| | |
|---|---|
| **Protocol Number:** | PHS IRB: 16-001 |
| **Title:** | A Pilot and Phase II Study to Assess the Safety, Tolerability and Efficacy of Pembrolizumab Plus Chemotherapy in Metastatic Triple Negative Breast Cancer Patients |
| **Version Date:** | January 9, 2018 |
| **Previous Version:** | July 7, 2017 |
| **Sponsor:** | Providence Portland Medical Center<br>Earle A. Chiles Research Institute<br>Robert W. Franz Cancer Research Center<br>4805 NE Glisan Street, Room 2N35<br>Portland, OR 97213<br>503-215-6805 |
| **Principal Investigator:** | David Page, MD<br>Earle A. Chiles Research Institute<br>4805 NE Glisan Street, 2N87<br>Portland, OR 97213<br>503-215-5696<br>FAX 503-215-5695<br>David.Page2@Providence.Org |
| **Co-Investigators:** | Alison Conlin, MD<br>Todd Crocenzi, MD<br>Brendan Curti, MD<br>John Godwin, MD<br>Rom Leidner, MD<br>Rui Li, MD, PhD<br>Rachel Sanborn, MD<br>Walter J. Urba, MD, PhD<br>Herschel Wallen, MD<br><br>Anupama Acheson, MD<br>Nicholas Barber, MD<br>Regan Duffy, MD<br>Stacy Lewis, MD<br>Christine Lin, MD<br>Christie Moore, MD<br>Heather McArthur, MD |
| **Responsible Research Nurses:** | Nicole Moxon, RN<br>Providence Portland Medical Center<br>Robert W. Franz Research Center<br>4805 NE Glisan Street, 2N35<br>Portland, OR 97213<br>503-215-2691 |

Fax 503-215-6725
Nicole.moxon@providence.org

Staci Mellinger, RN
Providence Portland Medical Center
Robert W. Franz Research Center
4805 NE Glisan Street, 2N35
Portland, OR 97213
503-215-2642
Fax 503-215-6725
Staci.Mellinger@providence.org

**Responsible Data Manager:**

Amanda Seino
Providence Portland Medical Center
Robert W. Franz Research Center
4805 NE Glisan Street, 2N35
Portland, OR 97213
(503) 215-2818
Fax 503-215-6725
Amanda.Seino@providence.org

# PROTOCOL SIGNATURE PAGE

**Protocol Number:** PHS IRB 16-001 Version January 9, 2018

**Protocol Title:** A Pilot and Phase II Study to Assess the Safety, Tolerability and Efficacy of Pembrolizumab Plus Chemotherapy in Metastatic Triple Negative Breast Cancer Patients

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

| David Page, MD | | |
|---|---|---|
| Investigator Name (print) | Investigator Signature | Date |

Table of Contents

**1.0 PROTOCOL SUMMARY AND/OR SCHEMA** ..... 6
**2.0 OBJECTIVES AND SCIENTIFIC AIMS** ..... 11
**3.0 BACKGROUND AND RATIONALE** ..... 11
**4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION** ..... 18
4.1 Design ..... 18
4.2 Intervention ..... 18
4.3 Estimated Duration of Subject Participation ..... 19
**5.0 THERAPEUTIC/DIAGNOSTIC AGENTS** ..... 19
**5.1.5 Clinical supplies disclosure** ..... 21
**6.0 CRITERIA FOR SUBJECT ELIGIBILITY** ..... 22
6.1 Subject Inclusion Criteria ..... 22
6.2 Subject Exclusion Criteria ..... 24
**7.0 RECRUITMENT PLAN** ..... 25
**8.0 PRETREATMENT EVALUATION** ..... 25
**9.0 TREATMENT / INTERVENTION PLAN** ..... 26
9.1 Monitoring of Dose Administration ..... 26
9.3.2 Resynchronization of Pembrolizumab with chemotherapy following scheduling delay ..... 32
9.4 Discontinuation of Study Therapy after CR ..... 33
9.6 Supportive Care Guidelines ..... 34
9.8 Diet ..... 37
9.9 Use in subjects with childbearing potential ..... 37
9.10 Use in Pregnancy ..... 37
9.12 Clinical Criteria for Early Trial Termination ..... 38
**10.0 EVALUATION DURING TREATMENT/INTERVENTION** ..... 39
10.1.1 Informed Consent ..... 44
10.1.7 Adverse Event (AE) Monitoring ..... 45
10.1.15 Withdrawal/Discontinuation ..... 48
10.1.16 Visit Requirements ..... 49
**11.0 TOXICITIES/SIDE EFFECTS** ..... 49
11.1 Summary of toxicities of investigational agents ..... 49

11.1.1 Weekly paclitaxel ..... 49

11.3 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck ..... 51

11.4 Reporting of Pregnancy and Lactation to the Sponsor and to Merck ..... 52

11.5 Immediate Reporting of Adverse Events to the Sponsor and to Merck ..... 52

11.6 Evaluating Adverse Events ..... 54

**12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT** ..... 57

CT scan with contrast of the chest, abdomen, and pelvis ..... 58

MRI scans ..... 58

**13.0 CRITERIA FOR REMOVAL FROM STUDY** ..... 62

**14.0 BIOSTATISTICS** ..... 63

**15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES** ..... 65

15.1 Research Participant Registration ..... 65

15.2 Randomization ..... 65

**16.0 DATA MANAGEMENT** ..... 65

16.1 Data collection ..... 65

16.1 Quality Assurance ..... 65

16.2 Monitoring ..... 65

**18.0 INFORMED CONSENT PROCEDURES** ..... 66

**19.0 REFERENCES** ..... 67

# 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

**Name of Investigational drug:** Pembrolizumab

**Title of Study**: A Pilot and Phase II Study to Assess the Safety, Tolerability and Efficacy of Pembrolizumab Plus Chemotherapy in Metastatic Triple Negative Breast Cancer Patients

**Study Centers:** Providence Portland Medical Center, Cedars-Sinai Medical Center

| **Study Period:** 12 months (Pilot); 12 months (Phase II) | **Phase of Development:** Pilot/ Phase II |
|---|---|

**Objectives:**

Primary objectives:

**Pilot phase:**

- To establish the safety and tolerability of pembrolizumab when administered in combination with either of two chemotherapy regimens (weekly paclitaxel or capecitabine) in unresectable/metastatic triple negative breast cancer (MTNBC) patients

**Optional phase II expansion cohort(s):**

- To estimate the week 13 objective response rate (ORR), as measured by RECIST v1.1, of pembrolizumab when administered in combination with chemotherapy in MTNBC

Secondary objectives:

**Pilot phase:**

- To evaluate the week 13 ORR based on RECIST v1.1 and immune related RECIST criteria

**Optional phase II expansion cohort(s):**

- To evaluate the week 13 ORR based on immune-related RECIST criteria
- To evaluate the safety and tolerability of pembrolizumab plus chemotherapy

Exploratory objectives (both cohorts):

- To evaluate immunologic biomarkers that may correlate with activity of pembrolizumab plus chemotherapy in MTNBC, or prospectively identify MTNBC patients likely to respond to treatment

**Study Design:** This will be a pilot feasibility design followed by optional phase II expansion cohorts. It will be conducted to determine the safety and tolerability of pembrolizumab plus chemotherapy in subjects with MTNBC for whom chemotherapy is indicated, and to estimate the efficacy of pembrolizumab plus chemotherapy.

Eligible patients will have RECIST1.1-measurable MTNBC, as defined by estrogen receptor negativity (defined by IHC<1%) and HER2-receptor negativity (defined by IHC 0-1 (or) IHC 2 and ISH HER2/CEP17<2.0).

In the pilot phase, patients will be enrolled to one of two experimental arms, which will be selected by the treating investigator (arm A: pembrolizumab + weekly paclitaxel; arm B: pembrolizumab + capecitabine). First and second line therapy is allowed, and patients must not have previously received the same chemotherapeutic agent(s), either in the metastatic setting, or in the (neo)adjuvant setting (unless ≥12 months from consent). Subjects will receive pembrolizumab via IV infusion at 200mg every three weeks (Q3W), and continue treatment Q3W until progression of disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment occur, up to 24 months. Patients will concurrently receive one of two chemotherapy regimens, and continue treatment until progression of disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue chemotherapy occur. Chemotherapy dose delays and modifications will be allowed at the discretion of the treating investigator, per section 9. Furthermore, at the discretion of the treating investigator, chemotherapy may be discontinued with ongoing dosing of pembrolizumab after week 7.

Patients will be evaluated by physical exam and routine blood tests every three weeks during the study period. CT or MRI will be performed during screening, at week 13 and subsequently at 12 week intervals as per the standard of care for MTNBC. Safety will be evaluated routinely using the CTCAE 4.0 toxicity reporting criteria. Tumor measurements and determination of tumor response will be performed according to RECIST 1.1. Subjects may continue to receive pembrolizumab beyond radiographic progression in the absence of clinical deterioration, and after discussion with the Principal Investigator.

**Figure 1.0-1: Protocol Schema**

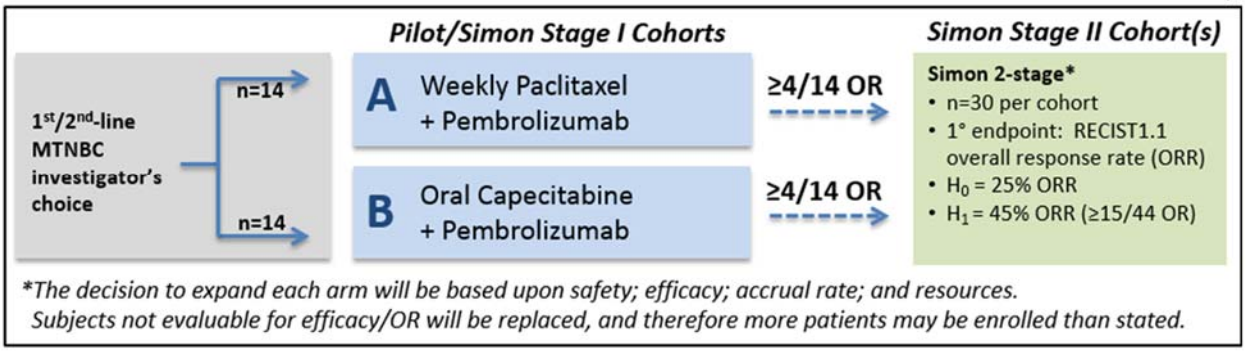



**Table 1.0-1: Therapeutic agents, by arm**

| Study arm | Drug | Dose | Cycle Frequency | Route | Regimen |
|---|---|---|---|---|---|
| All | Pembrolizumab | 200mg | Q3W | IV infusion | Day 1 of each 3 week cycle |
| A | Paclitaxel | 80mg/m2 | Q3W | IV infusion | Day 1, 8, and 15 of each 3 week cycle |
| B | Capecitabine | 2000mg | Q2W | Oral | BID, Days 1-7 of each 2 week cycle |

The primary endpoint of the pilot phase is to establish safety and tolerability of chemotherapy plus pembrolizumab. For each subject, the therapy will be deemed tolerable if the following criteria are met:

- Subjects receive at least 7 weeks of pembrolizumab (2 cycles) and remain free of serious adverse events and grade III/IV treatment-associated adverse events requiring discontinuation of pembrolizumab during that period;
- Subjects receive at least 7 weeks of chemotherapy within an acceptable therapeutic dosing/scheduling range without chemotherapy discontinuation or chemotherapy dosing delay ≥21 days. Shorter chemotherapy delays (<21 days) and dose modifications are acceptable if they conform to guidelines specified in section 9.3.3.

In previously reported phase II/III studies, 78-91% of patients treated with chemotherapy (weekly taxol or oral capecitabine) tolerated therapy without requiring dose discontinuation. Accordingly, we will deem the therapy safe if at least 60% of evaluable patients in the pilot phase (i.e. 9 or more out of 14 patients) are able to tolerate therapy. Assuming that all 14 patients are evaluable for safety/tolerability, there is a .49 probability that the therapy will be deemed safe if we assume a .6 true safety/tolerability probability. If the true probability is assumed to be .7 and .8, the probability of deeming the therapy tolerable is .78 and .96 respectively. The rate of grade I/II toxicities, grade III/IV toxicities, and chemotherapy dose delays and modifications will be reported as additional, descriptive measures of tolerability.

Subjects who clinically progress prior to week 13 will be included as treatment failures in the determination of ORR. Subjects who are enrolled but do not initiate the first infusion of therapy will be replaced and not included in the determination of safety/tolerability or ORR. Subjects who withdraw consent prior to week 13, and therefore are not evaluable for ORR, will be replaced and not included in the determination of ORR. Subjects will be included in the determination of safety/tolerability only if they remained evaluable for safety/tolerability for at least 6 weeks from the first dose.

In addition to safety/tolerability, clinical efficacy will also be assessed in the pilot cohort, as measured by RECIST1.1 ORR and immune-related RECIST ORR. If the therapy is deemed tolerable and if an efficacy futility boundary is exceeded in the pilot cohort, clinical efficacy and safety/feasibility may be further evaluated via an expansion cohort(s) of one or more treatment arms. For a treatment arm to be eligible for expansion, RECIST1.1 overall response in the pilot stage must exceed ≥4/14 objective responses (OR). This boundary is modeled after a Simon 2-stage optimal design, whereby the first Simon stage is the pilot phase arm (n=14), and the second Simon stage is the expansion cohort (n=30). This design is powered, with a type I error rate of 10% and type II error rate of 10%, to discriminate between ORR of 25% (the estimated response rate for chemotherapy alone for each of the chemotherapy regimens based on historical trials) versus 45%. Safety/feasibility will continue to be assessed in the expansion cohort(s) using the same criteria as in the pilot phase.

