ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A012103

OPTIMICE-PCR: DE-ESCALATION OF THERAPY IN EARLY-STAGE TNBC PATIENTS WHO ACHIEVE PCR AFTER NEOADJUVANT CHEMOTHERAPY WITH CHECKPOINT INHIBITOR THERAPY

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[X]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[ ]	Data Submission / Forms changes		
[ ]	Editorial / Administrative changes		
[X]	Other: Updated Pembrolizumab CAEPR		

The changes included in this update to A012103 have been made in response to the NCI Action Letter from Dr. Brian Ko. This Action Letter is posted on the A012103 study page on the CTSU website. Therefore, the model consent form has been revised to incorporate these new risks, consistent with the NCI Model Consent Template instructions. A revised CAEPR for pembrolizumab with new risks has been added to the protocol. The model consent form has been updated, however, there are no changes to the risk/benefit ratio.

No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site.

Patient reconsent is required for patients who have consented but have not received protocol treatment and patients who are currently receiving treatment on the pembrolizumab arm. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Section 9.4 (Comprehensive Adverse Events and Potential Risks List (CAEPR) for pembrolizumab (MK-3475, NSC 776864)

This section has been revised to include the updated pembrolizumab (MK-3475) CAEPR (Version 2.9, January 31, 2025) provided by CTEP. Changes from Version 2.8 to Version 2.9 include the following:

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Anemia

- Changed to Less Likely from Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution: Constipation; Cough; Dyspnea

- Deleted Risk:
  - Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution: Alopecia; Dry skin

UPDATES TO THE MODEL CONSENT:

What risks can I expect from taking part in this study?

Based on the updated CAEPR described above, the following changes have been made to the NCI condensed risk profile for pembrolizumab (MK-3475) (found under "Possible Side Effects of Pembrolizumab"):

- The tables under the **"Possible Side Effects of Pembrolizumab"** heading have been updated per CAEPR Version 2.9 with the following risk list changes:

  - The Table Version Date has been updated to Version 2.9 January 31, 2025
  - Increase in Risk Attribution:
    - Changed to Common from Occasional: Anemia which may require blood transfusion
    - Changed to Occasional from Rare: Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath
    - Changed to Occasional from Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Constipation; Cough
  - Provided Further Clarification:
    - Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives (under Occasional) is now reported as Skin: itching; acne; rash (can be severe); blisters and peeling on the skin; skin changes; hives (under Occasional).
    - Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin, diarrhea or muscle weakness (under Rare and Serious), should have been reported as Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin (under Rare and Serious).

A replacement protocol and model consent form have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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Commercial agent(s): Pembrolizumab (NSC #776864)
IND Holder: Alliance; IND #163952
ClinicalTrials.gov Identifier: NCT05812807

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Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/SWOG, CCTG/Canadian Cancer Trials Group

Study Resources:

Expedited Adverse Event Reporting https://ctepcore.nci.nih.gov/ctepaers	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

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Protocol-related questions may be directed as follows:

Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox pharmacovigilance@alliancenctn.org
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Washington University (WUSTL)
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

OPTIMICE-PCR: DE-ESCALATION OF THERAPY IN EARLY-STAGE TNBC PATIENTS WHO ACHIEVE PCR AFTER NEOADJUVANT CHEMOTHERAPY WITH CHECKPOINT INHIBITOR THERAPY

Eligibility Criteria (see Section 3.0)

-Age ≥ 18 years
-ECOG Performance Status 0-2
-History of clinical stage T1cN1-2 or T2-4N0-2 (clinical stage II or III prior to preoperative therapy) breast cancer at time of diagnosis, per AJCC 8th edition
-Patients must have no residual invasive disease in the breast or lymph nodes after the completion of neoadjuvant therapy
-ER and PR ≤10%; HER2-negative by ASCO/CAP guidelines (IHC and FISH)
-If invasive disease was present in both breasts, participation in the study is permitted as long as the eligibility criteria are met for both tumors/breasts.

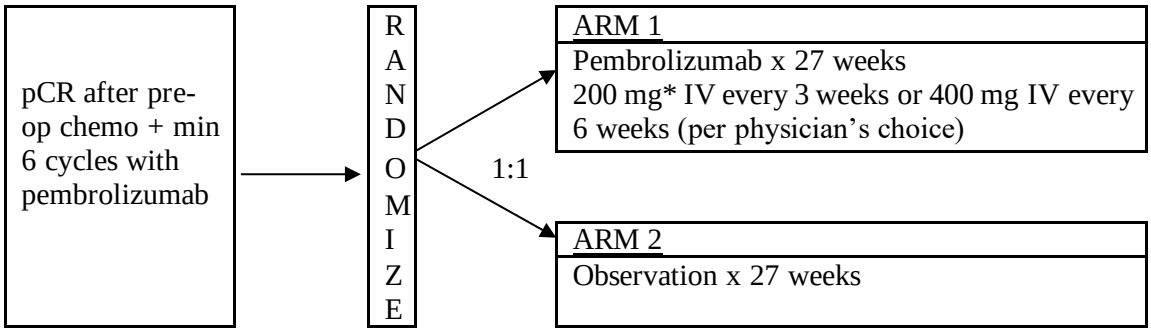
Required Initial Laboratory Values

ANC	≥ 1000/mm^3
Platelet count:	≥ 100,000/mm^3
eGFR:	≥ 15 mL/min/1.73m^2
Total bilirubin:	≤ 1.5 x ULN*
AST/ALT:	≤ 3 x ULN

*Patients with Gilbert's disease with a total bilirubin ≤ 2.5 x ULN and direct bilirubin within normal limits are permitted.

-Patients must have received neoadjuvant chemotherapy in combination with pembrolizumab for a minimum of 6 cycles. All systemic chemotherapy must have been completed preoperatively.
-An interval of no more than 12 weeks between the completion date of the final surgery and the date of randomization. See Section 3.2.4.2.
-Use of investigational anti-cancer agents must be discontinued at time of registration.
-If breast-conserving surgery was performed but patient will not be receiving breast radiation, the patient is not eligible.
-Adequate excision per Section 3.2.4.4
-Not pregnant and not nursing
-Patients must be willing to provide tumor tissue from diagnostic core biopsy. If inadequate tumor tissue is available, patients are still eligible to participate in the trial.
-No stage IV (metastatic) breast cancer
-Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
-No history of any prior (ipsi- or contralateral) invasive breast cancer. Prior DCIS is allowed.
-No evidence of recurrent disease following preoperative therapy and surgery.
-No known active liver disease, e.g. due to HBV, HCV, autoimmune hepatic disorders, or sclerosing cholangitis
-Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
-Patients with known HIV infection who are on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible for this trial.
-No history of intolerance, including Grade 3 or 4 infusion reaction or hypersensitivity to pembrolizumab or murine proteins or any components of the product. See Section 3.2.8.8.
-No medical conditions that require chronic systemic steroids (>10 mg prednisone daily or equivalent) or any other form of immunosuppressive medications and has required such therapy in the last two years. See Section 3.2.8.9.
-Patients who are unable or unwilling to comply with the requirements of the protocol per investigator assessment are not eligible.

Schema



*For Canadian sites only: Pembrolizumab 2 mg/kg (maximum dose to 200 mg) IV is alternative dosing permitted at CCTG sites.

Treatment or observation is to continue for 27 weeks or until unacceptable adverse event. Patients will be followed for 5 years after registration or recurrence. Thereafter, patients will be followed annually (+/- 3 months) for overall survival for a total of 10 years after registration.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Until institutions receive a formal notice from the Alliance regarding termination to patient follow-up, institutions must not close this trial with the IRB of record for the study. Please contact the Alliance Regulatory team at regulatory@alliancenctn.org with any questions.

Table of Contents

1.0 BACKGROUND

1.1 Rationale for Selected Approach and Trial Design

Triple-negative breast cancer (TNBC), which lacks expression of the estrogen receptor (ER) and progesterone receptor (PR), as well as overexpression of HER2, accounts for approximately 15% of invasive breast cancers [1]. Early-stage TNBC typically responds well to neoadjuvant chemotherapy, with pathologic complete response (pCR) rates of approximately 25-33% [2, 3]. Patients who achieve a pCR after neoadjuvant therapy have a significantly lower risk of recurrence than patients with residual invasive disease. The CTNeoBC pooled analysis demonstrated a strong association between pCR and event-free survival (EFS; HR: 0.24; 95% CI: 0.18-0.33) and overall survival (OS; HR: 0.16; 95% CI: 0.11-0.25) in patients with early-stage TNBC who received neoadjuvant therapy [4]. In addition, a recent meta-analysis of 36,480 patients with early-stage TNBC revealed that patients who achieved pCR after neoadjuvant chemotherapy had improved invasive disease-free survival (iDFS) and OS compared to patients who received adjuvant chemotherapy [5]. Another meta-analysis of 27,895 early-stage breast cancer patients revealed that patients who achieved a pCR after neoadjuvant chemotherapy derived no further survival benefit from additional adjuvant systemic chemotherapy [6]. These findings suggest that adjuvant systemic therapy may not be necessary for early-stage TNBC patients who achieve a pCR after neoadjuvant chemotherapy.

The addition of immune checkpoint inhibitors (ICIs) to neoadjuvant chemotherapy significantly improves the rates of pCR in TNBC. The randomized, double-blind phase III Impassion031 trial enrolled patients with stage II-III TNBC, who were randomized 1:1 to receive neoadjuvant chemotherapy plus atezolizumab 840 mg or placebo every 2 weeks. Chemotherapy consisted of nab-paclitaxel 125 mg/m^2 every week for 12 weeks, followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks for 8 weeks. Co-primary endpoints were pCR in all randomized patients in the ITT population and in PD-L1-positive patients (SP142 IC $\geq$ 1%). The pCR rate was 58% (95% CI: 50%-65%) in the atezolizumab plus chemotherapy arm and 41% (95% CI: 34%-49%) in the placebo plus chemotherapy arm (one-sided p = 0.0044 [significance boundary 0.0184]). In the PD-L1-positive population, the pCR was 69% (95% CI: 57%-79%) in the atezolizumab plus chemotherapy group and 49% (95% CI: 38%-61%) in the placebo plus chemotherapy group (one-sided p = 0.021 [significance boundary 0.0184]). Impassion031 was not formally powered for EFS, iDFS, or OS [7].

Additional trials of neoadjuvant ICIs in combination with chemotherapy have indicated that achievement of a pCR can result in improved survival outcomes for patients with early-stage TNBC. The randomized phase II GeparNuevo trial investigated the addition of durvalumab to standard neoadjuvant chemotherapy in patients with early-stage TNBC. The primary endpoint was pCR; secondary endpoints included iDFS, distant disease-free survival (DDFS), and OS. Patients were randomized to receive durvalumab 1.5 g or placebo every 4 weeks. Durvalumab 0.75 g or placebo was given for the first two weeks (window phase), followed by durvalumab or placebo plus nab-paclitaxel 125 mg/m^2 weekly for 12 weeks, then durvalumab or placebo plus epirubicin/cyclophosphamide every 2 weeks for 4 cycles. The pCR rate was 53.4% (95% CI: 42.5%-61.4%) with durvalumab versus 44.2% (95% CI: 33.5%-55.3%) with placebo (OR = 1.45; 95% CI: 0.80-2.63; unadjusted Wald p = 0.224). Durvalumab effect was seen only in the window cohort (pCR 61.0% versus 41.4%; OR = 2.22; 95% CI: 1.06-4.64, p = 0.035; interaction p = 0.048) [8]. After a median follow-up of 42.2 months, the 3-year iDFS was 92.0% in patients who achieved pCR vs. 71.9% in patients who did not achieve pCR (log-rank p = 0.002). The 3-year iDFS was 84.9% with durvalumab versus 76.9% with placebo (HR: 0.54; 95% CI: 0.27-1.09; stratified log-rank p = 0.0559). The 3-year DDFS was 91.4% vs. 79.5% (HR: 0.37; 95% CI: 0.15-0.87, p = 0.0148) and the 3-year OS was 95.1% versus 83.1% (HR: 0.26; 95% CI: 0.09-0.79; p = 0.0076) in patients who received durvalumab or placebo, respectively. These results

indicate that the addition of durvalumab to standard neoadjuvant chemotherapy significantly improved long-term outcomes in patients with early-stage TNBC, even without continuation after surgery [9].

