purpose of performing physical examination prior to each cycle is for patient safety and to rule out progressive disease that would lead to study treatment discontinuation.

Additional Lymph Node Assessment
Lymph node assessment will be conducted according to institutional standard of care.

Mammogram
Bilateral mammogram must be obtained at baseline. The unaffected breast should have been imaged within 60 days prior to study start. The affected breast should be imaged within 28 days prior to study start. At the discretion of the treating team, imaging modality may include ultrasound, mammogram, or MRI. Subsequent mammograms are optional during neoadjuvant treatment and prior to surgery and should be performed per investigator's discretion. Optional procedure mammograms are not required to be entered into the eCRF.

Ultrasound guided biopsy: All US guided biopsies will be performed with at minimum a 14-gauge needled. Biopsy target will be the biopsy proven cancer, target lesion, defined by the pre-treatment diagnostic imaging study. Approximately X samples will be taken through one incision site and sent to pathology for analysis. A titanium marker will be placed post-biopsy under US guidance and a post-biopsy mammogram will be performed to document adequate positioning.

Breast MRI: All patients undergoing NAC at our institution have a pre- and post-NAC standard-of-care clinical breast MRI. We will be performing two additional not standard of care MRI studies at week 6 and week 12 in all patients that meet the defined criteria. All MRI studies will be performed on either a 1.5 or 3.0-Tesla GE Signa whole-body MRI unit (GE Medical Systems, Waukesha, WI) equipped with a dedicated 8 or 16-channel surface breast coil. All sequence parameters will be similar. The pre, 6-week and 12-week diagnostic MRI with incorporate the (1) EPI-MRF sequence and (2) CEST-MRF. The acquisition time for both the EPI-MRF and CEST-MRF sequences together will take less than 10 minutes, which will ensure all MRI examination will be successfully completed within the allocated time slot.
MRI Interpretation: All MRI studies will be interpreted by a fellowship-trained breast imaging radiologist according to the Breast Imaging-Reporting and Data System (BI-RADS) Lexicon. Co-investigator Sutton or one of the study radiologists will be present at the MRI scanner to review in real time the examination and begin planning below described MRI guided biopsy.

Percutaneous MRI biopsy*:* All MR guided biopsies will be performed with either a 1.5-T or 3.0T whole-body MRI GE unit equipped with a dedicated 8- or 16-channel surface breast coil. Our biopsy protocol will include at minimum a localizing sequence and a sagittal T1-weighted fat-suppressed image post intravenous contrast. The pre, 6-week and 12-week MRI biopsies will incorporate the (1) EPI-MRF sequence and (2) CEST-MRF. The acquisition time for both the EPI-MRF and CEST-MRF sequences together will take less than 10 minutes, which will ensure all biopsies will be successfully completed within the allocated time slot. Acquiring the sequences at the time of MRI biopsies will ensure direct radiologic-pathologic correlation.
Biopsies will be performed with a 9-guage vacuum-assisted MRI compatible biopsy system (ATEC Breast Biopsy System, Suros Surgical Systems, Indianapolis, IN). Biopsy target will be the enhancing tumor and/or treated tumor bed defined by the accurately positioned pre NAC biopsy marker (US guided biopsy). Approximately 12 samples will be taken through one incision site and sent to pathology for analysis. A titanium marker will be placed post-biopsy under MRI guidance and a post-biopsy mammogram will be performed to document adequate positioning.

Pathologic analysis: The percutaneous biopsy pathology and surgical specimen will be evaluated for treatment response. A pCR is defined as ypT0/Tis ypN0. Miller-Payne will be used to assess the tumor response.
1- *Percutaneous biopsy:* The on-treatment biopsies will be reviewed by the study breast pathologist.
2- *Surgical specimen*: This will be evaluated, per standard clinical practice, by a breast pathologist, blinded to the pathology results of the percutaneous MRI biopsy, and results will be collected retrospectively from the final surgical pathology report.

Surgical Treatment Plan
A surgeon with experience of breast cancer surgery should evaluate patients. The proposed surgical treatment plan at baseline should be documented. Patients should be reassessed after completion of neoadjuvant therapy/prior to surgery.

Distant Site Tumor Assessment
Baseline distant sites tumor staging procedures should be performed in alignment with National Comprehensive Cancer Network (NCCN) or national guidelines, within 28 days prior to randomization. As a reference, as per NCCN guidelines, staging procedures are based on clinical stage:

- For clinical stage I-IIB consider additional studies only if directed by signs or symptoms.

- Bone scan indicated if localized bone pain or elevated alkaline phosphatase.
- Abdominal +/- pelvic diagnostic CT with contrast or MRI with contrast indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms or abnormal physical examination of abdomen and/or pelvis.
- Chest diagnostic CT with contrast if pulmonary symptoms
- If ≥ clinical stage IIIA strongly consider:
- Bone scan
- Abdominal +/- pelvic diagnostic CT with contrast or MRI with contrast
- Chest diagnostic CT with contrast if pulmonary symptoms

OR

- FDG PET/CT

In addition, liver function tests, bone scans, chest X-ray/diagnostic CT scan, liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease.

Disease Follow-Up and Confirmation of Disease Progression or Recurrence
During the neoadjuvant treatment, diagnosis of disease progression or second primary breast cancer should be supported by clinical, laboratory, radiological, and/or histological findings. The designation of disease recurrence, whether local, regional or distant, or a diagnosis of a second primary cancer can be made only when clinical, laboratory, radiological and/or histological findings support the diagnosis. Given the mechanism by which immune-modulating therapies work, patients with radiographic lesions suspicious for disease recurrence are strongly recommended to undergo biopsy for histologic confirmation of cancer versus immune-mediated inflammatory process. The earliest date of diagnosis of disease progression, recurrent disease, or a diagnosis of a second primary cancer should be used and recorded. This date should be based on objective clinical, radiological, histological, or cytological evidence.

Recurrent disease includes local, regional, or distant recurrence and contralateral breast cancer. While ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) will not be counted as progressive disease or recurrent disease, these events should be recorded. Patients who have a diagnosis of in situ breast disease or second (non-breast) malignancies should be maintained on a regular follow-up schedule whenever possible in order to fully capture any subsequent recurrent disease events.

Surgical Specimen Pathology
Secondary endpoint of the study (pCR) will be as identified by local pathology review. Guidelines regarding pathology specimen preparation, labeling, and review as well as calculation of the RCB index are outlined in Section 12.2.