For a study arm to be eligible for expansion in an optional phase II cohort, the arm must meet both safety/tolerability and efficacy criteria. If these criteria are met, the decision to open an expansion cohort will be determined by a committee consisting of study site principal investigators and Merck representatives. The decision will be based upon: safety/tolerability of the treatment in the pilot study; efficacy observed in the pilot study; feasibility of accrual (which will be estimated during the pilot study); immunologic correlatives data; resources, and other considerations.

All subjects will be followed for at least 18 weeks from the start of therapy to evaluate for delayed toxicities. Patients with ongoing clinical benefit will be eligible to receive pembrolizumab for up to 2 years from the first dose. The study will terminate after the primary endpoints (safety/tolerability and 13-week ORR) have been achieved for all enrolled patients. Based upon the observed ORR and available resources, the committee may elect to prolong the study to assess for 1-year and/or 2-year progression free survival. This study will accrue a minimum of 28 subjects (or fewer if an arm closes prematurely for unanticipated excess toxicity), and up to 88 subjects if both cohorts are expanded. If one of the two arms expand, the estimate for total accrual is 58 subjects. Additional subjects may be enrolled to replace subjects that are inevaluable for efficacy.

Based upon conservative estimates of enrollment of 1-2 subjects per month across each of two sites, the accrual time for the pilot phase is estimated to be 1 year, and accrual time for the expansion phase is estimated to be 1 year. Tumor biopsies for research purposes will be mandatory for all patients. Biopsies will be obtained at baseline (or archival if there is no intervening anti-neoplastic therapies) and at 6 weeks following initiation of therapy +/- 1 week. Peripheral blood samples will be obtained in all patients at baseline at specified follow-up weeks at the time of routine standard-of-care blood assessments.

Tumor biopsies and peripheral blood will be used to conduct laboratory immunologic assessments, which will be used to support clinical findings in the trial. Furthermore, these findings will be correlated with clinical outcome in an exploratory manner in order to identify predictive makers for response, and to further our understanding of pembrolizumab when administered in conjunction with chemotherapy in MTNBC.

**Diagnosis and Main Criteria for Inclusion in the Study:**

**Inclusion Criteria**

1. Willing and able to provide written informed consent;
2. ≥ 18 years of age on day of signing informed consent.
3. HER2-negative breast cancer (defined by IHC 0-1 (or) IHC 2 and ISH HER2/CEP17<2.0);
4. ER and PR-negative breast cancer (defined by IHC<1%);
5. Measurable metastatic or unresectable disease based on RECIST 1.1.
6. Indicated for treatment with either weekly paclitaxel or oral capecitabine as first or second-line chemotherapy in the metastatic or unresectable setting
7. Consent for tumor biopsies and blood draws for research purposes.
8. Consent for use of available archived tissue for research purposes.
9. Performance status of ECOG 0 or 1.
10. Adequate organ function, defined as:
    - Absolute Neutrophil Count ≥ 1,500/$mm^3$.
    - Platelet count ≥ 100,000/$mm^3$.
    - Serum creatinine ≤ 1.5 x ULN or CrCl ≥60 mL/min.
    - AST and ALT ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with liver metastases.
    - Bilirubin ≤ 1.5 × ULN or Direct bilirubin ≤ ULN (except subjects with Gilbert's Syndrome, who will be allowed in consultation with the Principal Investigator).
    - INR/PT and PTT ≤1.5 X ULN unless on anticoagulant therapy and PT/PTT within therapeutic range.
11. Women of childbearing potential must avoid becoming pregnant while on treatment, and men must avoid fathering a child while on treatment.

**Exclusion Criteria**

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment (inhaled steroids are permitted).
3. Has a known history of active TB (Bacillus Tuberculosis)
4. Hypersensitivity to pembrolizumab or any of its excipients.
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study, Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. Denosumab is allowed.
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. Note: Subjects with ≤ Grade 2 neuropathy and alopecia are an exception to this criterion and may qualify for the study.
7. Has received the assigned chemotherapy regimen previously in the metastatic setting, or has received the assigned chemotherapy regimen previously in the (neo)adjuvant setting within 12 months of consent
8. If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
9. Has a known additional malignancy that progressed or required active treatment in the last 5 years (history of synchronous breast cancer is allowed at the discretion of the principal investigator)
10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new

or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

11. 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.
12. Has history of/active pneumonitis requiring treatment with steroids or history of/active interstitial lung disease.
13. Has an active infection requiring systemic therapy.
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
17. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or has participated in a pembrolizumab Merck-sponsored study.
18. Has a known history of Human Immunodeficiency Virus (HIV).
19. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
20. Has received a live vaccine within 30 days of planned start of study therapy. *Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*

**Number of Subjects:** n=28 for pilot phase, n=30 for each phase II cohort

# 2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objectives

Pilot phase:
To establish the safety and tolerability of pembrolizumab when administered in combination with either of two chemotherapy regimens (weekly paclitaxel or capecitabine) in unresectable/metastatic triple negative breast cancer (MTNBC) patients

Optional phase II expansion cohort(s):
To estimate the week 13 objective response rate (ORR), as measured by RECIST v1.1, of pembrolizumab when administered in combination with chemotherapy in MTNBC

2.2 Secondary Objectives:

Pilot phase:
To evaluate the week 13 ORR based on RECIST v1.1 and by immune related RECIST criteria
Optional phase II expansion cohort(s):

- To evaluate the week 13 ORR based on immune-related RECIST criteria
- To evaluate the safety and tolerability of pembrolizumab plus chemotherapy

2.3 Exploratory Objectives

To evaluate immunologic biomarkers that may correlate with activity of pembrolizumab plus chemotherapy in MTNBC, or prospectively identify patients likely to respond to treatment

# 3.0 BACKGROUND AND RATIONALE

An estimated 90% of deaths attributable to breast cancer are a consequence of metastases, with more than 40,000 deaths caused by metastatic breast cancer each year in the United States alone, for which the triple negative breast cancer (TNBC) subtype is disproportionately represented. Despite notable therapeutic innovations, patients with MTNBC have a median survival of only 2–3 years.

Combining standard-of-care cytotoxic therapy with a novel immunomodulatory agent, pembrolizumab, may enhance therapeutic efficacy and lead to improved patient outcomes. The primary goal of this protocol is evaluate the safety/tolerability of combining pembrolizumab with 2 of the most common cytotoxic regimens used in MTNBC. If this approach is safe, we will also estimate the efficacy of this approach in one or more expansion cohorts. These expansion cohorts will provide preliminary data, either in support or against, further evaluation of the combination chemotherapy/pembrolizumab approach in a larger, randomized trial.

## 3.1 TNBC

TNBC is clinically defined as lacking estrogen receptor (ER), progesterone receptor (PR) and HER2 receptor expression by immunohistochemistry (Society 2012). Although TNBC comprises 15-20% of incident breast cancers, it is over-represented among those with metastatic disease and is responsible for a disproportionately higher number of breast cancer deaths. Histologically, TNBC is poorly differentiated, more often an interval breast cancer (i.e., diagnosed between screening mammograms), and, when recurrent, it

preferentially relapses in visceral sites, including the lungs, liver, and brain. For TNBC patients, the risk of recurrence and death is significantly and dramatically higher in the first 3 to 5 years after diagnosis compared to women with ER/PR+ tumors. Currently, with an absence of a clinically relevant target, there are no targeted therapeutic approaches, leaving only nonspecific conventional chemotherapies as the mainstay of treatment for TNBC. While effective for some, cytotoxic therapy is not curative for any patient with metastatic disease.

### 3.1.1 Standard-of-care cytotoxic therapies for TNBC

The National Comprehensive Cancer Network (NCCN) endorses numerous single-agent cytotoxic chemotherapy regimens for TNBC, including anthracyclines (doxorubicin or pegylated doxorubicin), taxanes (paclitaxel or docetaxel), anti-metabolites (gemcitabine or capecitabine), and other microtubule inhibitors (vinorelbine or eribulin).

*Weekly Paclitaxel*

Of these agents, the taxanes and anthracyclines are the most clinically active, however anthracycline use in the metastatic setting is limited by constraints on cumulative dosing, and frequent anthracycline use in the adjuvant setting. Single agent taxane regimens are among the most frequently-employed therapies for metastatic TNBC. Weekly paclitaxel (Mauri, Kamposioras et al. 2010) is well tolerated and improves survival over every three week regimens, and therefore is a frequently employed regimen, with impressive first-line objective response rates (ORRs, 18%-49%).(Miller, Wang et al. 2007, Seidman, Berry et al. 2008, Fountzilas, Dafni et al. 2009, Brufsky, Valero et al. 2012, Miles, Dieras et al. 2013) In contemporary practice, the response rate is likely closer to 20-30%, likely owing to increased use of paclitaxel in the (neo)adjuvant setting.

*Oral Capecitabine*

An alternative and frequent first-line systemic therapy is oral capecitabine, owing to its convenience of administration (oral), relative tolerability, and respectable clinical activity (overall response rate of 18-30% in randomized trials).(Oshaughnessy, Blum et al. 2001, Fumoleau, Largillier et al. 2004, Brufsky, Valero et al. 2012, Miles, Dieras et al. 2013) The traditional dosing schedule is 1255mg/m2 twice daily, two weeks on, one week off. However, mathematical modeling and phase II clinical trials demonstrate similar efficacy and improved tolerability with fixed 1500mg-2000mg twice daily dosing delivered one week on, one week off, and is therefore an acceptable and frequently employed regimen.(Traina, Dugan et al. 2010, Gajria, Feigin et al. 2011, Gajria, Gonzalez et al. 2012)

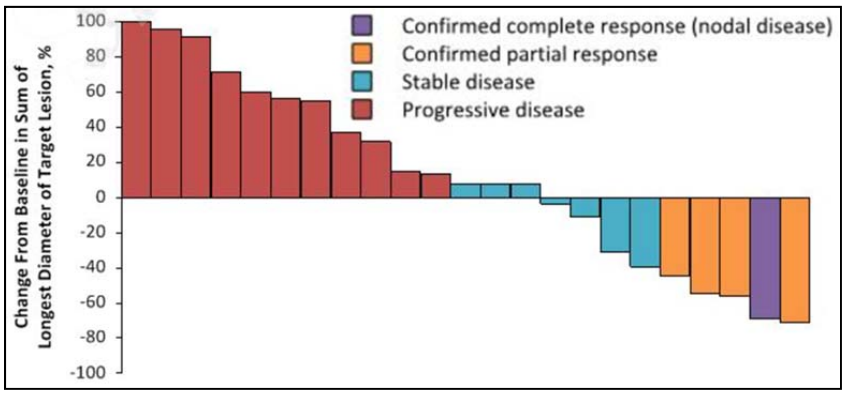
### 3.1.2 Immune augmentation in TNBC

Recently published studies suggest that distant metastatic invasion of TNBC may be potentially induced by immune/inflammatory deregulation. Among a set of 45-gene signature that was found to be statistically predictive in distant disease recurrence in TNBC, ten genes are found to be within TGF-β signaling pathway, associated with immune suppressed phenotype.(Kuo, Chang et al. 2012) In BC patients, either decreased number of effector CD8(+) T cells, or increased number of regulatory T-cells, was associated with adverse tumor characteristics such as lymph node metastasis, higher stage, and Ki-67 immunopositivity. (Miyashita, Sasano et al. 2014) Corroborating these findings, across multiple large adjuvant and neoadjuvant datasets, the quantity of tumor infiltrating lymphocytes in early stage triple negative breast cancers has been associated with improved survival, and increased likelihood of response to chemotherapy.(Salgado, Denkert et al. 2014) Functional assays demonstrate that adequate activation of tumor infiltrating lymphocytes (TILs) derived from BC tissue could restore the appropriate

antitumor immune responses. This emerging data underscores the potential of a therapeutic strategy that immune-mediated anti-tumor responses.

In light of these data, an immunomodulatory agent, pembrolizumab 10mg/kg q2wk, was evaluated in a phase Ib cohort of metastatic TNBC pts. Pembrolizumab is a therapeutic blocking antibody targeting programmed death 1 (PD-1), a surface receptor found on chronically antigen-exposed T-cells associated with downregulation of T-cell cytotoxic activity.(Topalian, Drake et al. 2012) In this population (median prior treatments = 2.5), the overall response rate was 18.5% by RECIST1.1, with an additional 25.9% with stable disease (figure 3.2.1-1). Responses were durable, with the median duration of response not reached (median follow-up 9.9mo). The treatment was safe (grade III/IV tox: 15.6%).[7] In a similar phase Ib cohort of the anti-programmed death ligand 1 (PD-L1) antibody, MPDL3470A, an objective response rate of 33% was observed in evaluable TNBC patients.(Emens, Braiteh et al. 2014)

**Figure 3.2.1-1: Waterfall plot of objective responses to pembrolizumab in TNBC**




### 3.1.3 Rationale and safety of combining cytotoxic therapy with immune augmentation

Response rates to anti-PD-1 in TNBC, while respectable, are lower than observed in melanoma and Hodgkin's lymphoma. Novel strategies may be required to optimize efficacy of immunotherapy in MTNBC. Furthermore, co-administration of pembrolizumab with chemotherapy in an earlier-line setting (when functional status and immune competency is preserved) might enhance efficacy.

Chemotherapy may induce immunogenic cell death, facilitating effective presentation of tumor-associated antigens to T-cells, which may in turn be primed for activation by concurrent administration with anti-PD-1 therapy.(Zitvogel, Apetoh et al. 2008) Several groups have demonstrated that the combination of chemotherapy plus checkpoint blockade results in synergistic regression of tumors in a TNBC murine 4T1 model and other models.(Lesterhuis, Salmons et al. 2013)

Two of the most prescribed regimens are weekly paclitaxel and oral capecitabine. Each of these regimens have been associated with favorable immunomodulatory effects, and therefore each of these regimens has the potential for synergy with immunotherapy (table 3.1.3-1).