Finally, in the phase III KEYNOTE-522 study, patients with treatment-naïve stage II-III TNBC were randomized 2:1 to receive neoadjuvant pembrolizumab or placebo in combination with two phases of neoadjuvant chemotherapy. The first phase consisted of 4 cycles of paclitaxel plus carboplatin, followed by 4 cycles of doxorubicin or epirubicin plus cyclophosphamide. After surgery, patients randomized to neoadjuvant pembrolizumab received an additional 27 weeks of adjuvant pembrolizumab, whereas patients on the placebo arm did not. The co-primary endpoints were pCR and EFS. Primary efficacy analysis at the first interim analysis revealed that the pCR rate was 64.8% in the pembrolizumab arm (95% CI: 59.9%-69.5%) versus 51.2% in the placebo arm (95% CI: 44.1%-58.3%; $p < 0.001$) [10]. Per the study protocol, pCR was not formally tested at the third interim analysis. Rather, a prespecified descriptive analysis was used to update pCR when data were available for all participants (n = 1174). At this point, the combination of pembrolizumab plus neoadjuvant chemotherapy continued to show a clinically meaningful increase in pCR over the placebo group. The pCR rates were 63.0% (95% CI: 59.5%-66.4%) in the pembrolizumab arm versus 55.5% (95% CI: 50.6%-60.6%) in the placebo arm [11]. At the fourth interim analysis, the EFS was 84.5% on the pembrolizumab arm versus 76.8% on the placebo arm ($p = 0.00031$). This result met the pre-specified p-value boundary of 0.00517 for statistical significance [12]. A series of pre-specified EFS sensitivity analyses confirmed the treatment benefit of neoadjuvant pembrolizumab plus chemotherapy over placebo plus chemotherapy. Furthermore, the benefit of pembrolizumab was maintained across patient subgroups and did not differ based on LDH level, PD-L1 status, disease stage, nodal status, or menopausal status [13].

Given the sustained EFS benefit with the addition of pembrolizumab with mature follow-up from KEYNOTE-522, the addition of pembrolizumab for stage II-III TNBC was approved in late July 2021. The combination of neoadjuvant pembrolizumab plus chemotherapy followed by 27 weeks of adjuvant pembrolizumab has now become standard of care for patients with stage II-III TNBC. However, the trial does not investigate whether adjuvant ICI therapy is necessary in this patient population. The best EFS outcomes were observed in patients who achieved a pCR, whether on pembrolizumab (3-year EFS: 94.4%) or placebo (3-year EFS: 92.5%). Among patients who did not achieve a pCR, the 3-year EFS was 67.4% for patients on pembrolizumab versus 56.8% for patients on placebo [12]. These findings further suggest that achieving a pCR after neoadjuvant therapy is the primary driver of improved survival outcomes. This could eliminate the need for adjuvant ICI therapy, which can introduce substantial additional toxicity [12] and financial cost for patients.

In the initial development of pembrolizumab across various tumour types, weight based and fixed dose has been evaluated. In a systematic review in 2016, it concluded that the tested doses of 2 mg/kg to 10 mg/kg every 3 weeks was statistically similar and was superior to 0.3 mg/kg every 3 weeks in terms of efficacy[14]. Furthermore, in an evaluation of exposure-response relationships and multiple dosing of pembrolizumab indicates that 2 mg/kg every 3 weeks with a 200 mg upper cap dose is the most efficient dosage to deliver target engagement of 95% based on the trough interval concentration[15]. Thus an alternative weight based dosing of pembrolizumab (2 mg/kg with a 200 mg upper cap dose) will be permitted on study for the pembrolizumab arm in centres in which this is the only option for delivery and reimbursement of pembrolizumab for inclusion on study.

The central hypothesis of OptimICE-pCR is that additional, adjuvant checkpoint inhibition is unlikely to improve survival outcomes for patients with early-stage TNBC who achieve a pCR after neoadjuvant ICI-containing therapy. Thus, the focus of the trial is on de-escalating adjuvant

therapy for these patients to avoid unnecessary toxicity and cost. To this end, the primary goal is to determine whether patients who achieve pCR to checkpoint inhibitor-based neoadjuvant therapy can achieve a similar recurrence-free survival (RFS) rate with observation compared to adjuvant pembrolizumab monotherapy.

1.2 Trial Importance

OptimICE-pCR will investigate whether adjuvant checkpoint inhibition offers any additional RFS benefit to early-stage TNBC patients who achieve a pCR after neoadjuvant chemotherapy with checkpoint inhibition. If there is no significant difference in RFS, then patients who achieve a pCR can avoid the additional toxicity, inconvenience, and cost of continued ICI treatment.

1.3 Pertinent Data

In the phase III KEYNOTE-522 trial, all patients who received pembrolizumab in the neoadjuvant setting continued to receive adjuvant pembrolizumab after surgery [10]. Currently, it is not known whether adjuvant pembrolizumab confers additional survival benefit in patients who achieved a pCR after receiving pembrolizumab-containing neoadjuvant therapy. A recent meta-analysis suggested that adjuvant chemotherapy does not offer additional survival benefits in early-stage TNBC patients who achieved a pCR after neoadjuvant chemotherapy [6]. In addition, recent results from the randomized phase II GeparNuevo trial demonstrated that the addition of durvalumab to standard neoadjuvant chemotherapy significantly improved long-term outcomes in patients with early-stage TNBC, even without continuation of durvalumab in the adjuvant setting [9]. Thus, in the OptimICE-pCR study of early-stage TNBC patients who achieve a pCR after neoadjuvant ICI-containing therapy, the control group will receive adjuvant pembrolizumab, versus observation in the experimental group. In this de-escalation setting, the goal is to determine whether observation confers non-inferior survival outcomes.

1.4 Protocol Summary

OptimICE-pCR is a randomized phase III trial that is enrolling early-stage TNBC patients with a pCR after the completion of neoadjuvant therapy consisting of a minimum of 6 cycles of chemotherapy in combination with an ICI. Patients are randomized 1:1 to receive 27 weeks of adjuvant pembrolizumab or observation. Schedule of pembrolizumab is per physician's choice, with a choice of either pembrolizumab 200 mg IV administered on day 1 of each 21-day cycle or 400 mg IV administered on day 1 of every 42-day cycle. If every 42 day (6 week dosing) is chosen, then 4 doses of 400 mg IV every 42 days can be administered followed by one cycle of 200 mg IV every 21 days, so that a total of 27 weeks of pembrolizumab is received.

2.0 OBJECTIVES

2.1 Primary objective

To evaluate whether observation results in a non-inferior RFS compared to adjuvant pembrolizumab in early-stage TNBC patients who achieve a pCR after neoadjuvant chemotherapy with pembrolizumab.

Hypothesis: Patients with clinical stage II-III TNBC who achieve a pCR after neoadjuvant chemotherapy with immune checkpoint inhibitor (ICI) therapy and who are observed without additional adjuvant systemic therapy will not have inferior RFS compared to patients who receive 27 weeks of adjuvant pembrolizumab. This will be designed as a de-escalation study, with a 3-year RFS rate of 94% estimated in the pembrolizumab arm and non-inferiority of the observation arm declared if the 3-year RFS rate is 91% or higher.

2.2 Secondary objectives

To evaluate whether observation compared to adjuvant pembrolizumab impacts the following:

2.2.1 RFS by stage at presentation and by receipt of prior anthracycline therapy

2.2.2 Adverse event rate: difference in Grade 3 or higher adverse event rates overall and Grade 3 or higher irAE rates

2.2.3 Overall Survival (OS)

2.2.4 Locoregional recurrence (LRR, both isolated LRR as first events and LRR events simultaneous with DM)

2.2.5 RFS, LRR, OS, adverse events, and QOL by age (≤45, 46-65, and >65), race, and ethnicity

2.2.6 Adverse events related to receipt of radiotherapy (as defined in Section 13.4)

2.3 Quality of Life and Patient-Reported Outcomes Objectives

2.3.1 Quality of Life - Primary objective

To compare quality of life (QOL) at approximately 27 weeks as assessed by the FACT-B Trial Outcome Index between patients randomized to adjuvant pembrolizumab versus observation.

2.3.2 Quality of Life - Exploratory objectives

- To describe trajectories of QOL over time among patients randomized to adjuvant pembrolizumab vs. observation
- To compare various QOL domains after approximately 27 weeks as assessed by the 5 subscales of the FACT-B Index between patients randomized to adjuvant pembrolizumab versus observation.
- To compare self-reported symptomatic adverse events as outlined in Section 14.1.1 at approximately 27 weeks assessed by the PRO-CTCAE between patients randomized to adjuvant pembrolizumab versus observation.

2.3.3 Value of Care – Primary objective

To assess the social value of de-escalation of adjuvant breast cancer immunotherapy at approximately 27 weeks and, by modelling, over a lifetime.

2.3.4 Value of Care – Secondary objectives

- To assess the value of de-escalation of breast cancer immunotherapy from the payer perspective at approximately 27 weeks and, by modelling, over a lifetime.
- To compare patient out-of-pocket costs at approximately 27 weeks between patients randomized to adjuvant pembrolizumab versus observation.
- To compare financial toxicity at approximately 27 weeks between patients randomized to adjuvant pembrolizumab versus observation.
- To compare work/productivity impairment at approximately 27 weeks between patients randomized to adjuvant pembrolizumab versus observation.

2.3.5 Value of Care – Exploratory objectives

- To describe trajectories of financial toxicity and work/productivity impairment over time from baseline to approximately 27 weeks among patients randomized to adjuvant pembrolizumab versus observation.
- To develop and assess a measure of value from the patient perspective at approximately 27 weeks. This measure, to be developed in collaboration with a patient advocate, will combine both costs and outcomes, and incorporate patient out-of-pocket costs and financial toxicity.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for four months following the last dose of study treatment due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). Breastfeeding should also be discontinued during study treatment and for four months following the last dose of study treatment.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Age ≥ 18 years**

___ **3.2.2 ECOG Performance Status 0-2**

___ **3.2.3 Triple Negative Breast Cancer**

___**3.2.3.1** Patients with a history of clinical stage T1cN1-2 or T2-4N0-2 (clinical stage II or III prior to preoperative therapy) breast cancer at time of diagnosis, according to the primary tumor-regional lymph node anatomic staging criteria of the American Joint Committee on Cancer (AJCC) 8th edition, as determined by the investigator in radiologic assessment, clinical assessment or both.

___**3.2.3.2** Patients must have no residual invasive disease in the breast or lymph nodes after the completion of neoadjuvant therapy. Residual DCIS is allowed. Isolated tumor cells are considered node-negative.

___**3.2.3.3** ER and PR ≤10%; HER2-negative by ASCO/CAP guidelines (IHC and FISH)

___**3.2.3.4** If invasive disease was present in both breasts, participation in the study is permitted as long as the eligibility criteria are met for both tumors/breasts.

___ **3.2.4 Prior Treatment**

___**3.2.4.1** Patients must have received neoadjuvant chemotherapy in combination with pembrolizumab for a minimum of 6 cycles. All systemic chemotherapy must have been completed preoperatively.