Laboratory, Biomarker, and Other Biological Samples
Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis as outlined in the Study Calendar (Section 10.1) and as clinically indicated:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate or total CO2, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST
- Coagulation: INR, aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine
- HBV serology: HBsAg, total HBcAb
- If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must be performed to rule out active HBV infection on the basis of HBV viral load per local guidelines.
- HCV serology: HCV antibody
- If a patient has a positive HCV antibody test at screening, an HCV RNA test should be performed to rule out active HCV infection prior to initiation of study treatment.
- Cortisol
- Pregnancy test
- All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A woman is considered to be of childbearing potential if she

is postmenarcheal, has not reached a postmenopausal state (> 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted
- Blood and plasma samples for exploratory research on biomarkers
- Tumor tissue sample collected at baseline for determination of PD-L1 expression; for confirmation of HER2, ER, and PgR negativity; and for exploratory research on biomarkers
- A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. After signing of the Informed Consent Form, retrieval and submission of a tumor sample can occur outside the 28-day screening period. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Tumor tissue should be of good quality based on total and viable tumor content. Acceptable samples include those from resections, core-needle biopsies (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsies. For multifocal tumors, three cores should be submitted for the main lesion, while one core is sufficient for each of the other foci. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, and cell pellets from cytology samples are not acceptable. Tissue should meet the tumor tissue requirements described in the eligibility criteria.
- Tumor samples for biomarker evaluation will be collected to promote, facilitate, and improve the treatment and mode of action of study therapy. On study biopsy will be performed at baseline, at 6 weeks and at 12 weeks for those patients who continued therapy with olaparib/pembrolizumab beyond 6 weeks of study therapy (>50%D, <50%D, +/- <25%E). Tissue will also be collected at eventual surgical resection.
- When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed, or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data. Data arising from sample analysis will be subject to the institutional confidentiality standards. Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law, with the exception of the report from MSK-IMPACT testing completed during the

course of the study. The aggregate results of any conducted research will be available in accordance with the institutional policy on study data publication.

Electrocardiograms
A 12-lead ECG is required at screening and when clinically indicated (Study Calendar Section 10.1). ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

Echocardiograms or Multiple-Gated Acquisition Scans
LVEF will be assessed by echocardiography (preferably) or MUGA scan as outlined in the Study Calendar (Section 10.1) and as clinically indicated. Patients should be reassessed with the same technique used for baseline cardiac evaluation throughout the study.

Tumor and Blood Samples for Correlative/Companion studies
All patients enrolled on this study will undergo paired tumor biopsies and blood sample collection for research purposes (correlative/companion studies) where feasible. All biospecimens being used for genomic testing, including cfDNA samples, will be collected, stored and analyzed as part of IRB #12-245.

<u>Tumor biopsy collection</u>
Tumor biopsies for research purposes will be done at baseline (within 28 days of the first dose of olaparib and pembrolizumab) and at Week 6 in all patients enrolled in this study where feasible. Similarly, at the 12-week timepoint, all patients who remain on olaparib/pembrolizumab for > 6 weeks will undergo another biopsy. The same primary tumor site will be biopsied at each time point, if feasible. At least three cores should be submitted for screening and on-study evaluation at each time point. Samples will be stored as follows: 1 core as FFPE and additional cores will be flash frozen per per standard institutional practice.

Biopsy procedures will otherwise be performed as per institution guidelines. Samples will be labeled using an adherent, liquid nitrogen proof label with the following information:

1. Procurement date
2. Study IRB number
3. Study patient MRN/study ID

4. Time point (baseline or on-treatment)
5. Anatomical biopsy site

Research blood sample collection
Blood samples for research purposes will be obtained at screening, week 3, 6, 12, postoperatively and at the date of the off-study visit (± 3 days).

At each research blood collection time point the following samples will be collected:

Samples will be labeled with the following information:

1. Procurement date
2. Study IRB number
3. Study patient MRN/study ID
4. Time point (baseline or week-X)

Specimen Collection, Processing, and Storage Guidelines

KIT PREPARATION: REQUIRED SUPPLIES
Kits for each blood draw will be created by study staff and will contain the following items:

- Plasma and PBMC Isolation:
  - 4 X 8mLCPTtubes
  - Biohazard zip seal bag(s)
  - Laboratory requisition form(s)
- cfDNA Extraction and Buffy Coat Isolation:
  - 2 X 10 mL STRECK tubes
  - Biohazard zip seal bag(s)
  - Laboratory requisition form(s)

BLOOD COLLECTION PROCEDURES

- A research kit will be assembled by the study team containing all required draw tubes and labels. Tubes should not be prelabeled.
- The research kit will be dropped off at the appropriate phlebotomy collection location prior to the participant's appointment.
- Phlebotomists should follow the instructions listed on the laboratory requisition form. Standard tubes should be inverted 5-8 times post-draw.
- When notified, the study team will pick up the bloods and bring speimens to the appropriate processing location.

SPECIMEN PROCESSING
For Plasma and PBMC Isolation: CPT tubes will be transported to the Immune

Monitoring Core Facility (Room Z-1513) in the Zuckerman Research Center (417 East 68th Street) for processing and storage at MSK per lab work flow and SOP.

For cfDNA Extraction and Buffy Coat Isolation: STRECK tubes will be transported to the cfDNA Extraction Lab within the Department of Lab Medicine (327 East 64th Street) for processing per lab work flow and SOP. After processing, samples will be stored at MSK in -80 C freezer.

11.1 Planned correlative analyses
Expression of Selected Immune Markers

Rationale: Previous immune checkpoint inhibitors (ICI)-based neoadjuvant studies conducted in patients with NSCLC and melanoma have shown the capacity of neoadjuvant ICI therapy to increase and revinvigorated TILs and to cause clonal CD8 T cell expansion in peripheral blood and tumor microenvironment (TME). More important, serially biopsied during anti-PD-1 treatment showed a parallel increase in T cells at both the invasive margin and the tumor center in patients responding to therapy, but not patients with progressive cancer, suggesting the capacity of dynamic markers to predict treatment benefit.

Goal: We plan to determine changes in expression of selected immune markers comparing paired samples at baseline collected from patients prior to PARP/ICI therapy, with tissue collected during treatment (at 6 weeks) and at the completion of PARP/ICI treatment. We hypothesize that significant differences in innate and adaptative immune cell subsets will underlie differences in pathologic response rates between patients. To examine these hypotheses, the following comparisons will be made using tumors collected before, on-treatment and at end of treatment in patients treated on study.

Methods:
H&E TIL Score: TILs will be scored according to the recommendations of the international TILs working group, on fresh frozen paraffin embedded (FFPE) tumor specimens
Multiplex IHC (mIHC): FFPE slide sections will be stained with the appropriate validated antibodies (including, but not limited to CD3, CD8, FoxP3, CD163, and PDL1). We will specifically focus on the markers of specific leukocyte subsets, including but not limiting to tumor-associated macrophages, natural killer cells, CD4, CD8, Tregs, as well as known immune inhibitory proteins (e.g. PD1/PDL1, IDO, B7H3/B7x). Parameters derived from the analyses include quantification of individual cell types, percent and intensity of expression of activation and inhibition markers on T cells and other immune cells, and association and proximity between different cell types. Sections will also be stained for kmacrophage markers

including CD11b/c, CD163, and CD68 which can distinguish M1-like from M2-like macrophage phnoetypes.

cGAS-STING pathway expression

Rationale: Olaparib-mediated cell death, via either PARP trapping or via increased DNA damage, has the potential to release antigens into the tumor microenvironment, promoting effective antigen presentation; this has been described for other therapies that lead to increased tumor cell death (Galluzzi et al. 2017). Secondly, DNA damage promotes inflammation via two alternative pathways, the first being activation of the NF-κB pathway (Ioannidou et al. 2016), and the second being activation of the stimulator of interferon genes (STING) signaling pathway via generation and detection of cytosolic DNA (Hartlova et al. 2015; Parkes et al. 2017). Activation of these pathways leads to increased pro-inflammatory signaling that enhances effective recognition and infiltration of tumors by immune cells and has recently been shown to be critical to the response to checkpoint inhibition in mice (Wang et al. 2017). More recently, Dr. Bakhoum group and others have shown that chronically activation of cGAS–STING signaling can also have tumor and metastasis-promoting functions, and its chronic activation can paradoxically induce an immune-suppressive tumor microenvironment (Bakhoum et al. Nature, 2018 and Bakhoum et al. Cell 2018). Therefore understanding the context-dependence of this pathway is critical toward our ability to select patients who might benefit from innate immune activation as well as harnessing this pathway for a therapeutic benefit.