**Table 3.1.3-1:** Immunologic effects of chemotherapeutic regimens in metastatic TNBC

| Regimen | Immunologic Effects |
|---|---|
| Paclitaxel | • T-cell activation; T-reg depletion[14]<br>• Enhanced NK and T-cell function[14]<br>• Myeloid derived suppressor cell (MDSC) depletion[15] |
| Capecitabine | • T-cell activation<br>• Induction of heat-shock proteins/antigen presentation[16]<br>• T-reg and MDSC depletion[15] |

Additionally, chemotherapy may induce inflammation and interferon gamma in the tumor microenvironment, which may induce adaptive expression of PD-L1 by the tumor.(Sistigu, Yamazaki et al. 2014, Tumeh, Harview et al. 2014)

**3.1.3.1 Prior Safety and Efficacy Data of combining immune modulation with chemotherapy in humans**

In a phase I-III clinical trials, immunologic checkpoint agents (including anti-PD-1 agents) have been combined safely with chemotherapy.(Robert, Thomas et al. 2011, Lynch, Bondarenko et al. 2012, Reck, Bondarenko et al. 2013, Weber, Hamid et al. 2013, Antonia, Brahmer et al. 2014) In a phase II study of ipilimumab with carboplatin plus paclitaxel in non-small-cell lung cancer, the phased combination of carboplatin/paclitaxel followed by the addition of ipilimumab, improved immune-related progression free survival compared to chemotherapy alone (HR 0.72, p=0.05), and toxicities were acceptable enough to support further study, with grade III/IV immune related toxicity rates of 15% compared to 6% with chemotherapy alone.(Lynch, Bondarenko et al. 2012) In a similar study in small cell lung cancer, progression free survival was highest with chemotherapy followed by the addition of ipilimumab (HR=0.64, p=0.03), with similar grade III/IV immune-related toxicity rates of 17%, compared to 9% with chemotherapy alone.(Reck, Bondarenko et al. 2013) In melanoma, a phase I study of ipilimumab versus ipilimumab plus chemotherapy (carboplatin/paclitaxel or DTIC) demonstrated no pharmacokinetic or pharmacodynamic interactions.(Weber, Thompson et al. 2009) Finally, in a large phase III study of DTIC versus DTIC plus ipilimumab, the combination improved overall survival, however the combination led to greater grade III/IV adverse events compared to chemotherapy alone (56% versus 28%).(Robert, Thomas et al. 2011) The adverse events were similar in nature to ipilimumab alone, however with greater rates of elevated liver function values.

Compared to ipilimumab, relatively few trials combining anti-PD-1 plus chemotherapy have been reported. However, a phase 1 dose de-escalation trial evaluated the safety of the anti-PD-1 antibody nivolumab, when combined with platinum-based doublet chemotherapy (gemcitabine/cisplatin or pemetrexed/cisplatin or paclitaxel/carboplatin). (Antonia, Brahmer et al. 2014) Chemotherapy was given for 4 cycles, and thereafter nivolumab was continued. Grade III/IV adverse events were reported in 45% of patients, however there were no DLTs reported. Encouraging one year overall survival rates of 59-87% were reported.

In summary, sufficient previous data exist to suggest that the combination of pembrolizumab plus chemotherapy will be safe in metastatic triple negative breast cancer at the standard chemotherapy dose levels. However, a pilot study is necessary to confirm

safety/tolerability of combining pembrolizumab to therapeutic doses of systemic chemotherapy.

## 3.2 Background of therapeutic agents

### 3.2.1 Pembrolizumab

#### 3.2.1.1 Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its

ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

**3.2.1.2 Non-Clinical Toxicology Summary of results**

In the 1-month and 6-month toxicology study in cynomolgus monkeys, pembrolizumab administered once a week and once every other week respectively, intravenously up to 200 mg/kg resulted in no adverse treatment related effects. The exposure multiple based on a predicted $AUC_{0\text{-}tau}$ of 4464 µg/day/mL at the maximum anticipated human clinical dose of 10 mg/kg Q2W or Q3W is 15-fold at 200 mg/kg, the NOAEL for the 6-month monkey study. Additionally, in the tissue cross-reactivity study of pembrolizumab with human and monkey tissues demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. Off-target cross-reactivity staining was also noted in both species but was limited to cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix), and was considered related to the experimental method artifacts, i.e. tissue processing for IHC, that are well recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant.

No reproductive or developmental toxicity studies are planned with pembrolizumab. Therefore, inclusion of women of childbearing potential in clinical trials should be in accordance with the study protocol and applicable regulatory guidance (e.g., ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

**3.2.1.3 Clinical Summary of Results**

As of 18-Oct-2013, 1,000 patients have been treated with pembrolizumab at several dose- schedules, including 10 mg/kg every 2 weeks. Pembrolizumab has been generally well tolerated, as expected based on preclinical findings and other anti-PD-1 monoclonal antibodies. As of 18-Oct-2013 no serious infusions reactions have been reported in PN001, however, since the potential exists in anti-PD-1 monoclonal antibodies, investigators should be vigilant to this possibility. Less than 1% of patients thus far assayed had confirmed positive ADA samples and among these, no or no clear impact on exposure has been observed. There is no contraindication to further clinical investigation with pembrolizumab. Pharmacokinetics were as expected, based on pembrolizumab being an IgG mAb and based on preclinical data, which support dosing once every 2 or 3 weeks. pembrolizumab monotherapy induces an ORR of 25%/27% in patients with ipilimumab- exposed melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. Pembrolizumab monotherapy induces an ORR of 39%/43% in patients with ipilimumab-naive melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. These responses are remarkably durable. The preliminary 1-year survival rate for patients, many of whom have had multiple therapies, including ipilimumab, who receive pembrolizumab is 81%. Pembrolizumab monotherapy induces an ORR of 21%/24% in patients with previously-treated NSCLC by central independent RECIST/investigator assessed irRC, respectively, with these responses also remarkably durable. Preliminary data suggest higher levels of PD-L1 expression in tumors of NSCLC are associated with increased activity (ORR 67% by investigator assessed irRC/57% by central independent RECIST); additional data are required to define the optimal PD-L1 cut

point.

The most commonly reported treatment emergent AEs experienced are fatigue (43.8%), nausea (26.7%), cough (25.3%), pruritus (24.6%), diarrhea (22.3%) and rash (21.5%). Immune-related adverse events were reported in 21.4% of melanoma patients; most of these events (15.8%) were considered drug-related by the investigator. The most commonly reported, immune-related adverse events across the dose-schedules are rash (3.2%), pruritus (2.9%), vitiligo (2.9%), hypothyroidism (2.7%), arthralgia (2.2%), diarrhea (2.2%), and pneumonitis (1.9%). Review of the overall benefit:risk ratio of pembrolizumab favors enrollment of eligible patients into clinical trials of pembrolizumab.

**3.2.1.4 Rationale for dose selection and schedule**

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

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

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

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response

relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

#### 3.2.2 Chemotherapeutic regimens

This study will evaluate the safety of pembrolizumab when combined with standard-of-care, frequently administered chemotherapy regimens, weekly paclitaxel or oral capecitabine. The clinical efficacy and toxicity profiles of these two regimens are well-described in the literature and in the Providence/Cedars-Sinai chemotherapy guidelines.

## 4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

### 4.1 Design

#### 4.1.1 Pilot phase

This is a pilot study of pembrolizumab in combination with chemotherapy (either weekly paclitaxel or oral capecitabine). It will be conducted to determine the safety/tolerability of these combinations in subjects with metastatic or unresectable TNBC. The treatment arm will be determined by the treating investigator.

#### 4.1.2 Phase II expansion cohorts

Based upon the safety/tolerability and efficacy of therapy observed in the pilot cohorts, the trial may expand one or more of the treatment cohorts to enroll additional patients, so that the anti-tumor activity and safety/tolerability of the combination may be further estimated. Statistical methods for evaluating efficacy, and criteria for expanding the cohorts, are described in detail in sections 10 and 14.

### 4.2 Intervention

Eligible patients will have measurable disease by RECIST v1.1 criteria and will meet the criteria for triple negative breast cancer based upon biopsy assessment. A research biopsy must occur prior to initiation of the first dose of investigational therapy unless archival tissue with sufficient material is available for analysis, and as long as no intervening systemic therapy has been administered (1 tumor-bearing tissue block, or 18 5-micron FFPE slides).

All subjects will receive chemotherapy (as per the standardized dosing schedule described in section 5.0), and pembrolizumab via IV infusion at 200mg every three weeks (q3w).

Pembrolizumab will be continued q3w until progression of disease, initiation of an alternative cancer therapy, unacceptable toxicity, or another reason to discontinue treatment occur, up to 24 months. Subjects may continue to receive pembrolizumab beyond radiographic disease progression in the absence of clinical deterioration, and after discussion with the Principal Investigator.

Chemotherapy will be continued as per section 5 and 9 until at least week 7, at which point chemotherapy may be discontinued if clinically indicated at the discretion of the treating investigator for reasons such as toxicity or chemotherapy intolerance. Chemotherapy dose/schedule modifications may be conducted in accordance with the guidelines described in section 9.0. *The rationale for allowing chemotherapy modification/discontinuation is to simulate real-world conditions whereby clinicians can tailor chemotherapy to the individual patient to optimize palliation and minimize toxicities.*

Patients will be evaluated by physical exam and routine blood tests every three weeks during the study period. Research bloods will be obtained periodically as per the schedule in section 10. CT CAP with or without PET or bone scan will be performed during screening, and then at 12 week intervals. Additional scans will be conducted if there is a clinical indication, for example to evaluate the etiology of a new symptom. Tumor measurements and determination of tumor responses will be performed according to RECIST 1.1, and according to immune related RECIST as a secondary endpoint.

Patients who have ongoing response to pembrolizumab will discontinue after 24 months, but will continue clinic visits, routine blood work, and q12w imaging assessments as per standard-of-care. Any patient with a prior response to pembrolizumab, who discontinues for a reason other than toxicity/progression, may resume treatment for an additional 12 months upon disease progression.

Exploratory research studies to evaluate the effect of this therapy will be performed in patients using research blood draws, and tumor biopsy at baseline and week 7 +/- 1 week for research purposes.

### 4.3 Estimated Duration of Subject Participation

Subjects may be treated for up to 24 months, with the option to resume treatment for an additional 12 months upon disease progression, unless there is another reason to discontinue treatment. All subjects will be followed for at least 18 weeks from the start of therapy to evaluate for delayed toxicities. The study will terminate after the primary endpoints (safety/tolerability and 13-week ORR) have been ascertained for all patients. Based upon the observed ORR and available resources, the committee may elect to prolong the study to assess for 1-year and/or and 2-year progression free survival.

## 5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The treatments to be used in this trial is outlined below in table 5.0-1

Table 5.0-1: Trial Treatment

| Study arm | Drug | Dose | Cycle Frequency | Route of Administration | Regimen/ Treatment Period | Use |
|---|---|---|---|---|---|---|
| All | Pembrolizumab | 200mg | Q3W | IV infusion | Day 1 of each 3 week cycle | Experimental |
| A | Paclitaxel | 80mg/m2 | Q3W | IV infusion | Day 1, 8, and 15 of each 3 week cycle | FDA approved |
| B | Capecitabine | 2000mg | Q2W | Oral | BID, Days 1-7 of each 2 week cycle | FDA approved |

Trial treatment should begin as close as possible to the date on which treatment is allocated/assigned.

## 5.1 Pembrolizumab

### 5.1.1 Formulation, packaging, and storage

Drug will be provided by Merck as summarized in Table 5.1-1. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

**Table 5.1-1 Product Descriptions**

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

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.

### 5.1.2 Preparation

The pharmacy manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

### 5.1.3 Administration

Pembrolizumab will be administered as a 30 minute IV infusion. Given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e. infusion time is 30minutes -5 minutes/+10 minutes). The reason for any delay in infusion outside of the protocol specified window should be documented and recorded in the case report form (CRSs). Central venous catheters (CVCs) or vascular access devices (VADs) may be used to administer treatment. Pembrolizumab will be administered following completion of infusion of standard-of-care chemotherapy (i.e. following completion of paclitaxel).

### 5.1.4 Returns and reconciliation

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

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

### 5.1.5 Clinical supplies disclosure

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

## 5.2 Weekly paclitaxel

Paclitaxel is a taxane originally derived from the bark of the Pacific yew tree (Taxus Brevifolia), and is one of the most active and commonly used agents for the treatment of breast carcinoma. Paclitaxel binds to the dimeric tubulin preventing microtubule disassembly by stabilizing microtubules so that the spindle cannot be dismantled. This microtubule disruption halts mitosis, interferes with other critical interphase functions, and subsequently leads to cell death.

### 5.2.1 Formulation, packaging, and storage

Paclitaxel is supplied as 30mg (5mL), 100mg (16.7mL), and 300mg (50mL) multi-use vials. Commercial supply for paclitaxel will be utilized for this study. Paclitaxel is a clear colorless to slightly yellow viscous solution. Paclitaxel is supplied as a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous solution. Each mL of sterile nonpyrogenic solution contains 6mg paclitaxel, 527mg of purified Cremophor® EL and 49.7% of v/v dehydrated alcohol.

Unopened vials of paclitaxel injection are stable until the date indicated on the package when stored between 20-25°C. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the paclitaxel vial may precipitate, but will re-dissolve upon reaching room temperature with little or no agitation.

### 5.2.2 Preparation

Prior to infusion paclitaxel should be diluted in 0.9% sodium chloride injection or 5% dextrose injection or 5% dextrose and 0.9% sodium chloride, or 5% dextrose in ringers lactate, to a final concentration of 0.3 to 1.2 mg/mL. Paclitaxel must be prepared in glass, prolypropylene, or polyolefin containers and non-PVC containing (nitroglycerin) infusion sets. Prepared solutions are stable at room temperature (20-25°C) and protected light, up to 72 hours. In-line filtration with micropore no greater than 0.22 micron filter is required. Chemo dispensing pin devices or similar devices with spikes should not be used with paclitaxel vials since they can cause the stopper to collapse resulting in loss of sterile integrity.