___**3.2.4.2** An interval of no more than 12 weeks between the completion date of the final surgery and the date of randomization.

Note: Adjuvant radiation can be given on study; however, it is recommended to complete adjuvant radiation prior to registration. If radiation is given on study, it is encouraged to be given concurrently with pembrolizumab if the patient is on the pembrolizumab arm, per investigator discretion. Treatment with adjuvant pembrolizumab is strongly discouraged prior to participation in this trial, but if administered (e.g., if patients are awaiting pathology results), pembrolizumab may be administered for up to 6 weeks (i.e., up to 2 q3week doses or up to one q6week dose) post-surgery and must be completed prior to registration.

___**3.2.4.3** Use of investigational anti-cancer agents must be discontinued at time of registration.

___**3.2.4.4** Adequate excision: Surgical removal of all clinically evident disease in the breast and lymph nodes as follows:

___ Breast surgery: Total mastectomy or breast-conserving surgery with histologically negative margins, including no ink on tumor for DCIS, at the time of excision.

___ For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of ductal carcinoma in-situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates DCIS at the line of resection, additional operative procedures may be performed to obtain clear margins. If DCIS is still present at the resected margin after re-excision(s), the patient must undergo total

mastectomy to be eligible. Patients with margins positive for classic lobular carcinoma in situ (LCIS) are eligible without additional resection.

___ Lymph node surgery:

___ For a patient with clinically N0 disease, a sentinel lymph node biopsy should have been performed at time of surgical evaluation, and if pathologically node positive, the patient is no longer eligible. Isolated tumor cells are considered node-negative.

___ For a patient with clinically N1 disease at diagnosis (with positive results from a fine-needle aspiration, core biopsy, or sentinel node biopsy performed prior to preoperative therapy) additional surgical evaluation of the axilla following preoperative therapy is required.

- If they become cN0 (no palpable adenopathy), then a sentinel lymph node biopsy could have been performed at time of surgery (axillary dissection would also be permitted); if the sentinel lymph node biopsy is positive, the patient is no longer eligible

___ If sentinel node biopsy performed before preoperative therapy was negative, no additional surgical evaluation of the axilla is required after preoperative therapy. If sentinel node biopsy performed before preoperative therapy was positive, an ALND is required after preoperative therapy.

___ If the only sentinel node identified by isotope scan is in the internal mammary chain, surgical evaluation of the axilla is still required.

___ If sentinel node evaluation after preoperative therapy is negative, no further additional surgical evaluation of the axilla is required.

___ Axillary dissection without sentinel node evaluation is permitted as the initial or sole axillary evaluation after preoperative therapy.

___3.2.4.5 If breast-conserving surgery was performed but patient will not be receiving breast radiation, the patient is not eligible.

___ **3.2.5 Not pregnant and not nursing,** because this study involves an agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative serum or urine pregnancy test done ≤ 7 days prior to randomization is required.

___ **3.2.6 Adequate hepatic, renal, and bone marrow function.**

Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 1,000/mm^3
Platelet Count	≥ 100,000/mm^3
Estimated glomerular filtration rate (eGFR)	≥ 15 mL/min/1.73m^2
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN)*
AST(SGOT) / ALT(SGPT)	≤ 3 x institutional ULN

*Patients with Gilbert's disease with a total bilirubin ≤ 2.5 x ULN and direct bilirubin within normal limits are permitted.

___ **3.2.7** Patients must be willing to provide tumor tissue from the diagnostic core biopsy. If inadequate tumor tissue is available, patients are still eligible to participate in the trial.

___ **3.2.8 Comorbid conditions**

___3.2.8.1 No stage IV (metastatic) breast cancer

___3.2.8.2 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

___3.2.8.3 No history of any prior (ipsi- or contralateral) invasive breast cancer. Prior DCIS is allowed.

___3.2.8.4 No evidence of recurrent disease following preoperative therapy and surgery.

___3.2.8.5 No known active liver disease, e.g. due to HBV, HCV, autoimmune hepatic disorders, or sclerosing cholangitis

___3.2.8.6 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

___3.2.8.7 Patients with known HIV infection who are on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible for this trial.

___3.2.8.8 No history of intolerance, including Grade 3 or 4 infusion reaction or hypersensitivity to pembrolizumab or murine proteins or any components of the product.

Note: Prior immune-related adverse events (irAEs) are allowed if they resolved to ≤ grade 1 and the patient tolerated subsequent therapy without requiring chronic steroids for the irAE.

___3.2.8.9 No medical conditions that require chronic systemic steroids (>10 mg prednisone daily or equivalent) or any other form of immunosuppressive medications and has required such therapy in the last two years. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic therapy

___3.2.8.10 Patients who are unable or unwilling to comply with the requirements of the protocol per investigator assessment are not eligible.

- -

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Alliance Patient Number _____

Patient's Initials (L, F, M) _____

Research RN/CRP Signature and Date _____

Physician Signature and Date _____

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this study.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges; and
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓	
GCP training	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional)	✓	✓	✓	

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating through the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;

- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.1 Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to CTSU members' website (https://www.ctsu.org)
- Click on *Protocols* in the upper left of the screen:
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A012103*.
- Click on *Documents, Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

4.2.4 Checking Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go:

- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.5 Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application which is accessible via the Delegation Log link on the CTSU members' website or directly at https://dtl.ctsu.org. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

Canadian sites participating under the Canadian Cancer Trials Group (CCTG) should complete the DTL in CCTG's Roster Interface Program & Participants List Environment (RIPPLE) application when CCTG holds the Clinical Trials Agreement with Health Canada. RIPPLE is integrated with the CTSU DTL application for this trial.

4.3 Patient Registration Requirements

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.3.2 Patient-reported outcomes (optional)

This study includes the use of the optional patient-completed measures: PRO-CTCAE, FACT-B, WPAI:SHP, FACIT-COST and CoPaQ. These measures are available in English and Spanish.

Patient questionnaire booklets

The current version of the patient-completed booklets can be downloaded from the CIRB Approved Documents tab of the A012103 page of the CTSU website at the time of patient registration. Patient questionnaire booklets will only be available in English and Spanish.

4.4 Patient registration/randomization procedures (Step 1)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS)

for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN Corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in the Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.5 Registration to substudies and companion studies

4.5.1 Registration to Substudies described in Section 14.0

There is one optional substudy within Alliance A012103. This correlative science study must be offered to all patients enrolled on Alliance A012103 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A012103 is:

- Quality of Life Substudy, Alliance A012103-HO1 (Section 14.1)

If a patient answers "yes" to "I choose to take part in the Quality of Life study and will fill out these forms," Question #1 in the model consent, they have consented to participate in the substudy described in Section 14.1. Patients registered to A012103-HO1 must speak either English or Spanish. The patient should be registered to Alliance A012103-HO1 at the same time they are registered to the treatment trial (A012103). Questionnaires should be submitted per Section 6.3.

CCTG sites: Please see Section 6.3.1 for information regarding French-translated questionnaires.

4.6 Stratification Factors and Treatment Assignments

The randomization routine is found in Section 13.0 (Statistical Considerations).

4.6.1 Stratification Factors

1) Nodal status prior to preoperative chemotherapy: node-positive (by FNA, core biopsy, or sentinel node evaluation) vs. node-negative
2) Receipt of preoperative anthracycline chemotherapy: yes vs. no

4.6.2 Treatment Assignments

The factors defined in Section 4.6.1 will be used as stratification factors.

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

1) Pembrolizumab
2) Observation

4.7 Co-enrollment

Co-enrollment on SWOG S2212 is allowed. Co-enrollment on Alliance A151804 (irAE biorepository study) is strongly encouraged.

Please contact the Study Chair, Primary Statistician, and Executive Officer for questions regarding co-enrollment on other trials.

5.0 STUDY CALENDARS

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-study Testing Intervals

The pre-study testing intervals are guidelines only. When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 28 DAYS before registration: All laboratory studies, history and physical.

5.1 Pembrolizumab (Arm 1) Study Calendar

	Prior to Registration*	Day 1 of each cycle (+/- 7 days)**	13-14 weeks after start of treatment (+/- 7 days)***	Within 3-9 weeks after last dose of treatment (+/- 7 days)**	Post treatment follow up****
Tests & Observations					
H&P, vital signs, weight, ECOG PS	X(1)	X(1)			X
Solicited Medical History – Immune-Related Adverse Events	X(2)				
Adverse Event Assessment - CTCAE	X	X			
Adverse Event Assessment - PRO-CTCAE	X(3)	X(3)			
Laboratory Studies					
CBC, Differential, Platelets	X	X			
Creatinine	X	X			
Albumin, glucose	X	X			
AST, ALT, Alk. Phos., Bili	X	X		X	
Serum or Urine HCG	X(4)				
TSH	X(5)		X		A(5)
Free T4	X(5)		X(5)		A(5)
Cortisol	X		X		A(5)
Tissue and blood samples	*Within 21 days after registration, 27 weeks/EOT, 6 months after EOT, 3 years after registration, and at recurrence. See Section 6.2.*				
Staging					
Mammogram, breast US or MRI	B				B
Correlative studies: For patients who consent to participate					
QOL/Value of Care	*After consent but prior to registration, 12 weeks after registration, and 27 weeks after registration. See Section 6.3 and Section 14.1.*				

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 72 hours prior to day of treatment.

** For patients on pembrolizumab 200 mg, a cycle is 21 days in length. For patients on pembrolizumab 400 mg, a cycle is 42 days in length.

*** This time point is intended to align with the corresponding study-related visit (C5D1 for 3-week dosing, C3D1 for 6-week dosing). A separate visit to collect these labs is not needed.

**** Physical examinations are required every 6 months (+/- 2 months, based on previous visit) through 5 years after registration or recurrence. Thereafter, patients will be followed annually (+/- 3 months) for overall survival for a total of 10 years after registration. Clinical follow-up visits may be done outside of the registering institution if patient records are available. See also Section 12.0.

A To be collected every 6 months (+/- 2 months) until one year after last dose of study treatment.

B Patients must have had a mammogram, breast ultrasound or MRI within one year prior to registration. Thereafter, mammogram, breast ultrasound, or MRI is required annually (+/- 60 days) during clinical follow-up, unless the patient had bilateral mastectomies.

1 ECOG PS to be collected at baseline only.

2 Prior immune (pembrolizumab)-related adverse events (irAEs) are to be entered in the "Medical History: Solicited Conditions" CRF in Medidata Rave after registration. Solicited irAEs include myocarditis, colitis, pneumonitis, dermatitis radiation, rash maculo-papular, adrenal insufficiency, hypothyroidism, and peripheral sensory neuropathy.

3 Optional. Please refer to the CTSU website for PRO-CTCAE items.

4 For women of childbearing potential (see Section 3.2.5). Must be done ≤ 7 days prior to registration.

5 As clinically indicated

5.2 Observation (Arm 2) Study Calendar

	Prior to Registration*	12 weeks (+/- 28 days) after registration	27 weeks (+/- 28 days) after registration	Post-treatment follow up**
Tests & Observations				
H&P, vital signs, weight, ECOG PS	X(1)	X(1)	X(1)	X(1)
Solicited Medical History – Immune-Related Adverse Events	X(2)			
Adverse Event Assessment - CTCAE	X	X	X	
Adverse Event Assessment - PRO-CTCAE	X(3)	X(3)	X(3)	
Laboratory Studies				
CBC, Differential, Platelets	X	X(5)	X(5)	
Creatinine	X	X(5)	X(5)	
Albumin, glucose	X	X(5)	X(5)	
AST, ALT, Alk. Phos., Bili	X	X(5)	X(5)	
Serum or Urine HCG	X(4)			
TSH, Free T4	X(5)	X(5)	X(5)	A(5)
Cortisol	X	X(5)	X(5)	A(5)
Tissue and blood samples	*Within 21 days after registration, 27 weeks/EOT, 6 months after EOT, 3 years after registration, and at recurrence. See Section 6.2.*			
Staging				
Mammogram, breast US or MRI	B			B
Correlative studies: For patients who consent to participate				
QOL/Value of Care	*After consent but prior to registration, 12 weeks after registration, and 27 weeks after registration.* *See Section 6.3 and Section 14.1.*			

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 72 hours prior to day of treatment.