Goal: We plan to determine changes in expression of cGAS-STING pathway markers (cGAS, STING, ENPP1, IRF3, RELB, and p65) comparing paired samples at baseline collected from patients prior to PARP/ICI therapy, with tissue collected during treatment (at 6 weeks) and at the completion of PARP/ICI treatment. This would allow us to evaluate activation of the cGAS-STING pathway in response to combining PARPi with anti PD1 therapy. This evaluation will also allow us to correlate the impact of baseline cGAS-STING pathway activation (including chronic activation) with the response rate to neoadjuvant PARPi/antiPD1 therapy. More importantly, we will be able to understand how breast tumors might be able to adapt to chronic cGAS-STING signaling thereby switching the pro-inflammatory process into an immun suppressive pathway through staining for ENPP1. ENPP1 was recently identified by the Bakhoum Laboraotry as a negative regulator of cGAS-STING signaling through its cGAMP hydrolase activity. Given that it is an extracellular enzyme anchored to the plasma membrane, ENPP1 prevents cGAMP-mediated paracrine signaling leading to suppression of type I interferon response and immune evasion.

Methods: FFPE slide sections will be stained with the appropriate validated antibodies (including, but not limited to cGAS, STING, ENPP1, IRF3, RelB, and

p65). All antibodies have been rigorously validated using knockdown/knockout conditions in the Bakhoum Laboratory

High-throughput sequencing of the TCR-β CDR3 region

Rationale: T cell receptor sequencing (TCRSeq) has emerged as a method to monitor and define dynamic changes in T cell populations of cancer patients treated with ICI therapy. Previous studies of neoadjuvant immune checkpoint blockade conducted in patients with melanoma and NSCLC have shown that clonal expansion (increasing clonality) correlated with pathologic response.

Goal: Examine changes in intratumoral and peripheral blood TCR repertoire (PMBC). We will compare pretreatment peripheral blood and intratumor TCR clonality to examine whether the repertoire diversifies, focuses, or is unchanged after initiation of treatment. Examples of metrics we will examine include Shannon entropy, clonality, and evenness. Then we will use these data to determine whether tumor-associated TCRs expand in the peripheral blood and intra-tumor during neoadjuvant therapy. This will demonstrate whether peripheral TCR expansion associates with better response, as it does in our preliminary data

Methods: DNA will be extracted from tumors and will be sent for deep sequencing of CDR3 regions. Rearranged TCRbeta CDR3 sequences will be amplified and sequenced. As described per study calendar, 4 CPT tubes will be collected at screening period, at C2D1 on olaparib/pembrolizumab treatment and at 12 weeks.

Molecular alterations during neoadjuvant pembrolizumab/olaparib

Rationale: Molecular characterization of breast cancer has become a standard of care, as it provides prognostic information and determines eligibility of patients for therapy with several FDA-approved agents (eg. PARPi for gBRCA1/2 mutation carriers in metastatic setting; PIK3CA inhibitor (Alpelisib) for patient with hormone receptor positive, HER2 negative, PIK3CA-mutated, advanced or metastatic breast cancer; Pembrolizumab in metastatic breast cancer with mismatch repair deficiency). Moreover, circulating tumor DNA (ctDNA) found in the plasma of cancer patients has been shown to constitute a source of tumor-derived DNA, which can be employed for the analysis of sequencing-based biomarkers. ctDNA provides possibilities for a sensitive detection of tumor DNA that could predict response to therapy, early recurrence and capture the full repertoire of tumor mutations that are otherwise limited by tumor heterogeneity

Goal: Examine changes in somatic mutation profile at baseline, on-treatment and post-treatment with pembrolizumab/olaparib. This evaluation would allow us to understand potential mechanisms of primary resistance to

pembrolizumab/olaparib, as well as interrogate the possibility of new predictive markers of treatment response.

Methods:
IMPACT: MSK-IMPACT data will be collected per standard of care. In addition, patients will be consented to both part A and C of 12-245 protocol, which will allow to capture both somatic and germline data. Alternatively, tissue samples could also be subjected to WES and WGS.
ctDNA analysis: We will collect serial blood samples in Streck tubes from patients prior to neoadjuvant pembrolizumab/olaparib and at weeks 3, 6, and 12 during treatment and postoperatively. cfDNA will be extracted from plasma, quantified and stored at MSK's cfDNA laboratory (Laboratory Medicine), following validated standard operating procedures. Tissue samples from the primary tumor will be collected at the time of initial biopsy and DNA extracted from the primary tumor and matched normal peripheral blood leukocytes will be subjected to MSK-IMPACT sequencing. Sequencing data will be analyzed using state-of-the-art bioinformatics approaches to identify the somatic mutations and copy number alterations for each tumor. cfDNA will be subjected to high-depth targeted massively parallel sequencing using MSK's cfDNA pan-cancer sequencing panel ("MSK-ACCESS" for High-Sensitivity Cell-Free DNA Profiling). Alternatively, cfDNA samples could also be subjected to other ultrasensitive ctDNA assays such as tumor-informed bespoke ctDNA assays to monitor tumor evolution or ddPCR. Selected ctDNA samples will undergo WES or WGS to better characterize the muitational landscape of the disease.

Ultra-high resolution single cell genomics and transcriptomics techniques

Rationale: The vast heterogeneity in tumor genetics and microenvironment observed in the recent studies necessitates implementation of novel methodologies capable of analyzing the tumor cell samples on a single cell level. These include single cell RNA-Sequencing (scRNASeq), as well as single cell DNAseq.

Goal: To evaluate the potential effects of neoadjuvant pembrolizumab/olaparib in malignant and immune cell diversity, by comparing baseline, on-treatment and post-treatment tissues analyzed with ultra-high resolution single cell genomics and transcriptomics techniques.

Methods: Tissue from tumor biopsies and resected tumors will be processed for generation of viable single cells, after which the cell suspensions will be FACS sorted into CD45+ cells, to characterize the tumor immune microenvironment, as well as CD45- cells, to characterize tumor cells and other components of the tumor

stroma. Viable single cell suspensions will be analyzed. Flash frozen tumor samples will be used for single cell DNA and RNA analysis.

11.2 Adverse Events Associated with Pembrolizumab

11.2.1 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

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

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events and/or unforseen circumstances not related to study intervention. However, intervention is to be restarted within 6 weeks (42 days) of the originally scheduled dose and within 84 days of the previously administered dose. The reason for study intervention interruption is to be documented in the participant's study record.