### 5.2.3 Administration

Intravenous paclitaxel should be administered over approximately 60 minutes. Paclitaxel will be administered intravenously on a weekly schedule at a dose of 80mg/m$^2$. Doses may be modified as per section 9.0.

### 5.3 Capecitabine

#### 5.3.1 Formulation, Packaging, and Storage

The commercial formulation will be used, as per standard-of-care. Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20ºC and is supplied as biconvex, oblong film-coated tablets for oral administration. Each peach-colored tablet contains either 150mg or 500 mg capecitabine. Capecitabine tablets will be stored at room temperature (15° to 30°C) in the container in which they are provided.

#### 5.3.2 Dosage Regimen and Administration

Commercially supplied capecitabine will be administered at total daily dose of 4,000 mg (2,000 mg BID). The dose of capecitabine will be fixed, not calculated on the basis of body surface area. Capecitabine will be administered as intermittent therapy given on days 1-7 in 14-day cycles.

Capecitabine will be taken orally. The total daily dose should be taken as two divided doses approximately 12 hours apart, within 30 minutes after the ingestion of food, ideally after breakfast and the evening meal. Tablets should be swallowed with approximately 200 ml of water (not fruit juices). Tablets are not scored and should not be split.

#### 5.3.3 Dispensing and Accountability of Medication

Commercially supplied drug will be dispensed by the patient's pharmacy as per the standard-of-care. The patient will also have the option to keep a diary or calendar to document each dose of capecitabine taken while on study. Doses may be modified as per section 9.0.

## 6.0 CRITERIA FOR SUBJECT ELIGIBILITY

### 6.1 Subject Inclusion Criteria

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

- Be willing and able to provide written informed consent/assent for the trial.
- Be ≥ 18 years of age on day of signing informed consent.
- HER2-negative breast cancer (defined by IHC 0-1 (or) IHC 2 and ISH HER2/CEP17<2.0);
- ER and PR-negative breast cancer (defined by IHC<1%);
- Measurable metastatic or unresectable disease based on RECIST 1.1.
- Indicated for treatment with either weekly paclitaxel or oral capecitabine, as first or second-line chemotherapy in the metastatic/unresectable setting (as determined by the consenting investigator);
- Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained during screening. Archival tissue is acceptable if no intervening anti-neoplastic therapy has been administered, and if sufficient material is available for analysis (see section 8.0 for requirements);*

- Have a performance status of 0 or 1 on the ECOG Performance Scale.
- Demonstrate adequate organ function as defined in
- Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| **Hematological** | |
| Absolute neutrophil count (ANC) | ≥1,500 /mcL |
| Platelets | ≥100,000 / mcL |
| Hemoglobin | ≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment) |
| **Renal** | |
| Serum creatinine **OR**<br><br>Measured or calculated[a] creatinine clearance<br><br>(GFR can also be used in place of creatinine or CrCl) | ≤1.5 X upper limit of normal (ULN) **OR**<br><br>≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN |
| **Hepatic** | |
| Serum total bilirubin | ≤ 1.5 X ULN **OR** |
| | Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN |
| Except subjects with Gilbert's Syndrome, who will be allowed in consultation with the Principal Investigator | |
| AST (SGOT) and ALT (SGPT) | ≤ 2.5 X ULN **OR**<br><br>**≤** 5 X ULN for subjects with liver metastases |
| Albumin | ≥2.5 mg/dL |
| **Coagulation** | |
| International Normalized Ratio (INR) or Prothrombin Time (PT)<br><br>Activated Partial Thromboplastin Time (aPTT) | ≤1.5 X ULN unless subject is receiving anticoagulant therapy<br>as long as PT or PTT is within therapeutic range of intended use of anticoagulants<br><br>≤1.5 X ULN unless subject is receiving anticoagulant therapy<br><br>as long as PT or PTT is within therapeutic range of intended use of anticoagulants |
| [a]Creatinine clearance should be calculated per institutional standard if using in place of serum creatinine. | |

- Female subjects of childbearing potential must have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Female subjects of childbearing potential must avoid becoming pregnant while on treatment. Men must avoid fathering a child while on treatment. This exclusion is required due to the toxicities that chemotherapy and anti-PD-1 antibody may have on the forming fetus, spermatogenesis, or the nursing child. Also, because pregnancy may alter immune function, it may limit treatment efficacy.

### 6.2 Subject Exclusion Criteria

- Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment (inhaled steroids are permitted).
- Has a known history of active TB (Bacillus Tuberculosis)
- Hypersensitivity to pembrolizumab or any of its excipients.
- Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study, Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. Denosumab is allowed.
- Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. Note: Subjects with ≤ Grade 2 neuropathy and alopecia are an exception to this criterion and may qualify for the study.
- Has received the assigned chemotherapy regimen previously in the metastatic setting, or has received the assigned chemotherapy regimen previously in the (neo)adjuvant setting within 12 months of consent;
- If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- Has a known additional malignancy that progressed or required active treatment in the last 5 years (history of synchronous breast cancer is allowed at the discretion of the principal investigator).
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
- 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 (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

- Has history of/active pneumonitis requiring treatment with steroids or history of/active interstitial lung disease.
- Has an active infection requiring systemic therapy.
- Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
- Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or has participated in a Merck-sponsored pembrolizumab study.
- Has a known history of Human Immunodeficiency Virus (HIV).
- Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- Has received a live vaccine within 30 days of planned start of study therapy. *Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*

## 7.0 RECRUITMENT PLAN

This study will be available to all patients seen at Cedars-Sinai Medical Center (Los Angeles, California), Providence Portland Medical Center, and Providence St. Vincent Medical Center (Portland, Oregon), who meet the eligibility criteria outlined in section 6.0.

Both Cedars-Sinai and Providence Cancer Center are referral centers for MTNBC. The inclusion of two referral sites was intended to hasten accrual while preserving the unique ability of these institutions to conduct extensive immunological monitoring of patients enrolled on study. Drs. Heather McArthur and David Page are longstanding collaborators, and will facilitate accrual across the two sites, respectively. Both Cedars-Sinai and Providence Medical Center are equipped with the necessary laboratory infrastructure (i.e. the Cedar-Sinai Immune Monitoring Facility and the Providence Health Immune Monitoring Unit) to conduct the immune monitoring exploratory studies described in section 12.0.

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described in section 15.0. Patients will not receive payment for their participation on this study.

## 8.0 PRETREATMENT EVALUATION

To be completed within 28 days of starting pembrolizumab:

- Those wishing to enroll in the study will sign a written informed consent prior to initiating any protocol specific evaluations or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before treatment. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to treatment may be used for screening assessments rather than repeating such tests.
- CT scan with contrast (chest, abdomen and pelvis). If patient is unable to receive CT contrast, or the abdominal/pelvic target lesion is indeterminate on CT scan, then MRI with contrast (abdomen and pelvis) plus CT chest without contrast may be performed. Non-contrast CT CAP may be used if the target lesion(s) do not require contrast for accurate measurements.
- 12-lead Electrocardiogram (EKG)
- History and physical examination, including height, weight, vital signs (temperature, pulse rate, respiration rate, blood pressure), and performance status (ECOG);
- Serum pregnancy test for all women of childbearing potential. If the test result is positive related to pregnancy, the patient will not be allowed to participate in this study. Note that urine or serum pregnancy test for all women of childbearing potential must be obtained within 72 hours of first dose. If the test result is positive related to pregnancy, the patient will not be allowed to participate in this study.
- CBC with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, CO2, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, albumin, total protein, lactate dehydrogenase, phosphorus, magnesium, uric acid, PT/INR/aPTT; T3, FT4 and TSH.
- Serology for HepBsAg, HepBcAb and hepatitis C antibody (negative test acceptable prior to screening period);
- Urinalysis
- Blood test for research purposes
- Perform baseline tumor biopsy for research purposes. Achival biopsy tissue may be used if sufficient tissue is available (at least 1 FFPE-preserved core containing tumor, or 18 unstained FFPE 5-micron slides), and if no anti-neoplastic therapies administered between the biopsy and start of pembrolizumab.

## 9.0 TREATMENT / INTERVENTION PLAN

The first day of dosing is considered Day 1. Subjects will receive pembrolizumab as an IV infusion, as well as chemotherapy according to the dosing and route described on table 5.0-1. Refer to 'MK-3475 Drug Preparation Instructions' manual.

Investigational drug dosing should be administered on Day 1 of each cycle. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Pembrolizumab will be administered as a 30 minute IV infusion (every effort should be made 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).

### 9.1 Monitoring of Dose Administration

Subjects will be monitored during and after infusion with assessment of vital signs per institutional practice.

In the event of an infusion-related reaction, refer to section 9.7.8 for guidance.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

## 9.2 Concomitant Medications

### 9.2.1 Permitted Concomitant Medication

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed in Section 9.3.2.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial, with the exception of steroids which are discussed in section 9.3.1.1. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

#### 9.2.1.1 Concomitant Steroids for patients enrolled in the paclitaxel arm

*Paclitaxel*

Patients treated with paclitaxel are at risk for allergic reactions as a result the Cremophor diluent. The standard-of-care is to pre-medicate with steroids (dexamethasone 10mg IV) 30 minutes before infusion to reduce the risk of allergic reaction. Steroid use to prevent infusion reaction will be permitted at the discretion of the treating investigator. However to minimize immunosuppression associated with steroids, we advise discontinuing or tapering steroids after the second administration of paclitaxel in patients who experience no signs or symptoms suggestive of infusion reaction.

### 9.2.2 Excluded Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The Principal Investigator must be notified if a subject receives any of these during the study.

- Any investigational anticancer therapy.
- Any concurrent chemotherapy (except as per study), immunotherapy, or biologic therapy. Note: concurrent use of bone-directed therapies (such as bisphosphonates or denosumab) are permitted;
- Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
- Immunosuppressive medications including, but not limited to systemic corticosteroids (>10 mg/day prednisone or equivalent, aside from described in 9.3.1.1), methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α)

blockers. Use of immunosuppressive medications for the management of investigational product-related AEs, in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.

## 9.3 Dose Modifications or Scheduling Delays

### 9.3.1 Pembrolizumab Dose Modifications

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

Pembrolizumab dose modifications will not be allowed. However, pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 9.3.1-1 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids to treat immune related AEs.

**Table 9.3.1-1: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab**

**General instructions:**

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

| Immune-related AEs | Toxicity grade or conditions (CTCAEv4.0) | Action taken to pembrolizumab | irAE management with corticosteroid and/or other therapies | Monitor and follow-up |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of pneumonitis<br>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment<br>• Add prophylactic antibiotics for opportunistic infections |
| | Grade 3 or 4, or recurrent Grade 2 | Permanently discontinue | | |
| Diarrhea / Colitis | Grade 2 or 3 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).<br>• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.<br>• 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<br>• Administer anti-hyperglycemic in participants with hyperglycemia | • Monitor participants for hyperglycemia or other signs and symptoms of diabetes. |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated. | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue[1] | | |
| Hyperthyroidism | Grade 2 | Continue | • Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders. |
| | Grade 3 or 4 | Withhold or permanently discontinue[1] | | |
| Hypothyroidism | Grade 2-4 | Continue | • Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care | • Monitor for signs and symptoms of thyroid disorders. |
| Nephritis and Renal dysfunction | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |
| Myocarditis | Grade 1 or 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |

| | | | | |
|---|---|---|---|---|
| | Grade 3 or 4 | Permanently discontinue | | |
| All other immune-related AEs | Intolerable/ persistent Grade 2 | Withhold | • Based on type and severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis | | |
| | Grade 4 or recurrent Grade 3 | Permanently discontinue | | |
| 1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.<br>**NOTE:**<br>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). | | | | |

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless on a steroid taper (<12 weeks), or otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

### 9.3.2 Resynchronization of Pembrolizumab with chemotherapy following scheduling delay

Treatment cycles will be defined by pembrolizumab dosing, with pembrolizumab being administered on day 1 of each cycle. In the setting of a delay in pembrolizumab dosing, an every-three week dosing interval should be re-established upon resuming pembrolizumab.

### 9.3.3 Chemotherapy dose modifications

Subjects will be monitored for adverse events while receiving chemotherapy. Dose interruptions or reductions may be required, and are permitted. Chemotherapy dose modifications must be determined according to standard practice, with clinical determination guiding whether dose modification is necessary. Dose reductions should abide by the options delineated in table 9.3.4-2, but do not necessarily have to occur in the listed sequence. However, dose reductions should be permanent and should not be re-escalated.

**Table 9.3.3-2: Dose Modifications of Chemotherapeutic Agents**

| | Paclitaxel | Capecitabine |
|---|---|---|
| Baseline dose | 80mg/m2<br>d 1,8,15 (q3w) | 2000mg BID<br>(7d on, 7d off) |
| Dose reduction option 1 | 80mg/m2<br>d 1,8 (q3w) | 1500mg BID<br>(7d on, 7d off) |
| Dose reduction option 2 | 70mg/m2<br>d,1,8 (q3w) | 1300mg BID<br>(7d on, 7d off) |
| Dose reduction option 3 | 60mg/m2<br>d,1,8 (q3w) | 1150mg BID<br>(7d on, 7d off) |
| Dose reduction option 4 | 50mg/m2<br>d,1,8 (q3w) | 1000mg BID<br>(7d on, 7d off) |
| Dose reduction option 5 | Discontinue | Discontinue |

In addition to the recommended dose modifications, chemotherapy can also be interrupted. Any subject who requires dose de-escalation beyond the recommended guidelines, or requires sustained interruption of chemotherapy for greater than 20 days, should either be discontinued from study (or) should permanently discontinue the chemotherapy. Subjects discontinued from chemotherapy treatment may optionally remain on the study and receive treatment with pembrolizumab monotherapy. Such patients will be included in determining clinical responses.