** Physical examinations are required every 6 months (+/- 2 months, based on previous visit) through 5 years after registration or recurrence. Thereafter, patients will be followed annually (+/- 3 months) for overall survival for a total of 10 years after registration. Clinical follow-up visits may be done outside of the registering institution if patients' records are available. See also Section 12.0.

A To be collected as clinically indicated every 6 months (+/- 2 months) until one year after registration.

B Patients must have had a mammogram, breast ultrasound or MRI within one year prior to registration. Thereafter, mammogram, breast ultrasound, or MRI is required annually (+/- 60 days) during clinical follow-up, unless the patient had bilateral mastectomies.

1 ECOG PS to be collected at baseline only.

2 Prior immune (pembrolizumab)-related adverse events (irAEs) are to be entered in the "Medical History: Solicited Conditions" CRF in Medidata Rave after registration. Solicited irAEs include myocarditis, colitis, pneumonitis, dermatitis radiation, rash maculo-papular, adrenal insufficiency, hypothyroidism, and peripheral sensory neuropathy.

3 Optional. Please refer to the CTSU website for PRO-CTCAE items.
4 For women of childbearing potential (see Section 3.2.5). Must be done ≤ 7 days prior to registration.
5 As clinically indicated

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located

on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management* > *Rave* section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.1.4 Supporting documentation to be submitted to the Alliance

This study requires supporting documentation for diagnosis, pathologic response, and any evidence of recurrence. Supporting documentation will include clinic notes and pathology reports. These must be submitted at the following time points:

- Clinic note from consent visit (baseline)
- Radiation treatment summary report (if applicable)
- Diagnostic core biopsy report (baseline)
- Surgical pathology report (baseline)
- Clinic notes from recurrence (at recurrence, if applicable)
- Biopsy report from recurrence (at recurrence, if applicable)

Supporting documentation is to be submitted via Rave and must be redacted to remove PII.

6.2 Specimen collection and submission

The Alliance A012103 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS and CTSU websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

For all patients registered to A012103: Whole blood and tissue submissions are required for biobanking for future research at the time points listed below. Rationale and methods for the scientific components of these studies are described in Section 14.0.

For patients consenting to optional biobanking: All participating institutions must ask patients for their consent to participate in biobanking for future research, although patient participation is optional. Biomarker and pharmacogenetic studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, blood will be collected at the time point listed below for these studies:

	≤ 21 days after registration	**27 weeks/End of treatment or observation (+/- 2 weeks)**	**6 months after end of treatment or observation (+/- 4 weeks)**	**3 years after registration (+/- 4 weeks)**	**At recurrence (if applicable)**
Mandatory for all patients registered to A012103					
Whole blood in EDTA tubes	2x10 mL	2x10 mL	2x10 mL	2x10 mL	2x10 mL
Tissue	X[1]				X[2]
For patients consented to A012103 optional biobanking					
Whole blood in EDTA tubes					3x10 mL

1. From both diagnostic core biopsy and from surgery if possible.

2. Tumor tissue from a site of tumor recurrence (when applicable), only if tissue was collected per standard of care. No new research biopsy is required.

6.3 Submission of Patient Completed Measures

The current version of the patient-completed booklets can be downloaded from the CIRB Approved Documents tab of the A012103 page of the CTSU website. Booklets must be given to patients to complete and patients should be instructed to return the booklets/responses to site staff (either in person, by mail, by email, or by phone), and site staff will enter patient responses into Rave. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results. The method of collection should be documented in Rave.

Please note that PRO-CTCAE is contained in a separate booklet and is optional for all patients per the study calendar. The schedule below only pertains to patients who consent to participate in the Quality of Life study. For patients registered to A012103-HO1, submit patient-completed questionnaires at the following time points:

Instrument	Baseline*	12 weeks (+/- 28 days) after registration	27 weeks (+/- 28 days) after registration
For patients registered to A012103-HO1, submit patient-completed questionnaires** at the following time points:			
FACT-B	X	X	X
WPAI:SHP***	X	X	X
FACIT-COST***	X	X	X
CoPaQ***	X	X	X

* After consent, prior to registration. Rave entry will occur after registration.

** Download questionnaires for IRB submission and review from the CIRB Approved Documents tab on the CTSU website.

*** For patients in the United States only. Canadian patients enrolled through CCTG should only complete the FACT-B and PRO-CTCAE measures.

Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

6.3.1 Patient Language Considerations

All measures are available in English and Spanish. The translated measures are available on the A012103 CTSU and Alliance study pages. Ad-hoc translation of patient-completed measures is not permitted.

CCTG institutions are to provide patient completed booklets (PRO-CTCAE and FACT-B only) translated into French to French speakers. The site is responsible for transcribing the patient responses from the French version into the English version within Medidata Rave to submit to the Alliance Statistics and Data Management Center. The institution should retain the completed French version as source documentation.

6.3.2 Instrument administered by site staff to patients

For patients who consent to participate in the Quality of Life study, one instrument, the Health Utilization Case Report Forms (CRFs), will be verbally administered to patients by a site nurse/research coordinator.

For patients in the United States registered to A012103-HO1, submit the staff-administered instrument at the following time points:

Instrument	Baseline*	12 weeks (+/- 28 days) after registration	27 weeks (+/- 28 days) after registration
For patients registered to A012103-HO1, submit the staff-administered instrument at the following time points:			
Staff-administered ViCC Questionnaire[1]	X	X	X

* After consent, prior to registration. Rave entry will occur after registration.

1. This Value in Cancer Care (ViCC) questionnaire is to be verbally administered to patients by site staff (e.g., nurse or research coordinator). The information collected will be used to complete the Health Care Utilization CRFs in Rave. A help sheet for collecting information for this questionnaire is available on the A012103 page of the CTSU website. This measure only applies to patients in the United States; Canadian patients at CCTG sites should not complete this measure.

7.0 TREATMENT PLAN/INTERVENTION

Patients are randomized 1:1 to receive 27 weeks of adjuvant pembrolizumab or observation.

Protocol treatment is to begin ≤ 7 calendar days after registration.

For questions regarding treatment, please see the study contacts page.

Patients must have completed neoadjuvant chemotherapy in combination with pembrolizumab, followed by definitive breast surgery, prior to the start of protocol treatment.

Treatment with adjuvant pembrolizumab is strongly discouraged prior to participation in this trial, but if administered (e.g., if patients are awaiting pathology results), pembrolizumab may be administered for up to 6 weeks post-surgery and must be completed prior to registration. If a patient is randomized to receive adjuvant pembrolizumab on this trial, the first dose of pembrolizumab on study should be administered no sooner than 21 days after their last dose of adjuvant pembrolizumab.

It is acceptable for individual pembrolizumab doses to be delivered within a 7-calendar-day window before and after the protocol-defined date for Day 1 of a new cycle. In addition, patients are permitted to have a new cycle of pembrolizumab delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

7.1 Pembrolizumab (Arm 1)

Agent	Dose*	Route	Day	ReRx
Pembrolizumab	200 mg *or* 400 mg**	IV***	Day 1	every 21 days every 42 days
	or (for Canadian sites only): 2 mg/kg (capped to 200 mg max)	IV***	Day 1	every 21 days

* Per physician's choice

** Dosing schedule will be 400 mg q6w x 4 doses, followed by 200 mg q3w x 1 dose, for a total of 27 weeks of pembrolizumab treatment.

*** Infused over approximately 30 minutes (range: 25-40 minutes)

See Section 8.1 for information regarding ancillary therapy, concomitant medications, and supportive care.

7.2 Observation (Arm 2)

Patients on the observation arm will receive no protocol treatment but will be assessed at standard clinical intervals to include baseline, 12 weeks and 27 weeks after registration (see Section 5.0). No non-protocol treatment is allowed for patients on the observation arm except adjuvant radiation therapy. Any adjuvant chemotherapy must be completed prior to registration and may not be given while patients are on the observation arm. Treatment with adjuvant

pembrolizumab is strongly discouraged prior to participation in this trial, but if administered (e.g., if patients are awaiting pathology results), pembrolizumab may be administered for up to 6 weeks post-surgery and must be completed prior to registration.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other adjuvant systemic chemotherapy which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 **Patients should receive full supportive care while on this study.** This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records. Steroids should not routinely be used as antiemetics.

Refer to Section 8.2 for diarrhea and other irAE management.

8.1.3 **Other chemotherapeutic agents may not be administered**.

8.1.4 **Adjuvant radiation therapy** may be administered concurrently with pembrolizumab.

8.1.5 **Major non-emergent surgical procedures (e.g., requiring inpatient hospitalization)** should be avoided during the course of study treatment. If performed, it is recommended that a morning cortisol test be collected within 7 days prior to surgery. Reconstructive surgery is permitted (with preoperative cortisol test).

8.1.6 **Hypersensitivity/infusion reactions**

Treat hypersensitivity and infusion reactions to pembrolizumab per institutional standards.

8.2 Dose Modifications

Pembrolizumab may be delayed because of adverse events. No dose reductions are allowed for pembrolizumab. Pembrolizumab doses may be delayed or made up at the completion of planned therapy; this is at the treating investigator's discretion.

AERS reporting may be required for some adverse events (See Section 9.0)

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol-directed action.

8.2.1 Dose modification guidelines for pembrolizumab for drug-related adverse events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of

infusion. Dose modification and toxicity management guidelines for irAEs and infusion reactions associated with pembrolizumab are provided in the table below.

Note that non-irAEs will be managed as appropriate, following clinical practice recommendations.

General instructions:

1. For non-endocrine-related severe and life-threatening irAEs, investigators should consider the use of IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Some non-endocrine irAEs do not require steroids. For example, celiac disease induced by pembrolizumab can be controlled by diet alone.
2. For non-endocrine-related toxicities, pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment.
3. Generally, when corticosteroids are used, investigators should begin a taper when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld due to a non-endocrine irAE, pembrolizumab may generally resume after the irAE has decreased to ≤Grade 1 after a corticosteroid taper.

irAEs	**Toxicity grade (CTCAE V5.0)**	**Action with pembrolizumab**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or	Monitor participants for signs and symptoms of enterocolitis (*i.e.*, diarrhea,

	Recurrent Grade 3 or Grade 4	Permanently discontinue	equivalent) followed by taper Patients who do not respond to corticosteroids should be seen by a gastroenterologist for confirmation of the diagnosis and consideration of secondary immune suppression	abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (*i.e.* peritoneal signs and ileus) Specifically assess for celiac disease serologically, and exclude *Clostridium difficile* infection Participants with ≥Grade 2 diarrhea suspecting enterocolitis should consider GI consultation and performing endoscopy to rule out enterocolitis and assess mucosal severity 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

AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 1 or 2	Continue		Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence, any grade hyperglycemia may be an indication of beta-cell destruction and pembrolizumab-induced diabetes akin to type 1 diabetes. This should be treated as a Grade 3 event. Given this risk, exercise caution in utilizing non-insulin hypoglycemic agents in this setting. After a thorough investigation of other potential causes, which may involve a referral to an endocrinologist, follow institutional guidelines. Monitor glucose control.