The following table includes 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 (CTCAEv5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2, 3 or 4 3 or 4	Permanently discontinue Permanently discontinue	• 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
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 liothyronine) 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: Guillain-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).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in the table below.

Pembrolizumab Infusion Reaction Dose modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** 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 participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
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: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruptions for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the PI. The reason for interruption should be documented in the patient's study record.

11.3 Adverse events associated with olaparib

11.3.1 Dose Modification and Toxicity Management for Olaparib

Any toxicity observed during the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed, and study treatment should be discontinued. Once dose is reduced, escalation is not permitted.

Dose reductions and modification will be made as indicated in the following table. The descriptions and grading scale found in the revised NCI CTCAE version 5.0 will be utilized for dose delays and dose modifications. For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see Section 5.3 Concomitant Medications/Vaccinations.

Dose Modification Table

Dose Level	Olaparib Dose
0	300 mg BID
-1	250 mg BID
-2	200 mg BID
Further dose reduction	NA; Treatment discontinuation

Management of hematological toxicity
Management of anemia

Hemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	-Give appropriate supportive treatment and investigate causality. -Investigator judgement to continue olaparib with supportive treatment as clinically indicated (eg transfusion) *or* interrupt dose for a maximum of 4 weeks.
Hb < 8 g/dl (CTCAE Grade 3/4)	-Give appropriate supportive treatment (e.g. transfusion) and investigate causality. -Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 10 g/dl. -Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence), refer to dedicated section "Management of prolonged hematological toxicities while on study treatment" for the management of these cases.

Management of neutropenia, leukopenia, and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE gr 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE gr 3-4	Dose interruption until recovered to CTCAE gr 1 for a maximum of 4 weeks, and dose reduction to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if required.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Study treatment can be interrupted for CTCAE grade 1/2 neutropenia or thrombocytopenia as per investigator's judgement. In case of CTCAE grade 3/4 neutropenia, leukopenia or thrombocytopenia, study treatment should be interrupted for a maximum of 4 weeks. Study treatment can be restarted at the same dose if an adverse event of neutropenia, leukopenia or thrombocytopenia have been recovered up to CTCAE grade 1 or less. Any subsequent interruptions will require study treatment dose reductions to 250 mg twice daily as a first step and to 200 mg twice daily as a second step.

Management of prolonged hematological toxicities while on study treatment.
If a patient develops prolonged hematological toxicity such as:

- ≥ 2 week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥ 2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 109/L)

- ≥ 2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (Platelets < 50 x 109/L)

Weekly differential blood counts including reticulocytes and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator.

Management of non-hematological toxicity

Management of new or worsening pulmonary symptoms
If new or worsening pulmonary symptoms (e.g. dyspnea or cough) or radiological abnormalities occur in the absence of clear diagnosis, an interruption in study treatment dosing is recommended and a diagnostic workup should be performed to exclude pneumonitis. Initial workup should consider the inclusion of a clinical evaluation, high-resolution CT scan, ruling-out infection, pulse oximetry, and other appropriate laboratory workup. Pulmonary consultation is highly recommended. Guidelines for the management of patients withimmune-related AEs including pneumonitis are provided above.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

Management of nausea and vomiting
Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, although it may be delivered. Patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. As per international guidance on antiemetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg dopamine receptor antagonist, antihistamines, dexamethasone.

Renal Impairment
If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200mg BD.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

Hepatic Impairment
If subsequent to study entry and while on study therapy, the patient develops hepatic impairment, the investigator should make every attempt to identify the underlying reason for the impairment.

Olaparib can be administered to patients with mild or moderate hepatic impairment (Child-Pugh Classification A or B) with no dose adjustment. Olaparib has not been studied in patients with severe hepatic impairment and is NOT recommended for use in these patients.

Management of toxicity due to either pembrolizumab or olaparib
Both olaparib and pembrolizumab treatment may be associated with the development of pneumonitis, hepatic impairment, and renal toxicity. For renal dysfunction and hepatic dysfunction follow the dose modification guidelines provided above for both olaparib and pembrolizumab.

Treatment with olaparib must be held for any grade of pneumonitis. Treatment with pembrolizumab must be held for pneumonitis ≥ Grade 2 as outlined above. Hold treatment for new or worsening respiratory symptoms such as cough, dyspnea, fever, wheezing, or radiologic abnormalities; evaluate promptly. Discontinue treatment if pneumonitis is confirmed.

Interruptions for intercurrent non-toxicity related events
Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks

for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Principal Investigator.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.
Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

MRI/MRI-guided biopsy
Patients will be counseled regarding the MRI biopsy, which is an FDA approved technique. Breast MRI biopsy is currently being offered to any patient that needs it at MSK both for high risk screening and in the context of a new diagnosis of breast cancer. The use of magnets to obtain chemical information has been studied previously with minimal side effects. As is the case for a standard MR exam, the presence of a pacemaker or aneurysm clips could pose a risk to the patient and patients with these contraindications will be excluded. A subject with sensitivity to noise or some neurological problems may have difficulty tolerating the MRI noise. Therefore it is recommended that patients talk to their referring physician regarding the noise of the MRI prior to taking part in the study. Some patients feel claustrophobic (afraid of enclosed spaces) in the MRI magnet.

Rare but Serious due to MRI:
Another possible hazard of the exam is localized heating of the body due to the radio waves used. If this were to happen, the patient would feel an intense heating or burning sensation. The patient will be asked to notify the MR technologist immediately. However, the MR scanner and the MR coil has been designed to prevent this from happening and there have been no reports of local heating in patients scanned to date. Because the MR instrument attracts iron, any iron-containing objects will accidentally fly into the magnet causing injury. Precautions have been made to prevent this from happening.The power absorbed in the tissue is limited by the manufacturer according to FDA guidelines. The manufacturer has made the necessary modifications to the imaging pulse sequences to stay within the FDA guidelines and, as at 1.5T, the 3.0T has a safety mechanism to prevent an imaging sequence from starting if power absorption limits are reached.

MRI Contrast injection/IV Needle Placement:
- Hematoma at the injection site
- Phlebitis;
- Bleeding;
- Infection;

- Bruising;
- Minor discomfort;
- Headache;
- Nausea;
- Vomiting;
- Hives;
- Temporary low blood pressure;
- Allergic-type reaction

Rare, but Serious due to MRI Contrast injection/IV Needle Placement:
Kidney impairment, details follow. Rare but severe adverse events occur in approximately 15/100,000 persons administered intravenous gadolinium. There is a risk of death in 1/100,000 persons. Precautions should be exercised for patients with severely impaired renal function or hemolytic anemia. The very unlikely possibility of a reaction, including anaphylactic-like or cardiovascular reactions, should be considered, especially for patients with a known sensitivity to gadolinium or history of asthma. Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD), kidney disorders, may occur in patients with moderate to end-stage kidney disease (glomerular filtration rate < 30 mL/min/1.73m^2) and in patients with renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period after they have had an MRI scan with gadolinium-based MR contrast agents. NSF causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF usually starts in the lower extremities. Fibrosis can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels.