### 9.3.5 Special considerations for overlapping toxicities

Some toxicities, such as elevated LFTs, diarrhea, cytopenias, or rash, may be attributable to either chemotherapy or pembrolizumab. In these cases, both chemotherapy and pembrolizumab should be withheld as per the above defined criteria, with consideration of dose modification of the chemotherapy backbone upon resumption of therapy.

**9.4 Discontinuation of Study Therapy after CR**

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in section 9.6.

**9.5 Second Course Phase (Retreatment Period)**

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either:**
  - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
  - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy, and
  - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared
- **Or:**
  - Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability, and
  - Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab, and
  - Did not receive any anti-cancer treatment since the last dose of pembrolizumab aside from the assigned chemotherapy backbone, and
  - Has a performance status of 0 or 1 on the ECOG Performance Scale, and
  - Demonstrates adequate organ function as detailed in inclusion criteria, and
  - Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator, and
  - Meets the following criteria regarding childbearing potential:
    - Female subjects of childbearing potential must avoid becoming pregnant while on treatment.
    - Male subjects must avoid fathering a child while on treatment.
    - This exclusion is required due to the toxicities that chemotherapy and anti-PD-1 antibody may have on the forming fetus, spermatogenesis,

or the nursing child. Also, because pregnancy may alter immune function, it may limit treatment efficacy.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year. Visit requirements are outlined in the schedule of assessments.

**9.6 Supportive Care Guidelines**

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

*Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 9 for dose modification.*

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

**9.6.1 Management of Pneumonitis**

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

**9.6.2 Management of Diarrhea/Colitis**

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

**9.6.3** When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. **Management of Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

**9.6.4 Management of Hypophysitis**

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

**9.6.5 Management of Hyperthyroidism or Hypothyroidism**:

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 1-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

**9.6.6 Management of Hepatic toxicities**

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

### 9.7.7 Management of Renal Failure or Nephritis

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

### 9.7.8 Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

**Table 9.7.8-1:** shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

**Table 9.7.8-1: Pembrolizumab Infusion Reaction Treatment Guidelines**

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

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br><br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | • Acetaminophen<br>• Narcotics<br>• Oxygen<br>• Pressors<br>• Corticosteroids<br>• Epinephrine<br><br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**Subject is permanently discontinued from further trial treatment administration.** | |
| Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. | | |

### 9.7.9 Management of Nausea/vomiting

Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

### 9.7.10 Use of anti-infectives

Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

## 9.8 Diet

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

## 9.9 Use in subjects with childbearing potential

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

Non-pregnant, non-breast-feeding women may be enrolled if they avoid becoming pregnant while on treatment. Men must avoid fathering a child while on treatment.

## 9.10 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the

site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 11.1.2.

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

### 9.11 Subject replacement strategy

Subjects will be treated on protocol on a modified intention to treat analysis, whereby the following subjects will be excluded from efficacy analysis and replaced with a newly-enrolled subject:

- subjects who fail to receive at least part of 1 dose of therapy;
- subjects who withdraw consent prior to week 13 and/or are lost to follow-up, precluding assessment of efficacy at week 13.

Subjects who clinically progress prior to week 13 and discontinue therapy will be included as treatment failures in the determination of ORR.

It may be possible that a subject is evaluable for safety/tolerability but not evaluable for efficacy. For example, a subject that withdraws consent and is lost to follow up at week 8 would be eligible for safety/tolerability (since they received 6 weeks of therapy), but not efficacy (which is determined at week 13). Such subjects will be replaced with an additional subject, however they will be still included in the determination of safety/tolerability. Therefore, more than 14 subjects may be evaluable for safety/tolerability in each arm of the pilot phase.

Conversely, subjects may be evaluable for efficacy but not safety/tolerability. For example, if a subject clinically progresses at week 4 and withdraws consent, this subject would not be included in the determination of safety/tolerability, but would be included in the determination of efficacy as a treatment failure. A strict cutoff of 60% of patients will be used as the threshold for determining safety/tolerability (i.e. at least, 8 of 13=61.5%, or 9 of 14=64.3%, or 9 of 15=60%, etc.).

### 9.12 Clinical Criteria for Early Trial Termination

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

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

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

## 10.0 EVALUATION DURING TREATMENT/INTERVENTION

The following tables summarize the required evaluation and interventions for each of the therapeutic arms.

**Table 10-1: Schedule of Interventions/Assessments for Weekly Paclitaxel Arm**

| **Trial Period** | | **Treatment Cycles** | | | | | | | | | **End Of Treatment** | **Post Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Screen Visit 1 | Cycles 1-4 | | | Cycle 5-6 | | | Cycles 7+ Repeating | | | Discon | Safety Follow-up | Follow-up | Survival Follow-up |
| Treatment Week | | 1, 4, 7, 10 | 2, 5, 8, 11 | 3, 6, 9, 12 | 13, 16 | 14, 17 | 15, 18 | 19 | 20 | 21 | | | | |
| Scheduling Window (Days) | -28 to -1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | | At time of Discon | 30 Days post discon | Every 12 weeks +/- 1 week | Every 12 weeks +/- 1 week |
| Treatment Administration | | | | | | | | | | | | | | |
| Pembrolizumab | | X | | | X | | | X | | | | | | |
| Paclitaxel | | X [10] | | | | | | | | | | | | |
| Administrative Procedures | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | |
| Inc / Exc Criteria | X | | | | | | | | | | | | | |
| Demographics / Medical History | X | | | | | | | | | | | | | |
| Medication Review | X | X | X [1] | | X | | | X | | | X | X | | |
| Post-study therapy | | | | | | | | | | | | | X [9] | X |
| Survival Status | | | | | | | | | | | | | | X |
| Clinical Procedures / Assessments | | | | | | | | | | | | | | |
| Adverse Events | X | X | X [1] | | X | | | X | | | X | | | |
| Full Physical Exam | X | | | | | | | | | | | | | |
| Directed Physical Exam | | X | X [1] | | X | | | X | | | X | X | X [9] | |
| ECG | X | | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | |
| Vital Signs and Weight | X | X | X [1] | | X | | | X | | | X | X | X [9] | |
| ECOG Performance status | X | X | X [1] | | X | | | X | | | X | X | X [9] | |
| Laboratory | | | | | | | | | | | | | | |

| **Trial Period** | | **Treatment Cycles** | | | | | | | | | **End Of Treatment** | **Post Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Screen Visit 1 | Cycles 1-4 | | | Cycle 5-6 | | | Cycles 7+ Repeating | | | Discon | Safety Follow-up | Follow-up | Survival Follow-up |
| Treatment Week | | 1, 4, 7, 10 | 2, 5, 8, 11 | 3, 6, 9, 12 | 13, 16 | 14, 17 | 15, 18 | 19 | 20 | 21 | | | | |
| Scheduling Window (Days) | -28 to -1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | | At time of Discon | 30 Days post discon | Every 12 weeks +/- 1 week | Every 12 weeks +/- 1 week |
| Pregnancy Test – Urine or Serum B-HCG | X (11) | | | | | | | | | | | | | |
| PT/INR and aPTT | X (11) | | | | | | | | | | | | | |
| CBC w/ Diff | X (11) | X (12) | X (1) | | X | | | X | | | | | | |
| HepBsAg, HepBcAB, Hep C antibody | X | | | | | | | | | | | | | |
| Serum Chemistry | X (11) | X (12) | X (1) | | X | | | X | | | | | | |
| Urinalysis | X (11) | | | | X(13) | | | X(13) | | | | | | |
| T3, FT4, and TSH | X (11) | X (6) | | | X (6) | | | | | | | | | |
| Tumor Markers (CEA, CA15-3) | | X (7) | | | X (7) | | | X (7) | | | | | | |
| Efficacy Measures | | | | | | | | | | | | | | |
| Tumor Imaging – CT CAP or MRI | X | | | | X (3) | | | X (4,5) | | | | | X (9) | |
| Correlative Studies | | | | | | | | | | | | | | |
| Archival or Fresh Tissue Collection | X | X (8) | | | | | | | | | | | | |
| Blood Draw | X | X | X (1) | | X (2) | | | | | | | | | |

1. Only during cycle 1 (week 2)
2. Correlative Studies Blood collection terminates following week 13. One additional blood draw is allowed for characterization of interesting clinical/immunologic scenarios
3. Imaging assessment to occur on week 13 +/- 1 week
4. Every 12 week imaging to be conducted in patients with ongoing clinical benefit
5. Additional imaging will be optional and will be conducted as per standard-of-care, for example to re-assess equivocal response or to assess new symptoms
6. Thyroid function tests to be obtained on week 7 and week 13
7. Tumor markers should be obtained on cycle 1, and every other cycle thereafter, in all subjects who have a history of elevated tumor markers.
8. Post-treatment biopsy to occur on week 7 +/- 1 week

9. Patients who discontinue therapy without progression will be followed every 12 weeks, for consideration of re-treatment if eligible. If no longer eligible for re-treatment, patient will enter survival follow-up
10. Ongoing treatment with paclitaxel following week 7 assessment is at the discretion of the treating investigator. Pembrolizumab can be given as monotherapy following week 7
11. Pregnancy test must be within 72 hours of dose 1 of pembrolizumab; laboratory tests must be within 10 days of dose 1. Results of standard-of-care tests or examinations performed prior to informed consent and within 28 days prior to study entry are acceptable (except where otherwise specified)
12. cycle 1 CBC and comprehensive serum chemistry (LDH, Uric Acid, Phos, Mg) do not need to be repeated at dose one if obtained within 7 days
13. Urinalysis with microscopic if indicated weeks 13 and 19 and every 12 weeks thereafter while receiving active treatment

**Table 10-2: Schedule of Interventions/Assessments for Capecitabine**

| **Trial Period** | | **Treatment Cycles** | | | | | | | | **End Of Treatment** | **Post Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Screen Visit 1 | Cycles 1-4 | | | Cycle 5-6 | | Cycles 7+ Repeating | | | Discon | Safety Follow-up | Follow-up | Survival |
| Treatment Week | | 1, 4, 7, 10 | 2, 5, 8, 11 | 3, 6, 9, 12 | 13, 16 | 14, 17, 15,18 | 19 | 20 | 21 | | | | |
| Scheduling Window (Days) | -28 to -1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | | At time of Discon | 30 Days post discon | Every 12 weeks +/- 1 week | Every 12 weeks +/- 1 week |
| Treatment Administration | | | | | | | | | | | | | |
| Pembrolizumab | | X | | | X | | X | | | | | | |
| Capecitabine | | X[10,11] | | | | | | | | | | | |
| Administrative Procedures | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | |
| Inc / Exc Criteria | X | | | | | | | | | | | | |
| Demographics / Medical History | X | | | | | | | | | | | | |
| Medication Review | X | X | X[1] | | X | | X | | | X | X | | |
| Post-study therapy | | | | | | | | | | | | X[9] | X |
| Survival Status | | | | | | | | | | | | | X |
| Clinical Procedures / Assessments | | | | | | | | | | | | | |
| Adverse Events | X | X | X[1] | | X | | X | | | X | | | |
| Full Physical Exam | X | | | | | | | | | | | | |
| Directed Physical Exam | | X | X[1] | | X | | X | | | X | X | X[9] | |
| EKG | X | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | |
| Vital Signs and Weight | X | X | X[1] | | X | | X | | | X | X | X[9] | |
| ECOG Performance status | X | X | X[1] | | X | | X | | | X | X | X[9] | |
| Laboratory | | | | | | | | | | | | | |
| Pregnancy Test – Urine or Serum B-HCG | X[11] | | | | | | | | | | | | |
| PT/INR and aPTT | X[11] | | | | | | | | | | | | |
| CBC w/ Diff | X[11, 12] | X | X[1] | | X | | X | | | | | | |
| HepBsAg, HepBcAB, Hep C antibody | X | | | | | | | | | | | | |
| Serum Chemistry | X[11, 12] | X | X[1] | | X | | X | | | | | | |
| Urinalysis | X[11] | | | | X[13] | | X[13] | | | | | | |
| T3, FT4, and TSH | X[11] | X[6] | | | X[6] | | | | | | | | |

| **Trial Period** | | **Treatment Cycles** | | | | | | | | **End Of Treatment** | **Post Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Screen Visit 1 | Cycles 1-4 | | | Cycle 5-6 | | Cycles 7+ Repeating | | | Discon | Safety Follow-up | Follow-up | Survival |
| Treatment Week | | 1, 4, 7, 10 | 2, 5, 8, 11 | 3, 6, 9, 12 | 13, 16 | 14, 17, 15,18 | 19 | 20 | 21 | | | | |
| Scheduling Window (Days) | -28 to -1 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | | At time of Discon | 30 Days post discon | Every 12 weeks +/- 1 week | Every 12 weeks +/- 1 week |
| Tumor Markers (CEA, CA15-3) | | X(7) | | | X(7) | | X(7) | | | | | | |
| Efficacy Measures | | | | | | | | | | | | | |
| Tumor Imaging – CT CAP or MRI | X | | | | X(3) | | X(4,5) | | | | | X(9) | |
| Correlative Studies | | | | | | | | | | | | | |
| Archival or Fresh Tissue Collection | X | X(8) | | | | | | | | | | | |
| Blood Draw | X | X | X(1) | | X(2) | | | | | | | | |

1. Only during cycle 1 (week 2)
2. Correlative Studies Blood collection terminates following week 13. One additional blood draw is allowed for characterization of interesting clinical/immunologic scenarios
3. Imaging assessment to occur on week 13 +/- 1 week
4. q12 week imaging to be conducted in patients with ongoing clinical benefit
5. Additional imaging will be optional and will be conducted as per standard-of-care, for example to re-assess equivocal response or to assess new symptoms
6. thyroid function tests to be obtained on week 7 and week 13
7. tumor markers should be obtained on cycle 1, and every other cycle thereafter, in all subjects who have a history of elevated tumor markers.
8. post-treatment biopsy to occur on week 7 +/- 1 week
9. patients who discontinue therapy without progression will be followed every 12 weeks, for consideration of re-treatment if eligible. If no longer eligible for re-treatment, patient will enter survival follow-up
10. ongoing treatment with capecitabine following week 7 assessment is at the discretion of the treating investigator. Pembrolizumab can be given as monotherapy following week 7
11. pregnancy test must be within 72 hours of dose 1 of pembrolizumab; laboratory tests must be within 10 days of dose 1. Results of standard-of-care tests or examinations performed prior to informed consent and within 28 days prior to study entry are acceptable (except where otherwise specified)
12. cycle 1 CBC and comprehensive serum chemistry (LDH, Uric Acid, Phos, Mg) do not need to be repeated at dose one if obtained within 7 days
13. Urinalysis with microscopic if indicated weeks 13 and 19 and every 12 weeks thereafter while receiving active treatment

### 10.1 Detailed explanation of required evaluations and interventions

Individual trial procedures are described in detail below. In addition to evaluations/interventions illustrated in tables 10-1 and 10-2, it may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

#### 10.1.1 Informed Consent

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

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

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

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

#### 10.1.2 Inclusion/Exclusion Criteria

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

#### 10.1.3 Medical History

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

### 10.1.4 Prior and Concomitant Medications Review

*Prior Medications*

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

*Concomitant Medications*

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

### 10.1.5 Disease Details and Treatments

*Disease Details*

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

*Prior Treatment Details*

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

### 10.1.6 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy, it is advised that the 30 day Safety Follow-up visit occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

### 10.1.7 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the schedule of assessments and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Please refer to section 11.2 for detailed information regarding the assessment and recording of AEs.