	New onset T1DM (evidence of β-cell failure) or Grade 3 or 4 hyperglycemia	Withhold [d] Resume pembrolizumab when symptoms resolve and glucose levels are stable	Initiate treatment with insulin If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc.*) reported	Monitor for glucose control Strongly consider referral to endocrinologist Obtain C-peptide level paired with glucose, autoantibody levels (*e.g.* GAD65, islet cell autoantibodies), and hemoglobin A1C level
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) Provide adrenal insufficiency precautions including indications for stress dose steroids and medical alert jewelry Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Consider withholding. Resume pembrolizumab when symptoms are controlled, and thyroid function is improving	Treat with nonselective beta-blockers (*e.g.*, propranolol) or thionamides as appropriate Initiate treatment with anti-thyroid drug such as methimazole or	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist

	Grade 3 or 4	Withhold or permanently discontinue [d]	carbimazole as needed	
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (*e.g.*, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function Strongly consider referral to nephrologist
	Grade 3 or 4	Permanently discontinue		
Cardiac Events (including myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month

	Grade 2, 3 or 4	Permanently discontinue	Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or pericardiocentesis as appropriate	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

8.2.2 Pembrolizumab infusion-related reactions

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

Infusion Reactions	**NCI CTCAE Grade**	**Treatment**	**Premedication at subsequent dosing**
Mild reaction; infusion interruption not indicated; intervention not indicated	Grade 1	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Grade 2	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (*e.g.* from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Prolonged (*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Grade 3	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (*e.g.* methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing.
Life-threatening; pressor or ventilator support indicated	Grade 4	Admit participant to intensive care unit (ICU) and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Follow Grade 3 recommendations as applicable.	No subsequent dosing.

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; ECMO=extracorporeal membrane oxygenation; GI=gastrointestinal; ICU=intensive care unit; IO=immuno-oncology; ir=immune related; IV=intravenous; MRI=magnetic resonance imaging; PO=per os; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal; VAD=ventricular assist device.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (*e.g.* vasculitis and sclerosing cholangitis).

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

8.2.3 Neurological Toxicities

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue pembrolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold pembrolizumab for up to 12 weeks after event onset. [a]
	• Investigate etiology and refer patient to neurologist.
	• Initiate treatment as per institutional guidelines.
	• For general immune-mediated neuropathy:
	  ○ If event resolves to Grade 1 or better, resume pembrolizumab. [b]
	  ○ If event does not resolve to Grade 1 or better while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]
	• For facial paresis:
	  ○ If event resolves fully, resume pembrolizumab. [b]
	  ○ If event does not resolve fully while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.

Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Pembrolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before pembrolizumab can be resumed.

[c] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis, Grade 1	• Continue pembrolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue pembrolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue pembrolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue pembrolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found on the CTSU website. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Events eCRFs are used for routine AE reporting in Rave.

9.1.1 Solicited adverse events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)	PRO-CTCAE Term (for patients who consent to PRO-CTCAE collection)
Anorexia	Metabolism and nutrition disorders	Decreased appetite
Nausea	Gastrointestinal disorders	Nausea
Vomiting	Gastrointestinal disorders	Vomiting
Diarrhea[1]	Gastrointestinal disorders	Diarrhea
Abdominal pain	Gastrointestinal disorders	Abdominal pain
Dyspnea	Respiratory, thoracic and mediastinal disorders	Shortness of breath
Dermatitis radiation	Skin and subcutaneous tissue disorders	Radiation skin reaction
Rash maculo-papular	Skin and subcutaneous tissue disorders	Rash
Myalgia	Musculoskeletal and connective tissue disorders	Muscle pain
Arthralgia	Musculoskeletal and connective tissue disorders	Joint pain

Breast pain	Reproductive system and breast disorders	Breast swelling and tenderness
Fatigue	General disorders and administration site conditions	Fatigue
Myocarditis	Cardiac disorders	
Colitis	Gastrointestinal disorders	
Pneumonitis	Respiratory, thoracic and mediastinal disorders	
Adrenal insufficiency	Endocrine disorders	
Hypothyroidism	Endocrine disorders	
Peripheral Sensory Neuropathy	Nervous system disorders	Numbness and tingling

1. Number of stools per day should also be collected for all patients at baseline.

Symptomatic adverse events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine Adverse Event data.

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

NOTE: For patients on the observation arm, only "other adverse events" ≥ grade 3 should be reported.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible			a, b	a, b	a, b
Probable			a, b	a, b	a, b
Definite			a, b	a, b	a, b

a) **Adverse Events CRF** - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date.

b) **Adverse Events: Late CRF** - Applies to AEs occurring greater than 30 days after the patient's last treatment date, or as part of the Clinical Follow-up Phase or Survival Follow-up Phase.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at:

ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators MUST immediately report to the sponsor (NCI) ANY SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

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

1) **Death**
2) **A life-threatening AE**
3) **An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours**
4) **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
5) **A congenital anomaly/birth defect.**
6) **Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).**

ALL SAEs that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

9.3.2 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

Exclusions

≤ grade 4 hematologic toxicity and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.

Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting.

Death

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS. In addition, the *Pregnancy Information Form* included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

Pregnancy loss and neonatal death

Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event

under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

New Malignancies

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via Rave.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

9.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) For Pembrolizumab (MK-3475, NSC 776864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for Pembrolizumab (MK-3475).

Version 2.9, January 31, 2025[1]

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia[2]		
		Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia)[2]
		Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)[2]
	Lymph node pain[2]	
CARDIAC DISORDERS		
		Myocarditis[2]
		Pericarditis[2]
ENDOCRINE DISORDERS		
	Adrenal insufficiency[2]	
		Endocrine disorders - Other (hypoparathyroidism)[2]
	Endocrine disorders - Other (thyroiditis)[2]	
	Hyperthyroidism[2]	
	Hypophysitis[2]	
	Hypopituitarism[2]	
	Hypothyroidism[2]	
EYE DISORDERS		
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)
		Uveitis[2]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis[2]	
	Constipation	
	Diarrhea[2]	
		Enterocolitis[2]
		Gastritis[2]
		Gastrointestinal disorders - Other (exocrine pancreatic insufficiency)

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Mucositis oral[2]	
	Nausea	
	Pancreatitis[2]	
	Small intestinal mucositis[2]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
Fatigue		
	Fever[2]	
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
		Hepatobiliary disorders - Other (sclerosing cholangitis)
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis[2]
		Cytokine release syndrome[2]
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]
	Immune system disorders - Other (sarcoidosis)[2]	
		Serum sickness[2]
INFECTIONS AND INFESTATIONS		
		Myelitis[2]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction	
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased[2]	
	Blood bilirubin increased	
		GGT increased
		Lipase increased
		Serum amylase increased
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyponatremia	
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2]	
	Arthritis[2]	
	Back pain	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Joint range of motion decreased	
	Myalgia[2]	
	Myositis[2]	
NERVOUS SYSTEM DISORDERS		
		Guillain-Barre syndrome[2]
		Myasthenia gravis
		Nervous system disorders - Other (autoimmune neuropathy)[2]
		Nervous system disorders - Other (demyelination)[2]
		Nervous system disorders - Other (myasthenic syndrome)[2]
		Nervous system disorders - Other (nerve paresis)[2]
		Nervous system disorders - Other (neuromyopathy)[2]
		Nervous system disorders - Other (non-infectious encephalitis)[2]
		Nervous system disorders - Other (non-infectious meningitis)[2]
		Nervous system disorders - Other (non-infectious myelitis)[2]
		Nervous system disorders - Other (optic neuritis)
		Nervous system disorders - Other (polyneuropathy)[2]
		Paresthesia
		Peripheral motor neuropathy[2]
RENAL AND URINARY DISORDERS		
		Acute kidney injury
		Renal and urinary disorders - Other (autoimmune nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
		Pneumonitis[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Bullous dermatitis[2]	
		Erythema multiforme[2]
	Erythroderma	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus[2]	
	Rash acneiform[2]	
	Rash maculo-papular[2]	
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]	
		Skin and subcutaneous tissue disorders - Other (Drug reaction

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		with eosinophilia with systemic symptoms [DRESS])[2]
	Skin hypopigmentation[2]	
		Stevens-Johnson syndrome[2]
		Toxic epidermal necrolysis[2]
	Urticaria[2]	
VASCULAR DISORDERS		
		Vasculitis[2]

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving Pembrolizumab (MK-3475). Adverse events potentially related to Pembrolizumab (MK-3475) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of Pembrolizumab (MK-3475), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with Pembrolizumab (MK-3475) who received hematopoeitic stem cell transplants.

Adverse events reported on Pembrolizumab (MK-3475) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Pembrolizumab (MK-3475) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Duodenal hemorrhage; Dysphagia; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - CPK increased; Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Joint effusion[2]; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion

RENAL AND URINARY DISORDERS - Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hypoxia; Laryngeal inflammation; Pleural effusion; Pleuritic pain[2]; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: Pembrolizumab (MK-3475) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 DRUG INFORMATION

10.1 General Considerations:

Pembrolizumab is to be administered at the registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

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

10.2 Pembrolizumab (MK-3475, SCH 900475, KEYTRUDA®, NSC 776864)

Agent ordering and agent accountability

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Investigator Brochure Availability

Consult the package insert for the most current and complete information.

Formulation

Commercially available for injection 25mg/ml (4ml) in a one-vial formulation. Each 1 mL of solution contains 25 mg of pembrolizumab (MK-3475) and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

Storage

Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light.

Stability

Refer to the package label for expiration.

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

Preparation

Follow institutional standards.

Pembrolizumab (MK-3475) solution for infusion must be diluted prior to administration. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of pembrolizumab (MK-3475) to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between 1 mg/mL to 10 mg/mL.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin.

Administration

Pembrolizumab must be administered by IV infusion only. Do not administer as an IV push or bolus injection.

Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

Drug Interactions

There are no known significant drug interactions.

Pharmacokinetics

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2993 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Distribution: The geometric mean value (CV%) for volume of distribution at steady state is 6.0 L (20%).

Elimination: Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] at steady state than that after the first dose [252 mL/day (37%)]; this decrease in clearance with time is not considered clinically important. The terminal half-life (t1/2) is 22 days (32%).

Specific Populations: The following factors had no clinically important effect on the CL of pembrolizumab: age (range: 15 to 94 years), sex, race (89% White), renal impairment (eGFR ≥ 15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or tumor burden. The impact of moderate or severe hepatic impairment on the pharmacokinetics of pembrolizumab is unknown.

Adverse Events

A list of the adverse events and potential risks associated with pembrolizumab can be found in Section 9.4. Consult the package insert for the most current and complete information.

Nursing Guidelines

1. Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life-threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

2. Diarrhea can be seen; however, it is less common than that seen with anti-CTLA-4 agents. However, it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
3. Rash/pruritus/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.
4. Monitor LFTs closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice or right upper quadrant pain to the study team immediately.
5. Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
6. Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well." Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
7. Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.
8. Fatigue is common and may or may not be associated with immune-related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.
9. Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.
10. Patients who have undergone an allogeneic bone marrow transplant have an increased risk of severe complications, including early GVHD and veno-occlusive disease, if they have previously been treated with pembrolizumab.
11. Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.
12. Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.
13. Rare neurologic disorders including Guillain-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, paresthesias or numbness, tingling to the study team immediately.

11.0 MEASUREMENT OF EFFECT

11.1 Definitions of Recurrence

11.1.1 Invasive Ipsilateral Breast Cancer Recurrence

Ipsilateral breast after previous lumpectomy

Defined as evidence of invasive tumor (not including DCIS and LCIS) in the ipsilateral breast after lumpectomy. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast should have a biopsy of the suspicious lesion to confirm the diagnosis. Confirmed by positive histology or cytology.