Due to biopsy:
For the biopsy the patient will receive percutaneous epinephrine and lidocaine. Potential side effects include: pain, infection and local allergic reaction.

Anticipated adverse events are those that may be expected from tissue biopsy. This may include pain, bleeding, bruising, hematoma, infection or wound healing complications. In addition, if there is a complication from the biopsy (for example a hematoma), this could lead to the removal of a bigger piece of breast tissue at the time of surgery than would normally be done, which could impact the appearance of your breast after surgery.

12.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study when any of the criteria listed below applies. The reason for removal from the study and the date the patient was removed must be documented in the Clinical Research Database system.

All patients who have received at least one dose of each study treatment will be assessable for safety of the combination therapy. Patients who discontinue the study

before receiving their first dose of the study treatments will not be evaluable for safety assessment and should be replaced. Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value must be followed until resolution or stabilization of the event. A dose delay >3 weeks from the date of the planned dose may require the patient to be discontinued from the study treatment.

Patients are evaluable if they have completed the 6-week assessment. Radiographic response is assessed at 6 and (for those continuing) 12 weeks. Biopsy-confirmation of disease status at 6 and 12 weeks will be conducted at the time of the 6 and (for those continuing) 12 week assessments. pCR/RCB is assessed at the time of surgery.

Patient may continue on study until one of the following criteria applies:

- Confirmed radiographic disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse experiences
- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Physician decides to withdraw a participant from the study treatment or from the study for a reason not listed here
- The participant has a confirmed positive serum pregnancy test
- The participant is lost to follow-up
- Inability of the participant to comply with the requirement of the protocol for treatment or evaluation.
- End of study, whichever occurs first.

12.1 Clinical Criteria for Early Trial Termination

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

- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
- Plans to modify or discontinue the development of the study drug

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

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

The two major effects to be measured in this study are: tumor/pathological response to study drugs and volumetric tumor assessment by MRI.

13.1 Target Lesions

A baseline and presurgical imaging study of the breast is required as necessary for clinical management; ultrasound, mammogram and MRI may be pursued. The baseline imaging must be obtained within 28 days (+/- 7 days) of beginning therapy. If the participant demonstrates clinical progression at any time, repeat imaging is required. If there is discordance (clinical progression, but radiographic stable disease or response), study PI should be contacted to solve discordance.

In the event of multifocal or multicentric disease in the breast, the investigator must determine which will represent the target lesion. This should remain consistent throughout the study. The target lesion should be selected on the basis of its size (lesion with the longest diameter) and suitability for accurate repetitive measurements (either by imaging techniques or clinically).

Response criteria are based on the RECIST 1.1 criteria:

Imaging Complete Response (CR):	Complete disappearance of the target lesion
Imaging Partial Response (PR):	Greater than or equal to 30% decrease in the longest diameter (LD) of the target lesion taking as reference the baseline LD
Imaging Progressive Disease (PD):	Greater than or equal to 20% increase in the LD of target lesion taking as reference the baseline LD or the appearance of one or more new lesions
Imaging Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the baseline LD

13.2 Pathological assessment

The MD Anderson Residual Cancer Burden (RCB) method will be used to assess pathologic response in the surgical specimen (Symmans et al. 2007; Provenzano et al. 2015). At least one complete cross-section of the largest dimension of tumor bed, and at least 1 section per centimeter of the tumor bed will be submitted for microscopic review. The entire tumor bed will be submitted if the largest diameter is less than 5 cm. The entire cross tumor bed section will be used to evaluate the following variables: tumor bed diameters (2 largest dimensions), tumor cellularity, percent of tumor cellularity that is DCIS, number of positive lymph nodes, and size of the largest nodal metastasis. If multiple tumors are present, the measurements of the largest will be used to calculate the RCB. If lymphovascular invasion is identified in the specimen in

the absence of residual invasive tumor or nodal involvement this will not be considered pCR.

RCB score will be calculated using the following online tool: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3. RCB 0/I will be considered good response; RCB II/III will be considered poor response. RCB0 is considered pCR. pCR will be defined as no residual invasive carcinoma and no lymph node metastasis regardless of the presence of DCIS.

13.3 Imaging assessment

Each participant will have a pre-therapy baseline MRI study. The longest diameter (LD) of the target lesion at the time of study initiation will be reported as the baseline LD. The baseline LD of the target lesion will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease. There is no size requirement defining residual disease; the determination of the presence of clinically significant residual disease will be made by the treating provider. The radiologic response to treatment should be noted as complete response (no visible tumor present), partial response (tumor present but reduced in size from baseline), stable disease (no change in size of tumor) or progressive disease (tumor larger than baseline). Both target and, in the event of multifocal or multicentric invasive cancer, nontarget lesions should be followed clinically and their clinical size recorded at baseline. Measurements thereafter are required; these lesions should be categorized at subsequent visits regarding whether there is evidence of progression. If progression occurs the study chair should be notified in order to determine whether the participant should come off protocol treatment. In addition to measuring the longest diameter of the target lesion, quantitative volumetric assessment will be performed of the target lesion on all MRI using commercially available software ***tararecon*** (Foster City, CA).

13.4 Pathology Response Central Review

Central review of pathology slides of the baseline and on-study breast biopsies and the post-treatment surgical specimen (excision or mastectomy with lymph nodes) will be performed by Dr. Maria Gabriela Kuba.

14.0 BIOSTATISTICS

This trial is designed as a single-arm, open-label, non-randomized study with sample size calculated using the Simon two-stage minimax design. The primary endpoint is pathologically negative MRI-guided biopsy after neoadjuvant combination olaparib-pembrolizumab therapy at 12 weeks. Patients are eligible for this study if they have newly diagnosed high-risk early-stage invasive breast cancer, either triple negative according to ASCO/CAP guidelines or hormone receptor positive breast cancer with a germline mutation in BRCA1, BRCA2, PALB2, RAD51C, or RAD51D. As noted in section 3.6, our preliminary work suggests that MRI-guided biopsy has high specificity

and sensitivity in diagnosing pCR compared with the reference of standard surgical pathology.

At the 6 week timepoint, patients will be categorized as follows:

Group 1: Decrease in tumor size
1a) Decrease in tumor size of at least 50% (≥50%D)
1b) Decrease in tumor size at 6-weeks of 0 to 50% (<50%D)

Group 2: Enlargement in tumor size of 0 to 25% (<25%E)

Group 3: Enlargement in tumor size of 25% or greater

All evaluable patients across the 4 categories will be included for the primary endpoint.

Patients who are responding (any decrease in tumor size, groups 1a and 1b above) will continue the study therapy for another 6 weeks. Patients who have increases in tumor size of 0-25% (group 2) at the 6-week timepoint can continue study therapy for another 6 weeks or elect SoC chemotherapy/pembrolizumab vs surgery. To ensure safety, patients who have a >25% increase in tumor size from the preceding imaging at any point (group 3) will immediately move to SoC chemotherapy vs surgery. For all 4 groups following completion of the study therapy, conventional treatment will commence. These group delineations are outlined in details because this determines how patients will be treated on study.

All patients who have received at least one dose of each study treatment will be assessable for safety of the combination therapy. Patients are evaluable for the primary endpoint if they have completed the 6-week assessment. Biopsy-confirmed radiographic complete response will be determined at the 12-week timepoint. pCR/RCB0 will be determined at the time of surgery.