### 10.1.8 Full Physical Exam

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

### 10.1.9 Directed Physical Exam

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

### 10.1.10 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of pembrolizumab treatment and at treatment discontinuation. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

### 10.1.11 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of pembrolizumab and discontinuation of trial treatment.

### 10.1.12 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis) are specified in Table 10.1.12-1

**Table 10.1.12-1: Laboratory Tests**

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hematocrit | Albumin | Blood | Serum β-human chorionic gonadotropin† |
| Hemoglobin | Alkaline phosphatase | Glucose | (β-hCG)† |
| Platelet count | Alanine aminotransferase (ALT) | Protein | PT (INR) |
| WBC (total and differential) | Aspartate aminotransferase (AST) | Specific gravity | aPTT |
| Red Blood Cell Count | Lactate dehydrogenase (LDH) | Microscopic exam *(If abnormal)* | Total thriiodothyronine (T3) |
| Absolute Neutrophil Count | Carbon Dioxide | results are noted | Free thyroxine (FT4) |
| Absolute Lymphocyte Count | *($CO_2$ or bicarbonate)* | Urine pregnancy test † | Thyroid stimulating hormone (TSH) |
| | Uric Acid | | PK |
| | Calcium | | |
| | Chloride | | Blood for correlative studies |
| | Glucose | | |
| | Phosphorus | | |
| | Potassium | | |
| | Sodium | | |
| | Magnesium | | |
| | Total Bilirubin | | |
| | Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)* | | |
| | Total protein | | |
| | Blood Urea Nitrogen | | |
| † Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. | | | |

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 3 days prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of pembrolizumab.

### 10.1.14 RESEARCH BLOOD AND BIOPSY SPECIMENS

#### 10.1.14.1 Research blood

For all patients, blood specimens will be obtained for research purposes during screening, on day 1, on day 8, then at weeks 4, 7, 10, and 13 (± 3 days). An additional blood draw beyond week 13 is permitted based upon interesting clinical/immunological findings.

Specimens should be collected prior to drug administration. One tube of blood (5cc) is to be collected in a cyto-chex BCT tube, and four 10cc tubes of blood are to be collected in sodium heparin tubes. Peripheral blood mononuclear cells and plasma/serum will then be isolated per institutional practice at immune monitoring facilities. The cyto-chex BCT tube is shipped same day overnight Monday-Wednesday for processing at the Providence Immune monitoring unit.

#### 10.1.14.2 Research biopsy

A pre-treatment tumor biopsy will be obtained during screening prior to initiation of pembrolizumab. Alternatively, archived tissue may be submitted for analysis if sufficient material is available (at least one tumor bearing FFPE core, or at least 18 5-micron FFPE slides) and if no intervening anti-neoplastic therapies were administered between the time of biopsy and initiation of study therapy. Fresh biopsy is preferred to archived biopsy if feasible. An on-treatment biopsy, from the same lesion biopsied during screening/prior to pembrolizumab if possible, will be obtained at week 7 (± 1 wk).

Patients will be permitted to continue enrollment and treatment on protocol in the event that insufficient material was obtained from the biopsy. The on-treatment biopsy will not be required if this is no longer considered appropriate at the time of the planned procedure, for example, if tumor is no longer accessible or the procedure is deemed to be unsafe. Tumor lesions planned for on-treatment biopsy may be an index lesion if $\geq$ 2 cm in at least one diameter.

If clinically practical, subjects will undergo up to 5 core biopsies. Core biopsies will be placed in formalin and processed for FFPE. All tissue obtained during biopsy procedures will be batch shipped to the Providence Regional Laboratories Department of Pathology for analysis under this study as indicated in the lab/path manual.

#### 10.1.14.3 Tumor Imaging Assessments

The preferred imaging modality is CT chest/abdomen/pelvis with intravenous contrast, which will be obtained as per the schedule of assessments. If patient is unable to receive CT contrast or the abdominal/ pelvic target lesion is indeterminate on CT, then MRI with contrast (abdomen and pelvis) plus CT without contrast (chest) may be performed.

### 10.1.15 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be

followed in accordance with the safety requirements outlined in the schedule of assessments. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Sections 9.4 and 9.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

#### 10.1.16 Visit Requirements

Visit requirements are outlined in the schedule of assessments, and described below.

#### 10.1.16.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

#### 10.1.16.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Sections 9.4 and 9.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Sections 9.4 and 9.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

#### 10.1.16.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be assessed for survival every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurs first.

## 11.0 TOXICITIES/SIDE EFFECTS

### 11.1 Summary of toxicities of investigational agents

#### 11.1.1 Weekly paclitaxel

Paclitaxel is an FDA-approved agent on formulary for the treatment of metastatic TNBC. A comprehensive list of toxicities may be found in the Lexicomp chemotherapy guidelines. Principal side effects are listed in table 11.1.1-1.

**Table 11.1.1-1: Principal side effects of paclitaxel**

| | |
|---|---|
| Hematologic | Neutropenia, leukopenia, thrombocytopenia, anemia |
| Gastrointestinal | Nausea/vomiting, diarrhea, mucositis |
| Cardiac | Heart block, bradycardia |
| Neurologic | Peripheral neuropathy, arthralgia/myalgia |
| Dermatologic | Alopecia, onycholysis |
| Miscellaneous | Moderate - severe hypersensitivity reactions, flushing, rash, dyspnea, fatigue, radiation sensitizer |

### 11.1.2 Oral Capecitabine

Oral capecitabine is an FDA-approved agent on formulary for the treatment of metastatic TNBC. A comprehensive list of toxicities may be found in the Lexicomp chemotherapy guidelines. Principal side effects of capecitabine are listed in table 11.1.2-1.

**Table 11.1.2-1: Principal side effects of capecitabine**

| | |
|---|---|
| Hematological | Neutropenia, anemia, and thrombocytopenia |
| Gastrointestinal | Diarrhea, mucositis, abdominal pain, nausea, vomiting, dyspepsia |
| Hepatic | Hyperbilirubinemia, elevated transaminases |
| Neurologic | Paresthesias |
| Cardiovascular | Increased risk of myocardial ischemia (in patients with history of ischemic heart disease) |
| Dermatologic | Hand-foot syndrome |
| Miscellaneous | Fatigue, myalgias, blepharitis |

### 11.1.3 Pembrolizumab

Pembrolizumab is an FDA-approved agent on formulary for the treatment of metastatic melanoma. It is investigational for use in metastatic TNBC. A comprehensive list of toxicities may be found in Lexicomp and in the investigator's brochure. Principal side effects of pembrolizumab are listed in table 11.1.5-1.

**Table 11.1.3-1: Principal side effects of pembrolizumab**

| | |
|---|---|
| Cardiovascular | Peripheral edema |
| Central Nervous System | Fatigue, headache, chills, insomnia, dizziness, optic neuritis (rare), uveitis (rare) |
| Endocrine | Hyperglycemia, hyponatremia, hypoalbuminemia, hypertriglyceridemia, hypocalcemia, adrenal insufficiency (rare), hypophysitis (rare) |
| GI | Nausea, decreased appetite, constipation, diarrhea, vomiting, abdominal pain, pancreatitis (rare), increased serum AST, hepatitis (rare) |
| Heme | Anemia, hemolytic anemia (rare) |
| Neurological/Muscular | Arthralgias, limb pain, myalgia, back pain, arthritis (rare), Lambert-Eaton syndrome (rare), myositis (rare), partial epilepsy (rare), rhabdomyolysis (rare), |
| Respiratory | Cough, dyspnea, upper respiratory tract infection |
| Miscellaneous | Fever |
| Derm | Exfoliative dermatitis (rare) |
| Renal | Interstitial nephritis (rare), nephritis (rare), |

## 11.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

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

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

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

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

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

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 11.5.1.

**11.3 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck**

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor (via email at OREACRISAEreporting@providence.org) and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

**11.4 Reporting of Pregnancy and Lactation to the Sponsor and to Merck**

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

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

**11.5 Immediate Reporting of Adverse Events to the Sponsor and to Merck**

**11.5.1 Serious Adverse Events**

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

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

Refer to Table 11.6.1 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor (via email at OREACRISAEreporting@providence.org) and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be

handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

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

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

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

### 11.5.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor (via email at OREACRISAEreporting@providence.org) and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220). Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 11.3 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

### 11.5.3 Additional adverse events

ECIs (both non-serious and serious adverse events) identified from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

**11.6 Evaluating Adverse Events**

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

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

## Table 11.6-1: Instructions of how an investigator should evaluate all adverse events

| | | |
|---|---|---|
| **V4.0 CTCAE Grading** | **Grade 1** | **Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.** |
| | **Grade 2** | **Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.** |
| | **Grade 3** | **Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.** |
| | **Grade 4** | **Life threatening consequences; urgent intervention indicated.** |
| | **Grade 5** | **Death related to AE** |
| **Seriousness** | A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that: | |
| | †**Results in death**; or | |
| | †**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or | |
| | †**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or | |
| | †**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or | |
| | †**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or | |
| | **Is a** new **cancer;** (that is not a condition of the study) **or** | |
| | **Is an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours. | |
| | **Other important medical events** that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †). | |
| **Duration** | Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units | |
| **Action taken** | Did the adverse event cause the Merck product to be discontinued? | |
| **Relationship to test drug** | Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.<br>**The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE): | |
| | **Exposure** | Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen? |
| | **Time Course** | Did the AE follow in a reasonable temporal sequence from administration of the Merck product?<br>Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)? |
| | **Likely Cause** | Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors |
| **Relationship to Merck product (continued)** | **The following components are to be used to assess the relationship between the test drug and the AE: (continued)** | |
| | **Dechallenge** | Was the Merck product discontinued or dose/exposure/frequency reduced?<br>If yes, did the AE resolve or improve?<br>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.<br>(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.) |

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

### 11.7 Sponsor Responsibility for Reporting Adverse Events

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

## 12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

### 12.1 Pilot phase: determination of primary endpoint

#### 12.1.1 Definition of safety/tolerability

The primary endpoint of the pilot phase is to establish tolerability of chemotherapy plus pembrolizumab. For each subject, the therapy will be deemed tolerable if the following criteria are met:

- Subjects receive at least 6 weeks of pembrolizumab (2 cycles) and remain free of serious adverse events and grade III/IV treatment-associated adverse events requiring discontinuation of pembrolizumab during that period;
- Subjects receive at least 7 weeks of chemotherapy within an acceptable therapeutic dosing/scheduling range without chemotherapy discontinuation or chemotherapy dosing delay ≥21 days. Shorter chemotherapy delays (<21 days) and dose modifications are acceptable if they conform to guidelines specified in section 9.4.4.

The first criterion is borrowed from similar phase Ib studies of combination immunotherapy, such as the phase 1b study of ipilimumab plus nivolumab in MTNBC (NCT01928394, MSKCC IRB #13-087, PI: Margaret Callahan). The rationale for stipulating only 2 cycles of pembrolizumab is that some patients may receive sustained clinical benefit from only one or two doses of immunotherapy.(Wolchok, Kluger et al. 2013) Furthermore, toxicities of pembrolizumab are generally reversible if intervened expeditiously with algorithm-based guidelines as summarized in section 9.

The second criterion is based upon the overarching goal of the pilot phase of the study, which is to demonstrate that pembrolizumab can be added to chemotherapy without impairing the ability of a clinician to administer chemotherapy, at clinically active doses, for a sufficient period of time to allow priming of the immune response. Because chemotherapy alone often requires dose modifications/delays, dose modifications and delays will be allowed on protocol and will not automatically constitute intolerance. However, chemotherapy discontinuations or sustained chemotherapy delays for ≥21 days will constitute intolerance of the regimen.

#### 12.1.2 Threshold for declaring safety/tolerability

In previously reported phase II/III studies, 71-91% of patients treated with chemotherapy (weekly taxol, oral capecitabine) tolerated therapy without requiring dose discontinuation (table 12.1.2-1).