Ipsilateral after previous mastectomy

Defined as evidence of invasive tumor in any soft tissue or skin of the ipsilateral chest wall. This includes the area bounded by the midline of the sternum, extending superiorly to the clavicle, and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or across the midline will be considered as evidence of local recurrence. Confirmed by positive histology or cytology.

11.1.2 Invasive Regional Recurrence

Defined as the development of tumor in the ipsilateral internal mammary lymph nodes, ipsilateral axillary lymph nodes or supraclavicular lymph nodes as well as extranodal soft tissue of the ipsilateral axilla. Regional recurrence does not include tumor in the opposite breast. Confirmed by positive histology or cytology, or radiologic evidence (especially in case of PET activity or visible internal mammary lymph nodes on CT or MRI if no biopsy was performed).

11.1.3 Distant Recurrence

Defined as evidence of tumor in all areas, except for those described above.

Confirmed by the following criteria:

- Skin, subcutaneous tissue, and lymph nodes (other than local or regional)
    - Positive cytology, aspirate or biopsy, OR
    - Radiological (CT scan, MRI, PET, or ultrasound) evidence of metastatic disease
- Bone
    - X-ray, CT scan, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, OR
    - Bone scan (requires additional radiological investigation, alone not acceptable in case of diagnostic doubt), OR
    - Biopsy proof of bone metastases or cytology
- Bone marrow
    - Positive cytology or histology or MRI scan
- Lung
    - Radiologic evidence of multiple pulmonary nodules consistent with pulmonary metastases, OR
    - Positive cytology or histology (practically rarely performed except for solitary nodules)
    - NOTE: For solitary lung lesions, cytological or histological confirmation should be obtained in case of diagnostic doubt. Proof of neoplastic pleural effusions should be established by cytology or pleural biopsy.
- Liver

- Radiologic evidence consistent with liver metastases, OR
- Liver biopsy or fine needle aspiration
- NOTE: If radiological findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans should be obtained if possible to document stability or progression.

- Central nervous system
  - Positive MRI or CT scan, usually in a patient with neurologic symptoms, OR
  - Biopsy or cytology (e.g., for a diagnosis of meningeal involvement). However, meningeal involvement may also be diagnosed by CT scan or MRI and depending on the general status of the patient additional investigations (including cytology of the cerebrospinal fluid).

11.2 Definitions of Analysis Variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol (Section 13.0).

12.0 End of Treatment/Intervention

12.1 Duration of Protocol Treatment

Protocol treatment (intervention) is to continue for 27 weeks. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and follow-up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- RFS event
- Disease progression (if applicable)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression (if applicable)
- Patient non-compliance
- Pregnancy (if applicable)
- All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent (if applicable)

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

Patients will be followed every 6 months (+/- 2 months) for 5 years after registration or recurrence. Thereafter, patients will be followed annually (+/- 3 months) for overall survival for a total of 10 years after registration. See Study Calendar in Section 5.0.

12.3.2 Follow-up for Patients who Stop Study Treatment/Intervention Early

Participants taken off study treatment for unacceptable adverse events will continued to be followed for recurrence and should remain on study. During the follow-up period, after completion of study treatment, all AEs that are related to study treatment should be recorded.

12.3.3 Follow-up for Specimen and QOL Submission

Blood samples will be collected at the 6-month follow-up visit and 3 years after registration. Blood and tissue will be collected at recurrence if applicable.

For patients who consent to optional PRO-CTCAE collection and/or A012103-HO1, measures should continue to be collected per Section 6.3 even in the event of a recurrence prior to the end of treatment or observation.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off treatment, and post-treatment follow up (i.e., recurrence and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study design

This trial is a two-arm, multicenter, randomized phase III trial to evaluate whether observation results in a non-inferior recurrence-free survival (RFS) compared to adjuvant pembrolizumab in early-stage TNBC patients who achieve a pCR after neoadjuvant chemotherapy with pembrolizumab. This is a de-escalation study, with a 3-year RFS rate of 94% estimated in the pembrolizumab arm and non-inferiority of the observation arm declared if the 3-year RFS rate is 91% or higher. The primary endpoint is RFS.

13.2 Sample Size, Accrual Time and Study Duration

The total sample size will be 1295 patients (~648 per arm). The determination of this sample size was performed with EAST (version 6.5) based on a one-sided level of significance of 0.05 and 80% power. Additional assumptions for the sample size calculation were:

- An average monthly accrual rate of 35 patients
- interim analysis for harm after 30% of the RFS events
- interim analysis for futility after 50% of the RFS events
- 3-year RFS rate for the pembrolizumab arm (control arm) of 94%
- A non-inferiority margin of a 3-year RFS rate of 91% for the observation arm; this corresponds to a non-inferiority HR of 1.52

The final analysis will be performed when there are 142 RFS events observed across these two arms. It is anticipated that the accrual will require approximately 37 months and that the total study duration will be approximately 86 months.

13.3 Statement for Primary Endpoint

The primary endpoint is recurrence-free survival (RFS), which is defined as the time from randomization to one of the following events: invasive local, regional or distant recurrence, or death from any cause [16]. Patients who are alive at the time of analysis without documented breast cancer recurrence will be censored at the time of their last disease evaluation.

13.4 Definitions of Secondary Endpoints

- Adverse event (AE) rate: Adverse events will be determined using the latest version of the CTCAE (see Section 9.0). The AE rates will be computed for each protocol treatment: pembrolizumab or observation. The AE rate for pembrolizumab will be the number of patients with the AE and who received at least one dose of adjuvant pembrolizumab (regardless of their treatment arm assignment) divided by the number of patients who received at least one dose of adjuvant pembrolizumab (for the pembrolizumab treatment). The AE rate for observation will be the number of patients with the AE and who did not receive any adjuvant pembrolizumab (regardless of their treatment arm assignment) divided by the number of patients who did not receive any pembrolizumab. The irAE rates will be determined in an analogous manner.

- Overall survival (OS): This is the time from randomization to death due to any cause. Patients who are not known to be dead at the time of the analysis will be censored at the date of their last contact.
- Locoregional recurrence incidence (LRRI): This will be determined as the time from randomization to a locoregional breast cancer recurrence. Patients who are alive and do not have a documented locoregional breast cancer recurrence will be censored at the date of their last disease evaluation. In addition, patients who had a distant recurrence prior to a locoregional recurrence will be censored at the time of the distant recurrence. Patients who have a locoregional recurrence and distant recurrence diagnosed at the same time will be determined to have a locoregional event.
- Radiation adverse events include pneumonitis, hypothyroidism and dermatitis. Radiation AE event rates will be determined for patients who received radiation. The numerator is the number of patients with the radiation AE and the denominator is the number of patients who received radiation.

13.5 Randomization Routine

Randomization will be 1:1. There will be two stratification factors used in the randomization:

- Nodal status prior to preoperative chemotherapy: node-positive vs node-negative
- Receipt of preoperative anthracycline chemotherapy: yes or no

We will use blocked randomization to account for the stratification factors.

13.6 Interim Analysis

The first interim analysis will occur after 43 (30%) RFS events have been observed. It will be recommended that the trial be stopped to accrual (if still accruing) due to potential harm to patients on the observation arm if the observed HR (observation arm compared to the pembrolizumab arm) is 1.89 or greater. This boundary was determined using an O'Brien/Fleming stopping boundary. The harm analysis at 43 events yields 24% likelihood of stopping for HR = 1.52 and 2% likelihood of stopping for HR = 1.

An additional interim analysis will be performed for futility after 50% of the RFS events have been observed (i.e., after 71 RFS events). A recommendation to stop study accrual (if the study is still accruing) for futility will be made if the observed HR $\geq$ 1.52 (observation arm compared to the pembrolizumab arm). This is based on the Weiand rule. The futility analysis at 71 events (50% information) yields 50% likelihood of stopping for HR = 1.52 and 4% likelihood of stopping for HR = 1.

13.7 Analysis Plan for Primary Endpoint

All randomized patients will be included in the final analysis according to an intent-to-treat analysis. The final analysis will be performed when there the necessary number RFS events (142 across the two arms). The Kaplan-Meier estimator will be used to estimate the survival curves and a stratified log-rank test will be used to compare the RFS of the two arms. The comparison of interest is the observation arm versus the pembrolizumab arm. A stratified Cox model will be used to estimate the HR for this comparison with a two-sided 90% confidence interval. If the interval contains the NI margin value (HR = 1.52) or lies entire above 1.52, the observation arm will be declared to be inferior to adjuvant pembrolizumab treatment.

13.8 Secondary Analysis Plans for Clinical Outcomes

If there appears to be clinically significant imbalances of baseline variables between the treatment arms, a secondary analysis of the primary endpoint will use a stratified Cox model to

compare the treatment effects that include the variables that are determined to be imbalanced between the arms as adjusting variables. The randomization stratification variables will be the stratified variables in the model. The adjusted HR comparing the treatments and corresponding 90% two-sided confidence interval will be generated. Again, if the interval contains 1.52 (or lies entirely above 1.52), the observation arm will be declared to be inferior to adjuvant pembrolizumab.

OS will also be summarized with Kaplan-Meier curves and compared between the two arms using a stratified log-rank test and stratified Cox model. The cumulative incidence of locoregional recurrences will be determined as the crude cumulative incidence using a Kaplan-Meier curves and compared using a log rank test.

The proportions of patients with a grade 3 or higher AE will be compared between the arms using a chi-square test. A similar analysis will be done to compare the grade 3 or higher irAE rates. The analysis of the radiation related adverse event rates will only include patients who received radiation treatment. The radiation AE rates will be compared between the two arms using a chi-square test.

13.9 Accrual Monitoring Stopping Rule

Accrual to the trial will be monitored closely. The study team will evaluate accrual within the 5^{th} to 6^{th} quarters from study activation. If accrual during these quarter is less than 50% of what is projected for these quarters, we will plan modifications including the potential for closure.

13.10 Monitoring

13.10.1 Data and Safety Monitoring Board

This study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

13.10.2 Data Mapping Utility (DMU)

This study has been assigned Demography monitoring.

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

13.11 Primary Endpoint Completion Time Estimation

It is anticipated that the primary endpoint will be mature about 86 months after the first patient is randomized. The final analysis can occur after 142 RFS events have been observed.

13.12 Inclusion of Women and Minorities

Over the last decade, innumerable cancer therapies have emerged, offering hope in the fight against cancer. Nevertheless, racial and ethnic disparities persist, and Black women continue to suffer 41% higher breast cancer mortality compared to White women [17]. There is now wide-ranging evidence for differences in tumor biology and altered anti-tumor immunity accounting in part for this disparity [18-21]. We and others have identified increased inflammation in breast tumors from Black patients relative to non-Black patients [22-24], with evidence of altered anti-

tumor immunity and T cell exhaustion. Agents targeting the immune system have emerged as a foundation of cancer treatment with approved checkpoint inhibitors now available for the routine care of early-stage and metastatic triple-negative breast cancer (TNBC) [25, 26]. However, ethnic minorities have been underrepresented in these trials; therefore, the interpretation of trial results might not reflect the true potential efficacy and tolerability of these drugs in minority patients. The inadequate representation of minority patients in immunotherapy clinical trials could perpetuate outcome disparity, because the unique biology of the host and the tumors from this subpopulation is not accounted for as new treatment algorithms to guide optimal use of immunotherapy in BC are being developed for use in the real world. Therefore, there is a vital need for adequate representation of minority patients in clinical trials to ensure that race-based differences in immune response are not overlooked in immunotherapy treatment algorithms.