Sample size
The primary endpoint is pathologic assessment of MRI biopsy after neoadjuvant combination olaparib-pembrolizumab therapy at 12 weeks. The primary efficacy endpoint will be evaluated following completion of neoadjuvant therapy with combination olaparib and pembrolizumab X 12 weeks. In the primary analysis, patients whose 12-week imaging assessment or biopsy is not available will be counted as failures in the primary endpoint.

Patients are evaluable for the primary efficacy analysis if they have completed the 6-week assessment. An exception to this includes the rare patients who progressed during the first 6 weeks. These patients will be included in the primary analyses as failures. Note that any patients with progression or who drop out of the study from week 6 to 12 will be counted as failures for primary 12 week endpoint. Also note that patients who require a switch to SOC chemotherapy/ pembrolizumab after the 6 weeks biopsy

will be considered failures for the primary endpoint. All patients are evaluable for the safety analyses.

All evaluable patients (groups 1-3) will be included in our primary analysis. The sample size for this study is calculated using a Simon two-stage minimax design comparing a null true imaging-based complete response rate of 50% vs 75%. Our null rate comes from published literature which reports pCR rates in the range of ~44-54% in patients receiving neoadjuvant cytotoxic chemotherapy and ~53-65% in patients receiving either neoadjuvant immunotherapy or a targeted agent like a PARPi[59, 73, 74,75]. In the first stage, 14 patients will be accrued. If there are 7 or fewer responses, then the study will be stopped. If 8 or more responses are observed, an additional 9 patients will be accrued for a total of 23 patients. If 16 or more responses are observed in 23 patients, the study regimen will be deemed successful. If 15 or fewer responses are observed, the study will be deemed unsuccessful. This design has a one-sided type I error rate of 0.05 and power of 0.80. The probability of stopping the study under the null is 0.60. At the end of the study, the image-guided biopsy CR rate will be calculated with a 95% confidence interval.

Up to 23 evaluable patients will be enrolled on this study. We anticipate enrolling 1-2 patients per month.

Secondary endpoints
There are several secondary endpoints. First, safety and tolerability of the study regimen will be summarized using frequencies according to the CTCAE Version 5. Common side effects are listed in Section 15.0. The rate of pathologically negative MRI-guided biopsy at 12 weeks will be calculated in the subpopulation of patients with PD-L1-positive disease. In the neoadjuvant setting the rates of PD-L1 positivity were reported in two large prospective trials: Keynote 522 ~80% of patients with TNBC were PD-L1+ and in the NeoTrip trial ~56% of tumors were PD-L1+. In the metastatic setting the numbers have been varied but in the large clinical trials the rate of PD-L1 positivity was ~40%.

Data on MRI-guided biopsies and MRI images will be collected at baseline, at 6 weeks and at 12 weeks following entry into the study. The correlation of response as measured by the MRI - guided biopsy vs MRI images will be evaluated at each timepoint using the McNemar's test for paired samples. The correlation of response as measured by the MRI-guided biopsy collected post-treatment vs pCR at surgery will be evaluated using the McNemar's test for paired samples and the Kappa statistic. The overall pathologic complete response rate will be calculated with a 95% confidence interval.

Analysis of exploratory endpoints
These exploratory analyses will be descriptive/graphical in nature, and are designed to generate new hypotheses to be tested in future clinical studies.

When parameters of immune response are measured (including TILS, multiplex IH and cGAS-STING pathway expression) continuous variables will be summarized with means and standard deviations. Dichotomous and categorical variables will be summarized using proportions with exact 95% confidence intervals and counts, respectively. These summaries will be computed for each treated patient at multiple time points, including before treatment, during and after pembro/olaparib administration, as indicated in the study schema. Plots will be used to show the changes in immune response over time for each individual. For each patient, comparisons in the pre and post-treatment responses will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and McNemar's test for dichotomous or categorical variables. Associations between immune responses will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. associations, $\chi 2$ tests). Associations between early ctDNA values and pathologic response will be evaluated descriptively and graphically.

Bioinformatic and biostatistical analysis of differentially expanded/contracted clones in PBMC and tumor tissue after 6 and 12 weeks of treatment will be performed using Fisher's exact test with multiple testing correction by Benjamini-Hochberg procedure which controls false discovery rate (FDR < 0.05). Differential clonotypes will be further analyzed for tissue and longitudinal PBMC representation in pCR and non-pCR patients.

Analysis of the EPI-MRF and CEST-MRF: Maps from these sequences will be correlated with the histopathology measures. We will evaluate changes pre, 6-week and 12-week post neoadjuvant chemotherapy. We will compare these parameters between patients with a pathologic complete response versus those with no-pathologic complete response using two sample t-tests, or Wilcoxon rank sum tests if data are highly skewed. Once significant parameter changes are identified by these tests, we will then run ROC/AUC analyses to identify optimal cut-points by maximizing the Youden index (i.e., sensitivity + specificity - 1). Depending on specific requirements we may consider assigning various weights to sensitivity and specificity as well. Predictive power quantified by AUC can also be compared across different imaging parameters (e.g., T1-weighted, diffusion and DCE scans) and statistical significance level will be derived by, e.g., the Delong-Delong test to compare the predictive power of both EPI-MRF and CEST-MRF to the standard protocol. For time-to-event type endpoints, we will apply the Cox proportional hazards regression model (endpoints will be landmarked to ensure they are baseline factors in the Cox model) to identify significant factors and compute the concordance index for their predictive power. We will also try to identify optimal cut-points using the maximal chi-square method. Graphical presentation of the parameter measurements will be examined for patterns and appropriate longitudinal analysis tools may be used if such analyses are deemed necessary.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

CTCAE Version 5 will be utilized for toxicity evaluation.

The anticipated (expected) side effects of pembrolizumab and their likelihood and frequency of occurring are noted below:

VERY COMMON
Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools
- Cough

COMMON
Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone, so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatremia)

UNCOMMON
Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs, so you may feel short of breath and cough (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus (colitis)
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e., peeling, itching and redness) could

also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection (Severe skin reactions, including Stevens-Johnson syndrome/or toxic epidermal necrolysis)

RARE
Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- Inflammation of the nerves that may cause pain, weakness, or tingling in your hands and feet, and may spread to your legs, arms, and upper body, leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome)
- Inflammation of the muscles, so you may feel weak or have pain in your muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels), so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness, or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- Type 1 diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination, and weight loss. You are likely to need regular insulin shots
- Inflammation of the kidney, so you may pass less urine or have cloudy or bloody urine, swelling, and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath, and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting (myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood

pressure, body temperature, and the rate at which food is converted into energy (thyroiditis)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:
- Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis)
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)

The anticipated (expected) side effects of olaparib and their likelihood and frequency of occurring are noted below:

Common, some may be serious
In 100 people receiving olaparib, more than 10 and as many as 65 may have:
- Cough
- Nausea
- Vomiting
- Diarrhea
- Rash
- Decreased appetite
- Fatigue. If you experience fatigue while you are taking olaparib, be careful when driving or operating machinery.