**Table 12.1.2-1 Safety/tolerability for each chemotherapy regimen**

| Therapeutic Arm | Published toxicity-associated chemotherapy discontinuation rate | Anticipated tolerability of chemotherapy (1- discontinuation rate) |
|---|---|---|
| Weekly paclitaxel | 9% (Fountzilas, Dafni et al. 2009) | 91% |
| Oral capecitabine | 22% (Gajria, Feigin et al. 2011) | 78% |

In this protocol, each therapeutic arm will be deemed tolerable if the percentage of patients tolerating therapy meets or exceeds 60%. Only subjects who are evaluable for at least 6 weeks will be considered in determining tolerability/safety. For example, if a subject tolerates therapy but experiences clinical progression at week 4 requiring alternative systemic therapy, this subject will not be evaluable for safety/tolerability, but will count as treatment failures in determination of ORR.

This threshold of 60% was selected because it acknowledges the limitations of statistical precision of the study, and because it acknowledges the possibility that pembrolizumab may potentially confer additive clinical benefit when combined with chemotherapy. This threshold applies to both the pilot phase as well as optional expansion phases.

**12.1.3 Descriptive reporting to toxicities and dose modifications/delays**

The rate of grade I/II toxicities, grade III/IV toxicities, and chemotherapy dose delays and modifications will be reported as additional, descriptive measures of tolerability. These data will not be used to determine the primary endpoint, but may be used to inform the decision of whether to advance a therapeutic arm to the phase II expansion phase. For instance, if virtually all patients of a given therapeutic arm require dose reductions for toxicity, then the committee may opt out of advancing that therapeutic arm to the phase II expansion cohort, or may consider amending the protocol to reduce the starting chemotherapy dose for the phase II expansion cohort.

**12.2 Phase II expansion cohort: determination of primary endpoint**

In addition to tolerability, clinical efficacy will also be assessed in the pilot cohort, as measured by RECIST v1.1 ORR. If the therapy is deemed tolerable and if an efficacy futility boundary is exceeded in the pilot cohort, clinical efficacy may be further evaluated via an expansion cohort(s) of one or more treatment arms. For a treatment arm to be eligible for expansion, overall response in the pilot stage must exceed ≥4/14 objective responses. This boundary is modeled after a Simon 2-stage design, whereby the first Simon stage is the pilot phase arm (n=14), and the second Simon stage is the expansion cohort (n=30). This design is powered, with a type I error rate of 10% and type II error rate of 10%, to discriminate between ORR of 25% (the estimated response rate for chemotherapy alone for each of the three regimens based on historical trials) versus 45%. Response will be adjudicated by the RECIST1.1 criteria.

**12.2.2 Objective response rate by RECIST v1.1**

For the purposes of this study, patients will be evaluated for response every 4 cycles (approximately 12 weeks), or as clinically indicated if interim toxicity occurs mandating cancer staging re-assessment. RECIST 1.1 criteria will be used.

<u>CT scan with contrast of the chest, abdomen, and pelvis</u>

- CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

<u>MRI scans</u>

- MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

**Measurability of Tumor Lesions**

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
  - 10 mm caliper measurement by clinical exam (when superficial)
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- **Target Lesions -** All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

- **Non-target Lesions -** It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”)

**Response Criteria**

**Evaluation of Target Lesions**

- **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be “0” if there are target nodes).

- **Partial Response -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive Disease -** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)

- **Stable Disease -** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

**Evaluation of Non-target Lesions**

- **Complete Response -** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

- **Non-complete response/Non-progressive disease -** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- **Progressive Disease -** Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

**Appearance of New Lesions**

The appearance of new lesions is considered PD according to RECIST v 1.1 guidelines. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive treatment with pembrolizumab.

**Evaluation of Overall Response**

Table 12.1-1 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

**Table 12.1-1 Evaluation of Overall Response**

| Target Lesions | Non-target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| Complete response | Complete response | No | Complete response |
| Complete response | Not evaluable | No | Partial response |
| Complete response | Non-complete response / non-progressive disease | No | Partial response |
| Partial response | Non-progressive disease and not evaluable [a] | No | Partial response |
| Stable disease | Non-progressive disease and not evaluable [a] | No | Stable disease |
| Not all evaluated | Non-progressive disease | No | Not evaluable |
| Progressive disease | Any | Yes/No | Progressive disease |
| Any | Progressive disease | Yes/No | Progressive disease |
| Any | Any | Yes | Progressive disease |

[a] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

### 12.3 Objective response rate by immune related RECIST v1.1

With immunomodulatory therapy, clinical benefit may be observed in the setting of new lesions (Wolchok, Hoos et al. 2009) or following initial progression. The immune-related RECIST v1.1 criteria account for these unique considerations by incorporating the following modifications: (Nishino, Gargano et al. 2014)

- The presence of new lesions does not define progression, however the measures of the new lesion(s) should be included in the sum of the measurements;
- A lymph node has to be ≥15mm in short axis to be a measurable new lesion, and its short axis measurement is included in the sum;
- Up to 2 new lesions per organ, and up to 5 new lesions in total can be added to the measurements.

As a secondary endpoint, response rate by irRECIST will be determined.

### 12.4 Correlative Studies

Pharmacodynamic changes may be evaluated for associations with clinical activity, and safety (adverse event) data. Core biopsies may be used for correlative studies such as IHC/immunofluorescence, tumor mutation analysis, proteomic analysis, and immunodiversity. Assessments will be performed at Providence Health & Services and Cedars-Sinai, or with third party collaborators under a Material Transfer Agreement.

#### 12.4.1 Whole Blood

Flow cytometry will be performed at baseline and during treatment to assess baseline and changes in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations (PBMCs). Lymphocyte subsets to be assayed may include, but are not limited to CD8+ and CD4+ T-cell subsets (activated; effector/memory; regulatory) and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers such as ICOS, HLA-DR, PD-1, CTLA-4, and/or intracellular IFNγ. Additional flow cytometry-based assays will focus on defining and monitoring the abundance of myeloid-derived suppressor cells (MDSCs), a cell type which appears to negatively impact anti-tumor activity and which has been shown to promote immune escape by limiting activated CD8 T-cell infiltration into the tumor microenvironment (Postow, Callahan et al. 2012). NK and other cell populations may be monitored in a similar fashion with a focus on characterizing subsets defined by the expression of activation markers. Immune cells may be evaluated using HLA-A2-restricted tetramer assays to detect and quantify the presence of T cells directed against specific antigens which are anticipated to be presented to the immune system due to study treatment. Detecting on-treatment increases in these T cell populations may be considered evidence of adaptive immune responses in TNBC.

#### 12.4.2 Plasma

To understand the prevalence of circulating proteins and the impact they may have on the clinical activity and/or safety of pembrolizumab treatment, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, soluble factors may be investigated by ELISA and/or other relevant multiplex-based protein assay methods. Examples of analytes to be assessed may include but are not limited to factors induced by IFNγ signaling (e.g., T cell chemoattractants CXCL9; CXCL10) and other factors generally involved in inflammatory processes. Plasma may be used also to assess the presence and/or concentration of anti-tumor antibodies using a mulitplex platform such as Invitrogen's Protoarray platform(c). Levels of sPD-L1 in peripheral blood may also be assessed.

### 12.4.3 Tumor Tissue

The presence of TILs within tumors in response to pembrolizumab treatment will be evaluated baseline and on-treatment biopsies. Archived tissue and biopsy tissue will be analyzed using immunohistochemistry/immunofluorescence for PD-L1 expression and other immune-related proteins. In samples where tissue quantity permits, gene expression (Nanostring and/or RT- QPCR) research platforms will be conducted to further characterize immune phenotype and correlate with response. Laser Capture Microdissection may be utilized to enrich specific regions of tumor material for use in similar or additional downstream applications, which may include in-situ hybridization, flow cytometry, ELISA, and/or assessment of miRNA. DNA may be sequenced to quantify the presence of T-cells and T-cell clonal subpopulations. In all cases, the goal may be to determine the abundance of a battery of immunoregulatory genes or proteins associated with cancer cells and/or cancer-interacting lymphocytes derived from biopsied material. Other biomarkers may be evaluated as determined by additional data. Remaining specimens may be stored for future studies related to TNBC immunity.

## 13.0 CRITERIA FOR REMOVAL FROM STUDY

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

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

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

  *Note*: A subject may continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.

- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with pembrolizumab

  *Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment at the discretion of the PI if they responded during the initial 24 months and then progressed after stopping study treatment.*

- Administrative reasons

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up, for up to 2 years. After documented disease progression

each subject will be followed by telephone for overall survival until death, withdrawal of consent, the end of the study, or 2 years, whichever occurs first.

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

## 14.0 BIOSTATISTICS

### 14.1 Sample Size Determination

The primary objective of the pilot phase is to establish safety/tolerability, whereas the primary endpoint of the expansion phase is to estimate efficacy of one or more of the treatment arms.

Sample size of the pilot arms and expansion cohorts are determined by a Simon two-stage optimal design which will discriminate whether pembrolizumab plus chemotherapy yields a week 13 ORR that is at least 20% greater than the anticipated ORR of chemotherapy alone. This design limits the expected number of subjects who receive pembrolizumab plus chemotherapy when the true week 13 ORR is not appreciably higher than with chemotherapy alone.

The Simon design will test the null hypothesis that the true ORR is ≤25% versus the alternative hypothesis that the true ORR is >45%. The 2-stage testing will target a Type I error rate of 10% and will have 90% power to reject the null hypothesis if the true ORR is ≤ 25%. Given that the therapy is deemed tolerable, the probability of terminating the study early .52 under the null.

The Simon design requires 14 treated subjects assigned to treatment for the first stage (the pilot phase) and prohibits expansion of that treatment arm if there are <4 subjects with OR amongst the 14 subjects treated in the pilot phase. Otherwise, if ≥4/14 subjects from the pilot phase achieve OR, then a phase II expansion cohort will be considered for that arm.

As delineated in 9.11, subjects who are not evaluable for OR at week 13 will be replaced.

*Assessment of safety/tolerability*

This pilot/phase II design enables 14 subjects to be treated across each of three chemotherapy arms, allowing for an adequate assessment of tolerability before an expansion cohort is considered. In previously reported phase II/III studies, 78-91% of patients treated with chemotherapy (weekly taxol or oral capecitabine) tolerated therapy without requiring dose discontinuation. Accordingly, we will deem the therapy safe/tolerable if at least 60% of the patients are able to tolerate therapy. Assuming that all 14 patients are evaluable for safety/tolerability, there is a 0.49 probability that the therapy will be deemed safe if we assume a 0.6 true safety/tolerability probability. If the true probability is assumed to be 0.7 and 0.8, the probability of deeming the therapy tolerable is 0.78 and 0.96 respectively. Safety will continue to be assessed in the expansion cohorts, using the same safety/tolerability threshold of at least 60% of all evaluable patients.

#### 14.1.1.1 Rationale of Alternative Hypothesis

The addition of pembrolizumab to chemotherapy could potentially enhance the clinical benefit of either therapy alone. We will evaluate for an improvement in OR by at least 20%

compared to historical controls, which is clinically meaningful improvement and can be readily identified with a sample size that is small enough to permit expeditious accrual.

#### 14.1.1.2 Rationale of Null Hypothesis

As per section 3.1.1, the reported response rates of the chemotherapy arms across large phase II/III trials are as follows:

- Weekly paclitaxel (Mauri, Kamposioras et al. 2010): 18%-49% (Miller, Wang et al. 2007, Seidman, Berry et al. 2008, Fountzilas, Dafni et al. 2009, Brufsky, Valero et al. 2012, Miles, Dieras et al. 2013). The contemporary response rate is estimated to be closer to 20-30% owing to increased use of paclitaxel in the (neo)adjuvant setting.
- Oral capecitabine: 18-30% (Oshaughnessy, Blum et al. 2001, Fumoleau, Largillier et al. 2004, Brufsky, Valero et al. 2012, Miles, Dieras et al. 2013)

From the above trials, the median historical ORRs is adopted as the null hypothesis for this pilot study (ORR 25%). In practice, response rates of chemotherapy decline with line of therapy, however we anticipate that we will accrue a mix of 1$^{st}$-line subjects and 2$^{nd}$-line subjects, thus emulating the patient populations treated in the above randomized trials. Therefore, we have selected a null hypothesis of 25% across each treatment arm.

### 14.3 Secondary clinical endpoints

The ORR by immune-related response criteria will be reported as secondary endpoints. The exact 80% and 95% CI of ORR will be estimated using the binomial distribution.

### 14.4 Exploratory biomarker analyses

This design also allows for indirect comparison of the immunologic effects of pembrolizumab when combined with each of two chemotherapy regimens. These data may be informative in generating hypotheses regarding the relative immune-stimulating properties of each of the three combination regimens. While a randomized design would be preferred to enable a direct comparative assessment, a randomized design would pose a significant barrier to patient accrual, which is the limiting factor in the design of a small, investigator-initiated trial.

Exploratory research studies will be done to evaluate the effect of this therapy using research blood draws and tumor biopsies at baseline and at week 7.

The pharmacodynamic effect of pembrolizumab and chemotherapy on Tumor Infiltrating Lymphocytes (TILs), such as CD4+ and CD8+ T-cells, and expression of tumor markers, will be assessed by summary statistics, and investigated graphically to explore patterns of change from pre-treatment to post-treatment specimens.

The pharmacodynamic effect of pembrolizumab chemotherapy on markers in peripheral blood, such as ICOS, HLA-DR, PD-1, CTLA-4; and, serum proteins, such as CXCL9; CXCL10, will be assessed by summary statistics, and investigated graphically to explore patterns of change over time.

In addition, the relationship of TIL changes and tumor marker expression with measures of peripheral blood markers will be summarized descriptively.

Associations between the markers and response by RECIST will be explored.

Fisher's exact test will be employed to assess associations between categorical variables while Spearman's rank correlation will be used for continuous variables. Wilcoxon signed rank test will be used to test for differences in continuous expression tumor markers between pre- and post-treatment specimens while McNemar's test will be used to assess these relationships for binary markers. Fisher's exact test will be employed to assess associations between categorical variables.