Furthermore, age appears to be another key driver for breast cancer heterogeneity, and breast cancer diagnosed at a young age has been correlated with inferior survival and higher recurrence rates when compared to older patients [27]. Thus, focusing on young patients with breast cancer is warranted to offer this poor-prognosis group of women superior therapeutic options. Additionally, age-dependent changes in peri-tumoral immunity and tumor mutational landscape have been reported [28], and older adults appear to have a unique immunobiology that may respond differently to immunotherapies [29]. Despite this, older adults with cancer are routinely underrepresented in clinical research. Therefore, deliberate study of immunotherapies in older adults is highly warranted given the paucity of data and significant knowledge gaps that limit our ability to optimize care for this growing and vulnerable population.

In this regard, we plan to focus on minority enrollment as a deliberate strategy that guides our clinical trial design, including age and race-based clinical and correlative endpoints. We hypothesize that unique clinical characteristics, including age and race, can impact treatment outcomes and immune responses. Our age and race-based goals include:

- To evaluate RFS and OS for observation compared to adjuvant pembrolizumab by race and ethnicity in patients with early-stage TNBC who achieve a pCR after neoadjuvant chemotherapy with pembrolizumab.
- To evaluate the adverse event rate and patient-reported quality of life for observation compared to adjuvant pembrolizumab by race and ethnicity in patients with early-stage TNBC who achieve a pCR after neoadjuvant chemotherapy with pembrolizumab.
- To evaluate RFS and OS for observation compared to adjuvant pembrolizumab by age (≤45 46-65, and >65) in patients with early-stage TNBC who achieve a pCR after neoadjuvant chemotherapy with pembrolizumab.
- To determine if PD-L1 expression, TILs, and genomic changes in the primary tumor, as well as detectable ctDNA after surgery are associated with RFS in minority patients including Black, Hispanic and Asian patients.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	10	0	0	0	10
Asian	29	0	0	0	29
Native Hawaiian or Other Pacific Islander	5	0	0	0	5
Black or African American	216	0	10	0	226
White	819	0	82	0	901
More Than One Race	37	0	4	0	41
Total	1116	0	96	0	1212

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	2	0	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	0	1	0	4
White	74	0	1	0	75
More Than One Race	2	0	0	0	2
Total	81	0	2	0	83

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

13.13 Other Pre-Specified Outcomes: NIH-Required Analyses for Trials with Phase III Components

Estimates of treatment effect and the corresponding 95% confidence intervals (CIs) will be provided as follows (with an understanding that sometimes the CI or estimate will not be computable because of scant data).

- Estimates of RFS and the corresponding 95% confidence intervals (CIs) by sex.
- Estimates of RFS and the corresponding 95% confidence intervals (CIs) by race.
- Estimates of RFS and the corresponding 95% confidence intervals (CIs) by ethnicity.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be one optional quality of life substudy and all patients are encouraged to participate. There will be one mandatory correlative science study.

14.1 Quality of Life (Alliance A012103-HO1)

This substudy has two distinct components – a Quality of Life component, and a Value of Care component. Each will be described in separate sections.

14.1.1 Quality of Life - Background

A patient-reported outcome (PRO) is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[30] PROs provide information regarding how patients perceive health and treatment effects, and how treatments influence outcomes, and they are useful in evaluating how disease and therapeutic interventions impact many aspects of a patients' life [31]. Compared to PRO data, clinician reporting of symptomatic outcomes has been shown to be incomplete and sometimes inaccurate[32-34]. The incorporation of PROs into therapeutic clinical trials is, therefore, critical to inform medical decision making between patients and their doctors.

For this study, information about the effect of treatment on quality of life (QoL) may inform treatment decision-making. Specifically, if the primary endpoint is not met, but observation is only slightly inferior to 6 months of adjuvant pembrolizumab, knowing about the effect of adjuvant pembrolizumab on QoL could be relevant to patients. For example, if QoL is worse for those who receive 6 months of adjuvant pembrolizumab, some patients make opt for no adjuvant pembrolizumab despite the small clinical benefit. However, if QoL is NOT different between the arms, then even a small benefit from adjuvant pembrolizumab would likely be preferred.

<u>QoL Outcome: FACT-B</u>

The Functional Assessment of Cancer Therapy-Breast (FACT-B) is a validated scale that is widely used in breast cancer clinical trials, including those already completed as well as others that are ongoing through the Alliance. Harmonization of QoL instruments across studies is critical to advancing the inclusion of PROs in clinical decision-making.

The FACT-B includes a measure of overall QoL in cancer patients (FACT-G), as well as a breast cancer specific subscale concerning breast cancer specific issues, including body image, sexual issues, and additional physical symptoms [35, 36]. The FACT-G has four subscales: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB) [37, 38]. In cancer therapy trials such as OptimICE-pCR, the domains of the FACT family of tools that are most likely to change are PWB, FWB, and the BCS. The other scales are less likely to change in a cancer

treatment trial (their focus is on psychosocial well-being, and they are generally more likely to change when the investigational intervention is psychosocial or behavioral in nature). The Treatment Outcome Index (TOI) combines the PWB, FWB, and BCS scales. The total FACT-B includes all scale scores, including the two that are less likely to change in a treatment trial. Including the two subscales that are unlikely to change may obscure a difference between treatment arms. Therefore, for this study, we will focus the primary analysis on the TOI in order to investigate whether QoL among patients in observation is non-inferior to QoL among patients treated with pembrolizumab. **Although the full FACT-B will be administered and analyzed, the TOI was chosen as the primary endpoint.** The minimally important difference in scores for the TOI is 5-6 points [37, 39]. The FACT-B takes approximately 10 minutes to complete.

Patient-reported symptoms: PRO-CTCAE

The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) was developed by the National Cancer Institute to capture patient self-reports of symptomatic toxicities during cancer treatment. The PRO-CTCAE is a standardized self-report measure that allows patients to report the frequency, severity, and interference of up to 78 symptoms that may be experienced [31]. The PRO-CTCAE has demonstrated favorable validity, reliability, and responsiveness in a large heterogeneous United States sample of cancer patients undergoing treatment [40]. Furthermore, the use of the PRO-CTCAE to collect information about participant symptoms in a multicenter trial is feasible, with high participant compliance with self-reporting (92.0%) in a recent Alliance study of patients undergoing treatment for rectal cancer [41].

In this study, we will assess symptomatic adverse events using PRO-CTCAE measures for anorexia, nausea, fatigue, diarrhea, vomiting, abdominal pain, dyspnea, dermatitis radiation, myalgia, arthralgia, breast pain, rash, and peripheral sensory neuropathy. These symptoms were selected based on the known toxicity profiles of pembrolizumab. Patients treated with pembrolizumab are likely to experience more frequent and severe symptoms compared to those in the observation arm. The incidence and severity of symptoms, as well as, where relevant, symptoms interference, will be compared by treatment arm. The PRO-CTCAE takes approximately 5 minutes to complete.

14.1.2 Quality of Life - Objectives

Primary objective

To compare quality of life (QOL) at approximately 27 weeks as assessed by the FACT-B Trial Outcome Index between patients randomized to adjuvant pembrolizumab versus observation. Hypothesis: QOL will be non-inferior in the pembrolizumab arm compared to the observation arm.

Exploratory objectives

- To describe trajectories of QOL over time among patients randomized to adjuvant pembrolizumab vs. observation
- To compare various QOL domains after approximately 27 weeks as assessed by the 5 subscales of the FACT-B Index between patients randomized to adjuvant pembrolizumab versus observation. This analysis is exploratory, though we anticipate the direction of the comparisons to be consistent with Primary and Secondary Hypotheses.
- To compare self-reported symptomatic adverse events as outlined in section 14.1.1 after approximately 27 weeks of the study assessed by the PRO-CTCAE between patients randomized to adjuvant pembrolizumab versus observation. This analysis is exploratory in nature.

14.1.3 Quality of Life - Methods

Participants on the pembrolizumab arm will complete the PRO-CTCAE at baseline and on day 1 of each cycle. Participants on the observation arm will complete PRO-CTCAE items at baseline, at 12 weeks, and at 27 weeks (parallel to their clinical assessments.) The FACT-B will be completed at registration, 12 weeks, and 27 weeks for both arms. Analyses will be coordinated by the Alliance SDC A012103 Statistician using the analysis dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

14.1.4 Quality of Life - Statistical Analysis

Primary endpoint

For the primary analysis, a linear model will be used. The linear model will compare the FACT-B Trial Outcome Index between patients randomized to adjuvant pembrolizumab versus observation. The difference of 5 points represents a clinically meaningful effect based on the work of Eton et al[37], using the pooled standard deviation (computed as 14.6 points) of the TOI scale as reported in Eton et al[37].

Group sample sizes of 181 and 181 (total sample size of 362 patients in USA) achieve 90% power to detect non-inferiority using a one-sided t-test. The margin of non-inferiority is -5.0. The significance level of the test is 0.025.

Exploratory endpoints

Graphical methods will be used to describe trajectories of QOL over time among patients randomized to adjuvant pembrolizumab vs. observation.

Linear models will be used to compare various QOL domains after approximately 27 weeks as assessed by the 5 subscales of the FACT-B Index between patients randomized to

adjuvant pembrolizumab versus observation. A Bonferroni correction will be performed to adjust for multiple comparisons using a familywise (two-sided) 0.05 level of significance.

14.1.5 Value of Care – Background (applies to USA patients only)

As a de-escalation clinical trial, OptimICE-pCR holds the potential to identify a lower-intensity approach to care that leads not only to minimal changes or even gains in clinical benefit, but also to substantially lower costs to patients and to society, resulting in higher value of care. The cost of nine cycles of pembrolizumab was over $92,000 in 2022, corresponding to out-of-pocket costs of over $18,000 for patients with the standard Medicare insurance benefit. When the higher costs and reduced quality of life attributable to immune-related adverse events are also considered, the potential value gains from de-escalation are substantial.

The value of de-escalation will be measured using multiple outcomes. By combining the *direct medical costs, direct nonmedical costs,* and *indirect costs,* the **total societal costs** will be calculated, and cost savings and cost-effectiveness of de-escalation (costs per Quality-Adjusted Life Year [QALY]) will be assessed from a full societal perspective. Individual components of these data will be used to measure value for different stakeholders. Out-of-pocket costs and patient financial toxicity will be the basis for measuring value from the patient perspective, for use in shared decision-making about breast cancer patients between patients and clinicians. Direct medical costs will underlie value measurement from the payer perspective, which will be useful to payers in determining coverage policies for breast cancer therapy.

14.1.6 Value of Care – Objectives (applies to USA patients only)

Primary Objective

To assess the social value of de-escalation of adjuvant breast cancer immunotherapy at approximately 27 weeks and, by modelling, over a lifetime. Hypothesis: The observation arm will be cost saving and cost-effective from the societal perspective compared to the pembrolizumab arm.

Secondary Objectives

- To assess the value of de-escalation of breast cancer immunotherapy from the payer perspective at approximately 27 weeks and, by modelling, over a lifetime. Hypothesis: The observation arm will be cost saving and cost-effective from the payer perspective compared to the pembrolizumab arm.
- To compare patient out-of-pocket costs at approximately 27 weeks between patients randomized to adjuvant pembrolizumab versus observation. Hypothesis: Patient out-of-pocket costs will be non-inferior in the pembrolizumab arm compared to the observation arm.
- To compare financial toxicity at approximately 27 weeks between patients randomized to adjuvant pembrolizumab versus observation. Hypothesis: Financial toxicity will be non-inferior in the pembrolizumab arm compared to the observation arm.
- To compare work/productivity impairment at approximately 27 weeks between patients randomized to adjuvant pembrolizumab versus observation. Hypothesis: Work-related/productivity Impairment will be non-inferior in the pembrolizumab arm compared to the observation arm.