- Indigestion and heartburn
- Dizziness
- Headache
- Taste changes that may affect the way food tastes
- Low number of red blood cells that can cause tiredness and shortness of breath (anemia), and may require a blood transfusion
- Low number of white blood cells called neutrophils, which may increase the risk of serious infections and cause fevers
- Low number of white blood cells (leukopenia), which may increase the risk of infections
- Increase in creatinine in your blood, which could be a sign of kidney damage. Increase in size of red blood cells (mean cell volume elevation), which may be related to myelodysplastic syndrome or acute myeloid leukemia.

Occasional, some may be serious
In 100 people receiving olaparib, between 1 and 10 may have:

- Upper abdominal pain
- Inflammation of the mouth and lips
- Skin inflammation that may make skin red, itchy, or scaly
- Low number of platelets in the blood, which may cause bleeding and bruising

Rare, and serious
In 100 people receiving olaparib, 1 or fewer may have:

- Hypersensitivity reaction, which may include dizziness or fainting, flushing, rash, fever, shortness of breath, or feeling sick to your stomach (nausea)
- Inflammation in the lungs, which may cause fluid to pool in the lungs and cause cough, chest pain, or shortness of breath. Rarely, this condition might lead to death. If you experience any new or worsening symptoms of shortness of breath, cough, and fever, contact your study doctor as soon as you can.
- Myelodysplastic syndrome and acute myeloid leukemia (MDS/AML), which have been reported in a few patients who were treated with olaparib; most of the reported cases resulted in death. It is not known whether olaparib caused the myelodysplastic syndrome and/or acute myeloid leukemia.
- Myelodysplastic syndrome is a pre-cancerous condition in which the bone marrow does not produce blood cells as well as it did before (red blood cells and/or white blood cells and/or platelets). This condition has the potential to become acute myeloid leukemia, a cancer of the bone marrow in which many abnormal and immature white blood cells (blast cells) are made, while normal functioning blood cells are not made.
- Development of another cancer. A small number of patients in other studies who were treated with olaparib developed a new cancer, other than MDS/AML. It is not known whether olaparib caused these secondary cancers.

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

- The report should contain the following information:
- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.2. External SAE Reporting

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

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 that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant 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 participant 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 whether or not related to the Merck product, must be reported within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to 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 Merck Global Safety.

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

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

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 215-661-6229) at the time of submission to FDA.

Events of Clinical Interest
Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 business days but no longer than 3 calendar days of learning of event Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

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 participant must be reported within 2 business days but no longer than 3 calendar days of learning of event to Merck Global Safety if it causes the participant 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 participant 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 2 business days but no longer than 3 calendar days of learning of event to Merck Global Safety.

Events of clinical interest for this trial include:

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

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

Definition of an Overdose for This Protocol and Reporting of Overdose to Merck

For purposes of this study, 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. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 2 business days but no longer than 3 calendar days of learning of event Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

Reporting of Pregnancy and Lactation to Merck

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

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant 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 infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of the study IP, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 2 business days but no longer than 3 calendar days of learning of event to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

16.0 PROTECTION OF HUMAN PARTICIPANTS

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the

participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

An MSK Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure internet-based system, Medidata Rave. Source documentation will be available to support the computerized patient record. MSK will be responsible for reporting to the funding source (as applicable) and governing agencies.

16.3 Quality Assurance

Registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."
There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.0 REFERENCES

1. Basu G, Ghazalpour A, Gatalica Z, et al. Expression of novel immunotherapeutic targets in triple-negative breast cancer. J Clin Oncol 2014; 32:1001.
2. Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006;295:1658-67.
3. Bremens RM, Al-Shibili K, Donnem T, et al. The role of tumor-infiltrating immune cells and chronic inflammation at the tumor site on cancer development, progression, and prognosis: emphasis on non-small cell lung cancer. J Thor Onc. 2011;6:824-833.
4. Budd GT, Barlow WE, Moore HCF, et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. J Clin Oncol 2015;33:58-64.
5. Cancer Genome Atlas N: Comprehensive molecular portraits of human breast tumours. Nature 2012; 490:61-70.
6. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013; 39:1-10.
7. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:2444-8.
8. Denkert, C, Loibl S, Noske A, et al., Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 2010; 28:105-13.
9. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429-34.
10. Disis ML. Immune regulation of cancer. J Clin Oncol. 2010;28:4531-4538.
11. Domcheck SM, Postel-Vinay S, Bang YJ, et al. An open-label, multitumor, phase II basket study of olaparib and durvalumab (MEDIOLA): results in germline BRCA-mutated (gBRCAm) HER2-negative metastatic breast cancer (MBC). In: San Antonio Breast Cancer Symposium; 5-9 Dec 2017; San Antonio, TX. 2017: Abstr PD6-11.

12. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23:2346-57.
13. Chemnitz JM, Parry RV, Nichols KE, et al. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.
14. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-1717.
15. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [resource on the Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr.
16. Finak, G, Bertos N, Pepin F, et al., Stromal gene expression predicts clinical outcome in breast cancer. Nat Med 2008;14:518-27.
17. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. N Engl J Med 2009;361:123-34.
18. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.
19. Galluzzi L, Buque A, Kepp O, et al. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol 2017; 17:97-111.
20. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011;12:852–61.
21. Ghebeh, H, Mohammed S, Al-Omair A, et al. The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer subjects with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors. Neoplasia 2006;8:190-8.
22. Ghebeh, H, Barhoush E, Tulbah A, et al. FOXP3+ Tregs and B7-H1+/PD-1+ T lymphocytes co-infiltrate the tumor tissues of high-risk breast cancer subjects: Implication for immunotherapy. BMC Cancer 2008;8:57.
23. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.
24. Haffty B, Yang Q, Reiss M, et al. Locoregional relapse and distant metastasis in conservatively manager triple-negative early-stage breast cancer. J Clin Oncol 2006;10:5652-7.
25. Hartlova A, Erttmann SF, Raffi FA, et al. DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity. Immunity 2015; 42:332-43.
26. Hay T, Matthews JR, Pietzka L, et al. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. Cancer Res. 2009;69:3850-5.

27. Helleday T. The underlying mechanism for the PARP and *BRCA* synthetic lethality: Clearing up the misunderstandings. Molecular Oncology 2011;5:387-393.
28. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.
29. Huang J, Wang L, Cong Z, et al. The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a BRCA1(–/–) murine model of ovarian cancer. Biochem Biophys Res Commun 2015;463:551–556.
30. Hunder NN, Wallen H, Cao J, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358:2698-703.
31. Ioannidou A, Goulielmaki E, Garinis GA. DNA damage: from chronic inflammation to age-related deterioration. Front Genet 2016;7:187.
32. Jemal A, Bray F, Center MM, et al. Global Cancer Statistics. CA Cancer J Clin 2011;61:69-90.
33. Kassam F, Enright K, Dent R, et al. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer 2009;9:29-33.
34. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015; 33:244-50.
35. Kubota E, Williamson CT, Ye R, et al: Low ATM protein expression and depletion of p53 correlates with olaparib sensitivity in gastric cancer cell lines. Cell Cycle 2014;13:2129-37.
36. Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 2011;121:2750-67.
37. Lord CJ, Ashworth A. The DNA damage response and cancer therapy. Nature 2012; 481:287-94.
38. Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet 2011; 43:879-82.
39. Mahmoud, S.M., et al. Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. J Clin Oncol 2011; 29(15):1949-55.
40. Mavaddat N, Barrowdale D, Andrulis IL, et al. Pathology of breast and ovarian cancers among *BRCA1* and *BRCA2* mutation carriers: results from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA). Cancer Epidemiol Biomarkers Prev. 2012;21:134–147.
41. McCabe N, Turner NC, Lord CJ, et al: Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res 2006;66:8109-15.
42. Mei Z, Liu Y, Liu C, et al. Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis. Br J Cancer. 2014;110:1595-1605.
43. Muenst, S, Schaerli AR, Gao F, et al. Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. Breast Cancer Res Treat 2014;146:15-24.