## 15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

### 15.1 Research Participant Registration

To register a patient, email the Data Management Office of the Robert W. Franz Cancer Research Center at OREACRIRandomization@providence.org with the following information:

- Investigator's name
- Patient's initials and date of birth
- Eligibility Verification
- Treatment Decision and date of first dose.

Patients must meet all of the eligibility requirements and undergo all pre-study procedures. If a patient enrolls in the study, but does not receive study therapy, the patient's enrollment may be canceled. Reasons for cancellation will be documented in writing. Any patient whose enrollment was canceled before receiving study therapy will be replaced.

Assignment of Study Numbers

Study Numbers will be assigned at enrollment based on order of enrollment. For example:

- MFH is the 4th patient enrolled to study. Study Number PPC - 04
- B-A is 9th patient enrolled to study. Study Number PPC - 09

All case report forms, study reports, and laboratory samples for research tests, including immune parameters or pharmacokinetics, will be labeled with the full patient Study Number.

### 15.2 Randomization

Randomization is not applicable in this protocol.

## 16.0 DATA MANAGEMENT

### 16.1 Data collection

Clinical data will be recorded on study-specific electronic case report forms (eCRFs) in the Velos eResearch clinical data management system (CTMS). The investigator will ensure the accuracy, completeness, and timeliness of data recorded on the eCRFs

### 16.1 Quality Assurance

All case report forms will undergo quality assurance review. All quality assurance reviews will include verification of the accuracy and integrity of data entered to case report forms. Incorrect data will be identified and corrected. The existence of adequate source documents for all data will be verified.

### 16.2 Monitoring

Monitoring will occur at intervals stipulated in the monitoring plan for the study. Monitoring may be performed on-site or remotely. Monitoring will include: review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness and accuracy compared to the source documents.

## 18.0 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.

## 19.0 REFERENCES


1. Antonia, S. J., J. R. Brahmer, S. N. Gettinger, L. Q. M. Chow, R. A. Juergens, F. A. Shepherd, S. A. Laurie, D. E. Gerber, J. W. Goldman, Y. Shen, C. Harbison, S. Alaparthy, A. C. Chen, H. Borghaei and N. A. Rizvi (2014). "Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) in advanced non-small cell lung cancer (NSCLC)." ASCO Meeting Abstracts **32**(15_suppl): 8113.

2. Brufsky, A., V. Valero, B. Tiangco, S. Dakhil, A. Brize, H. S. Rugo, R. Rivera, A. Duenne, N. Bousfoul and D. A. Yardley (2012). "Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial." Breast Cancer Res Treat **133**(3): 1067-1075.

3. Emens, L. A., F. S. Braiteh, P. A. Cassier, J. Delord, J. P. Eder, X. Shen, Y. Xiao, Y. Wang, P. S. Hegde, D. S. Chen and I. E. Krop (2014). Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastastic triple-negative breast cancer. 2014 San Antonio Breast Cancer Symposium, San Antonio, TX.

4. Fountzilas, G., U. Dafni, M. A. Dimopoulos, A. Koutras, D. Skarlos, P. Papakostas, H. Gogas, D. Bafaloukos, A. Kalogera-Fountzila, E. Samantas, E. Briasoulis, D. Pectasides, N. Maniadakis, F. Matsiakou, G. Aravantinos, C. Papadimitriou, M. Karina, C. Christodoulou, P. Kosmidis and H. P. Kalofonos (2009). "A randomized phase III study comparing three anthracycline-free taxane-based regimens, as first line chemotherapy, in metastatic breast cancer: a Hellenic Cooperative Oncology Group study." Breast Cancer Res Treat **115**(1): 87-99.

5. Fumoleau, P., R. Largillier, C. Clippe, V. Dieras, H. Orfeuvre, T. Lesimple, S. Culine, B. Audhuy, D. Serin, H. Cure, E. Vuillemin, J. F. Morere, F. Montestruc, Z. Mouri and M. Namer (2004). "Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer." Eur J Cancer **40**(4): 536-542.

6. Gajria, D., K. Feigin, L. K. Tan, S. Patil, S. Geneus, M. Theodoulou, L. Norton, C. A. Hudis and T. A. Traina (2011). "Phase 2 trial of a novel capecitabine dosing schedule in combination with bevacizumab for patients with metastatic breast cancer." Cancer **117**(18): 4125-4131.

7. Gajria, D., J. Gonzalez, K. Feigin, S. Patil, C. Chen, M. Theodoulou, P. Drullinsky, G. D'Andrea, D. Lake, L. Norton, C. A. Hudis and T. A. Traina (2012). "Phase II trial of a novel capecitabine dosing schedule in combination with lapatinib for the treatment of patients with HER2-positive metastatic breast cancer." Breast Cancer Res Treat **131**(1): 111-116.

8. Kuo, W. H., Y. Y. Chang, L. C. Lai, M. H. Tsai, C. K. Hsiao, K. J. Chang and E. Y. Chuang (2012). "Molecular characteristics and metastasis predictor genes of triple-negative breast cancer: a clinical study of triple-negative breast carcinomas." PLoS One **7**(9): e45831.

9. Lesterhuis, W. J., J. Salmons, A. K. Nowak, E. N. Rozali, A. Khong, I. M. Dick, J. A. Harken, B. W. Robinson and R. A. Lake (2013). "Synergistic effect of CTLA-4 blockade

and cancer chemotherapy in the induction of anti-tumor immunity." PLoS One **8**(4): e61895.

10. Lynch, T. J., I. Bondarenko, A. Luft, P. Serwatowski, F. Barlesi, R. Chacko, M. Sebastian, J. Neal, H. Lu, J. M. Cuillerot and M. Reck (2012). "Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study." J Clin Oncol **30**(17): 2046-2054.

11. Mauri, D., K. Kamposioras, L. Tsali, M. Bristianou, A. Valachis, I. Karathanasi, C. Georgiou and N. P. Polyzos (2010). "Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: A meta-analysis." Cancer Treat Rev **36**(1): 69-74.

12. Miles, D. W., V. Dieras, J. Cortes, A. A. Duenne, J. Yi and J. O'Shaughnessy (2013). "First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients." Ann Oncol **24**(11): 2773-2780.

13. Miller, K., M. Wang, J. Gralow, M. Dickler, M. Cobleigh, E. A. Perez, T. Shenkier, D. Cella and N. E. Davidson (2007). "Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer." N Engl J Med **357**(26): 2666-2676.

14. Miyashita, M., H. Sasano, K. Tamaki, M. Chan, H. Hirakawa, A. Suzuki, H. Tada, G. Watanabe, N. Nemoto, S. Nakagawa, T. Ishida and N. Ohuchi (2014). "Tumor-infiltrating CD8+ and FOXP3+ lymphocytes in triple-negative breast cancer: its correlation with pathological complete response to neoadjuvant chemotherapy." Breast Cancer Res Treat **148**(3): 525-534.

15. Nishino, M., M. Gargano, M. Suda, N. H. Ramaiya and F. S. Hodi (2014). "Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab?" J Immunother Cancer **2**: 17.

16. Oshaughnessy, J. A., J. Blum, V. Moiseyenko, S. E. Jones, D. Miles, D. Bell, R. Rosso, L. Mauriac, B. Osterwalder, H. U. Burger and S. Laws (2001). "Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer." Ann Oncol **12**(9): 1247-1254.

17. Postow, M. A., M. K. Callahan, C. A. Barker, Y. Yamada, J. Yuan, S. Kitano, Z. Mu, T. Rasalan, M. Adamow, E. Ritter, C. Sedrak, A. A. Jungbluth, R. Chua, A. S. Yang, R. A. Roman, S. Rosner, B. Benson, J. P. Allison, A. M. Lesokhin, S. Gnjatic and J. D. Wolchok (2012). "Immunologic correlates of the abscopal effect in a patient with melanoma." N Engl J Med **366**(10): 925-931.

18. Reck, M., I. Bondarenko, A. Luft, P. Serwatowski, F. Barlesi, R. Chacko, M. Sebastian, H. Lu, J. M. Cuillerot and T. J. Lynch (2013). "Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial." Ann Oncol **24**(1): 75-83.

19. Robert, C., L. Thomas, I. Bondarenko, S. O'Day, D. J. M, C. Garbe, C. Lebbe, J. F. Baurain, A. Testori, J. J. Grob, N. Davidson, J. Richards, M. Maio, A. Hauschild, W. H. Miller, Jr., P. Gascon, M. Lotem, K. Harmankaya, R. Ibrahim, S. Francis, T. T. Chen, R. Humphrey, A. Hoos and J. D. Wolchok (2011). "Ipilimumab plus dacarbazine for previously untreated metastatic melanoma." N Engl J Med **364**(26): 2517-2526.

20. Salgado, R., C. Denkert, S. Demaria, N. Sirtaine, F. Klauschen, G. Pruneri, S. Wienert, G. Van den Eynden, F. L. Baehne, F. Penault-Llorca, E. A. Perez, E. A. Thompson, W. F. Symmans, A. L. Richardson, J. Brock, C. Criscitiello, H. Bailey, M. Ignatiadis, G. Floris, J. Sparano, Z. Kos, T. Nielsen, D. L. Rimm, K. H. Allison, J. S. Reis-Filho, S. Loibl, C. Sotiriou, G. Viale, S. Badve, S. Adams, K. Willard-Gallo and S. Loi (2014). "Harmonization of the evaluation of tumor infiltrating lymphocytes (TILs) in breast cancer: recommendations by an international TILs-working group 2014." Ann Oncol.

21. Seidman, A. D., D. Berry, C. Cirrincione, L. Harris, H. Muss, P. K. Marcom, G. Gipson, H. Burstein, D. Lake, C. L. Shapiro, P. Ungaro, L. Norton, E. Winer and C. Hudis (2008). "Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840." J Clin Oncol **26**(10): 1642-1649.

22. Sistigu, A., T. Yamazaki, E. Vacchelli, K. Chaba, D. P. Enot, J. Adam, I. Vitale, A. Goubar, E. E. Baracco, C. Remedios, L. Fend, D. Hannani, L. Aymeric, Y. Ma, M. Niso-Santano, O. Kepp, J. L. Schultze, T. Tuting, F. Belardelli, L. Bracci, V. La Sorsa, G. Ziccheddu, P. Sestili, F. Urbani, M. Delorenzi, M. Lacroix-Triki, V. Quidville, R. Conforti, J. P. Spano, L. Pusztai, V. Poirier-Colame, S. Delaloge, F. Penault-Llorca, S. Ladoire, L. Arnould, J. Cyrta, M. C. Dessoliers, A. Eggermont, M. E. Bianchi, M. Pittet, C. Engblom, C. Pfirschke, X. Preville, G. Uze, R. D. Schreiber, M. T. Chow, M. J. Smyth, E. Proietti, F. Andre, G. Kroemer and L. Zitvogel (2014). "Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy." Nat Med.

23. Society, A. B. C. (2012). "Breast Cancer Facts & Figures 2011-2012." Retrieved May 9, 2013, from http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-030975.pdf.

24. Topalian, S. L., C. G. Drake and D. M. Pardoll (2012). "Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity." Curr Opin Immunol **24**(2): 207-212.

25. Traina, T. A., U. Dugan, B. Higgins, K. Kolinsky, M. Theodoulou, C. A. Hudis and L. Norton (2010). "Optimizing chemotherapy dose and schedule by Norton-Simon mathematical modeling." Breast Dis **31**(1): 7-18.

26. Tumeh, P. C., C. L. Harview, J. H. Yearley, I. P. Shintaku, E. J. Taylor, L. Robert, B. Chmielowski, M. Spasic, G. Henry, V. Ciobanu, A. N. West, M. Carmona, C. Kivork, E. Seja, G. Cherry, A. J. Gutierrez, T. R. Grogan, C. Mateus, G. Tomasic, J. A. Glaspy, R. O. Emerson, H. Robins, R. H. Pierce, D. A. Elashoff, C. Robert and A. Ribas (2014). "PD-1 blockade induces responses by inhibiting adaptive immune resistance." Nature **515**(7528): 568-571.

27. Weber, J., O. Hamid, A. Amin, S. O'Day, E. Masson, S. M. Goldberg, D. Williams, S. M. Parker, S. D. Chasalow, S. Alaparthy and J. D. Wolchok (2013). "Randomized phase I pharmacokinetic study of ipilimumab with or without one of two different chemotherapy regimens in patients with untreated advanced melanoma." Cancer Immun **13**: 7.

28. Weber, J., J. A. Thompson, O. Hamid, D. Minor, A. Amin, I. Ron, R. Ridolfi, H. Assi, A. Maraveyas, D. Berman, J. Siegel and S. J. O'Day (2009). "A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma." Clin Cancer Res **15**(17): 5591-5598.

29. Wolchok, J. D., A. Hoos, S. O'Day, J. S. Weber, O. Hamid, C. Lebbe, M. Maio, M. Binder, O. Bohnsack, G. Nichol, R. Humphrey and F. S. Hodi (2009). "Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria." Clin Cancer Res **15**(23): 7412-7420.

30. Wolchok, J. D., H. Kluger, M. K. Callahan, M. A. Postow, N. A. Rizvi, A. M. Lesokhin, N. H. Segal, C. E. Ariyan, R. A. Gordon, K. Reed, M. M. Burke, A. Caldwell, S. A. Kronenberg, B. U. Agunwamba, X. Zhang, I. Lowy, H. D. Inzunza, W. Feely, C. E. Horak, Q. Hong, A. J. Korman, J. M. Wigginton, A. Gupta and M. Sznol (2013). "Nivolumab plus Ipilimumab in Advanced Melanoma." N Engl J Med.

31. Zitvogel, L., L. Apetoh, F. Ghiringhelli and G. Kroemer (2008). "Immunological aspects of cancer chemotherapy." Nat Rev Immunol **8**(1): 59-73.