44. Murai J, Huang SN, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. AACR;72:5588–99.
45. Nanda R, Chow LQM, Dees EC, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. J Clin Oncol 2016;34: 2460-2467.
46. Nanda R, Liu MC, Yau C, et al. Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): results from I-SPY 2. J Clin Oncol. 2017;35:506.
47. [NCCN] National Comprehensive Cancer Network. NCCN Guidelines: Breast Cancer v2 [resource on the Internet]. 2016 Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
48. Okazaki T, Maeda A, Nishimura H, et al. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci USA 2001;98:13866-71.
49. Parkes EE, Walker SM, Taggart LE, et al. Activation of STING-dependent innate immune signaling by S-phase-specific DNA damage in breast cancer. J Natl Cancer Inst 2017;109:djw199.
50. Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25:9543-53.
51. Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379:432-44.
52. Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.
53. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 2017;377:523-533.
54. Rottenberg S, Jaspers JE, Kersbergen A, et al. High sensitivity of *BRCA1*-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci. 2008;105:17079-84.
55. Rugo H, Delord J-P, Im S-A, et al. Abstract S5-07: preliminary efficacy and safety of pembrolizumab (MK-3475) in patients with PD-L1–positive, estrogen receptor-positive (ER+)/HER2-negative advanced breast cancer enrolled in KEYNOTE-028. Cancer Res. 2016;76:S5-07-S5. https://doi.org/10.1093/annonc/mdy012.
56. Sant M, Allemani C, Capocaccia R, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. Int J Cancer 2003;106:416-22.
57. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2015;26;8-30.
58. Schalper KA, Velcheti V, Carvajal D, et al. In Situ Tumor PD-L1 mRNA Expression Is Associated with Increased TILs and Better Outcome in Breast Carcinomas. Clin Cancer Res 2014; 20:2773-82.
59. Schmid P, Cortes J, Dent R, et al. KEYNOTE-522: Phase III study of pembrolizumab (pembro) + chemotherapy (chemo) vs placebo + chemo as neoadjuvant therapy followed by pembro vs placebo as adjuvant therapy for triple-negative breast cancer (TNBC). Annals of Oncology (2019) 30 (suppl_5): v851-v934.
60. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense

doxorubicin and cyclophosphamide on pathologic complete response rates in Stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015;33:13-21.
61. Sheppard K-A, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.
62. Soriani A, Zingoni A, Cerboni C, et al. ATM-ATR-dependent up-regulation of DNAM-1 and NKG2D ligands on multiple myeloma cells by therapeutic agents results in enhanced NK-cell susceptibility and is associated with a senescent phenotype. Blood
2009;113:3503-11.
63. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008;358:1663-71.
64. Stagg, J. and B. Allard. Immunotherapeutic approaches in triple-negative breast cancer:
latest research and clinical prospects. Ther Adv Med Oncol 2013;5:169-81.
65. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 2007;25:4414-22.
66. Talmadge JE. Immune cell infiltration of primary and metastatic lesions: Mechanisms and clinical impact. Sem Can Bio. 2011;21:131-138.
67. Tan D, Marchio C, Jones, R, et al. Triple-negative breast cancer: molecular profiling and prognostic impact in adjuvant anthracycline-treated patients. Breast Cancer Res Treat 2008;111:27-44.
68. Tang ML, Khan MK, Croxford JL, et al. The DNA damage response induces antigen presenting cell-like functions in fibroblasts. Eur J Immunol 2014; 44:1108-18.
69. Tutt A, Robson M, Garber JE, et al. Oral poly(ADPribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010;376:235–44.
70. Wang H, Hu S, Chen X, et al. cGAS is essential for the antitumor effect of immune checkpoint blockade. Proc Natl Acad Sci U S A 2017;114:1637-1642.
71. Zhang X, Schwartz J-CD, Guo X, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.
72. Marinovich ML, Houssami N, Macaskill P, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. Journal of the National Cancer Institute. 2013;105(5):321-333.
73. Von Minckwitz G, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. The Lancet Oncology 2014; 15(7); 747-756
74. Sikov WM, et al. CALGB (Alliance) 40603: Long-term outcomes (LTOs) after neoadjuvant chemotherapy (NACT) +/- carboplatin (Cb) and bevacizumab (Bev) in triple-negative breast cancer (TNBC), Journal of Clinical Oncology 2019; 37(15) (suppl_15)

75. Litton, et al. Neoadjuvant Talazoparib for Patients With Operable Breast Cancer With a Germline BRCA Pathogenic Variant, Journal of Clinical Oncology. Journal of Clinical Oncology, 2019; 38 (5)
76. Schmid et al. Pembrolizumab for Early Triple-Negative Breast Cancer. NEJM Feb 27 2020.
77. Lala M, Li M, Sinha V, de Alwais D, Chartash E, Jain L. A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation. Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1 – 5. J Clin Oncol. 2018: 36 (15 suppl) Abstract no. 3062.
78. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e152. Epub 2017 Mar 2.

18.0 APPENDICES

Appendix A: Eastern Cooperative Oncology Group Scale of Performance Status

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 1982;5:649-55.

Appendix B Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)
Women in the following categories are not considered WOCBP:

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

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

Contraception Requirements

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below during the protocol-defined time frame.

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a: Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

Pregnancy Testing
WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix C: Contraindications to MRI scan

Patient must be able to undergo breast MRI with contrast enhancement. Patients unable to undergo breast MRI with contrast enhancement for any reason are ineligible.

- No history of untreatable claustrophobia.
- No presence of non MR compatible metallic objects or metallic objects that, in the opinion of the radiologist, would make MRI a contraindication.
- No history of sickle cell disease.
- No contraindication to intravenous contrast administration.
- No known allergy-like reaction to gadolinium or moderate or severe allergic reactions to one or more allergens as defined by the American College of Radiology (ACR); patient may be eligible if willing to undergo pre-treatment as defined by the institution's policy and/or ACR guidance (see http://www.acr.org/quality-safety/resources/contrast- manual for reaction definition and premedication guidance).
- No known or suspected renal impairment. Requirements for GFR prior to MRI as determined by local site standard practice.
- Weight more than or equal to the MRI table limit
- No patients who have had prior contrast enhanced mammography (CESM or CEDM).
- No patients who have breast prosthetic implants (silicone or saline).