Exploratory Objectives

- To describe trajectories of financial toxicity and work/productivity impairment over time from baseline to approximately 27 weeks among patients randomized to adjuvant pembrolizumab versus observation.
- To develop and assess a measure of value from the patient perspective at approximately 27 weeks. This measure, to be developed in collaboration with a patient advocate, will combine both costs and outcomes, and incorporate patient out-of-pocket costs and financial toxicity

14.1.7 Value of Care – Methods – 27-week time horizon (applies to USA patients only)

The assessment of the value of care during the first 27 weeks after registration is essentially a statistical analysis of the data collected during the trial, some of which is priced or weighted using external data sources.

Resource Utilization Instruments

We will employ four patient-reported resource use measurement data instruments (Table 1). These will be completed at registration, 12 weeks, and 27 weeks for both arms. The WPAI:SHP, FACIT-COST and CoPaQ will be self-administered by patients. The Health Utilization CRFs will be verbally administered to patients by a site nurse/research coordinator.

Table 1. Resource Utilization Instruments (applies to USA patients only)

Instrument Name	***Number of Items***	***Estimated time for completion (minutes)***
Health utilization CRFs	11	5
WPAI: SHP	6	3
FACIT-COST	11	2
CoPaQ: Cancer-related Direct non-Medical Costs	23	8

1. Health Care Utilization Case Report Forms (CRFs). These are slightly modified versions of Health Care Utilization CRFs used in a previous Alliance trial (A221602). They capture protocol and non-protocol use of health care services and pharmaceuticals (including pembrolizumab) by the patient, and approximate patient out-of-pocket expenses for this utilization, over an interval time window (the preceding 2 weeks for the registration assessment, the preceding 12 weeks for the 12th week assessment, and the preceding 15 weeks for the 27th week assessment). Verbal administration of the instrument by site staff to patients resulted in high and accurate rates of completion of the tool in A221602.

2. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP). The WPAI-SHP is a validated PRO tool to measure the amount of absenteeism, presenteeism, and daily activity impairment attributable to a specific health problem[42]. Work-related/daily activity impairment can be affected by symptomatic side effects from treatment and the need for time away from these activities. For this study, we will focus on a summary score for this tool, known as the WPAI overall score, which combines the number of hours that work or other activities were affected, weighted by the severity of affect.

3. Functional Assessment of Chronic Illness Therapy-COmprehensive Score for financial Toxicity (COST) (FACIT-COST). The FACIT-COST is a Likert scale-based PRO tool to measure the financial distress sustained by cancer patients that was shown to have high internal consistency and test-retest reliability[43]. It is designed to be administered with the FACT-G component of the FACT-B scale used for the primary Quality-of-Life outcome. For this study, we will focus on the summative score of the item responses in this tool, known as the FACIT-COST score.

4. Costs for Patients Questionnaire (CoPaQ). This is a comprehensive tool to measure the direct and indirect costs of a health condition for patients and their families and that was shown to have content and face validity[44]. We will employ all items in this tool that assess direct non-medical costs relevant to cancer patients and families – including travel costs, opportunity costs of time spent due to treatment, and informal care costs.

Value constructs

Quality-Adjusted Life Years (QALYs) will be calculated for each enrolled patient as their quality-of-life score (measured in utilities) at each PRO assessment time point (12 weeks and 27 weeks) times the year-equivalents covered by the intervening period (0-12 weeks and 13-27 weeks) for surviving patients. To obtain utilities, FACT-8D health status responses will be derived from the FACT-G instrument included in the protocol. They will be converted into utility weights using area-under-the-curve methods applied to a standard population value set[45].

Total societal costs will be calculated as the sum of *direct medical costs, direct non-medical costs,* and *indirect costs* over the 27 weeks of follow up – the sum of the costs captured in the 12th week and the 27th week periods resource use instrument assessments. Each of these components will be calculated for each patient as described below.

a. Direct medical costs. The health utilization CRFs capture quantities of each of several types of health care service and pharmaceutical used during the time window covered by the instrument. Exact mg of pembrolizumab used will be obtained from study records. We will multiply each of these quantities by the unit costs of each type of service or drug. Medical coders at Wayne State University/Karmanos Cancer Institute will define typical sets of ICD-9, CPT, HCSPS and NDC codes used for billing for each drug and category of service. Medicare unit costs will be used for consistency to price services defined by these billing codes for all patients, including for patients covered under other insurance plans[46]. Micromedex Red Book Wholesale Acquisition Cost (WAC) values will be used to price drugs.

b. Direct non-medical costs. The CoPaQ instrument items ask for the dollar value of direct non-medical cost components over the intervening period. We will sum to obtain all direct non-medical costs over 27 weeks.

c. Indirect costs. The WPAI-SHP instrument questions are asked regarding the period of *the previous seven days*. We will multiply the WPAI overall score (severity-weighted number of hours affected) by the national average wage rate in 2022 and multiply by the number of weeks covered in the assessment period to obtain the indirect costs of treatment during the period[47].

Additional value constructs for key stakeholders:

Patient out-of-pocket costs. The health utilization CRFs ask for the dollar value of out-of-pocket costs for each health care service and drug used over the intervening period. We will sum to obtain total out-of-pocket costs over 27 weeks for each patient.

14.1.8 Value of Care – Statistical Analysis – 27-week time horizon (applies to USA patients only)

Primary endpoints

Costs and QALYs: Comparison of societal costs between treatment arms must account for the right-skewed distribution of costs. Nonparametric bootstrap t-tests will be performed using the bias-corrected and accelerated bootstrap method to compare mean costs and to compare mean QALYs in a univariate analysis[48].

In a multivariate analysis, bootstrapped regression analysis will be used to adjust for baseline outcomes and other baseline imbalances, and multiple imputation by chained equations with predictive mean matching will be used to account for missing data under a Missing at Random assumption. The models for costs and QALYs will be estimated jointly using Seemingly Unrelated Regression to account for the correlation between costs and effects through correlated error terms[48].

Cost-utility ratios: The relative value of the observation arm over the pembrolizumab arm will be measured by the incremental cost-utility ratio: the ratio of the difference in average total societal costs over the difference in average QALYs gained between patients in the two comparative arms. In the case where average costs in the observation arm are lower than in the pembrolizumab arm, the cost-utility ratio would be positive if average QALYs are lower in the observation arm, and negative (observation arm would dominate the pembrolizumab arm) if average QALYs are higher in the observation arm.

A cost-effectiveness acceptability curve (CEAC), showing the probability that the observation arm is cost-effective (or dominant, which is also considered cost-effective) at different willingness to pay thresholds, will be used to visualize the stochastic uncertainty around the cost-utility ratio. Even if the point estimate of the cost-utility ratio were negative – indicating that the observation arm was dominant at the average values of costs and QALYs – the CEAC will reflect that the probability that the observation arm is cost-effective at different thresholds is generally less than 100%, due to uncertainty around those estimates.

Using a standard statistical power formula for cost-utility studies in clinical trials[49], with some plausible assumptions and drawing on parameters reported in the literature, group sample sizes of 82 and 82 (total sample size of 164 patients) achieve 80% power to demonstrate cost-utility of the observation arm over the pembrolizumab arm at 95% confidence levels. With an actual sample of 362 patients in this Quality of Life substudy powered to meet the Quality of Life endpoint, power for the cost-utility analysis will be correspondingly stronger.

Secondary endpoints

Costs, QALYs, and cost-utility ratios from the payer perspective: Methods parallel to those for the primary endpoints will be used, using direct medical costs instead of total societal costs in the analysis.

Patient out-of-pocket costs: The methods for statistical analysis of the costs primary endpoint will be used.

Financial toxicity and work/productivity impairment: Linear models will be used. The linear models will compare the FACIT-COST score and the WPAI overall score between patients randomized to adjuvant pembrolizumab versus observation.

Exploratory Endpoints

Graphical methods will be used to describe trajectories of financial toxicity and work/productivity impairment over time among patients randomized to adjuvant pembrolizumab versus observation.

Statistical methods for value from the patient perspective are to be determined once this measure has been developed.

Analyses will be coordinated by the Alliance SDC A012103 Statistician using the analysis dataset used for the analysis of clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

14.1.9 Value of Care – Methods – Lifetime time horizon (applies to USA patients only)

Practice guidelines for economic evaluation in health care[50] a lifetime time horizon as the standard that should be used in cost-effectiveness and cost-utility studies. A lifetime horizon captures all costs, QoL and survival outcomes starting with the clinical intervention and continuing over the entire remaining lifetime of the patient. Because most of the QoL substudy data is collected over only approximately the first 27 weeks after registration, modelling is necessary to extrapolate costs, QoL and survival outcomes for patients over their projected lifetimes. Indeed, most of the potential difference in the primary endpoint of RFS would be expected to occur beyond the initial 27 week period. Therefore, a lifetime modelling approach will be used to obtain a full measure of the value of observation versus adjuvant pembrolizumab; costs, QALYs, and cost-utility ratios will be assessed from the societal and payer perspectives. An overview of this model is provided below.

Following prior economic models of adjuvant therapy[51], the model will focus on tracking patients through three health states: an RFS state, a post-recurrence state, and death. To populate the costs and health utilities in these models, the means and distributions of daily costs and health utilities of patients with and without recurrence during the initial 27 week period will be estimated and costs and QALYs will be cumulated over the time patients spent in each health state as they move through the model. The model will split into two parts based on the timeframe after registration:

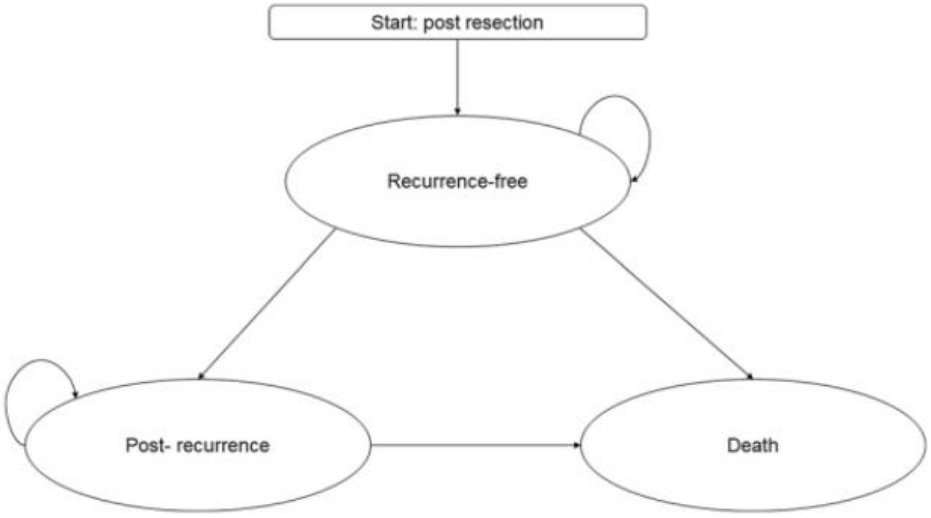
28^{th} week to end of year 5:

During this period, patients are monitored clinically under the trial protocol. Exact times of recurrence and death (if any) are known. The only modelling element will be assigning costs and utilities based on the distribution of values from the earlier, 27 week period.

Year 6 to end of lifetime:

At the end of year 5, each patient is known to be in one of the three health states. To project forward, a state transition model with these three states will be constructed, with transition probabilities between each (Figure 1):

Figure 1



Multi-state modeling – a generalization of a survival model with more than two states – will be used to estimate the transition probabilities for this model off of the 5 years of clinical data for all patients enrolled in the trial (including those outside the substudy). We will fit the model as a semi-Markov model, so that the transition probabilities from one state to another vary based on the time spent in the current state[52]. We will employ flexible parametric spline forms for the multi-state models, as they demonstrate better predictive accuracy in extrapolating cancer survival data than alternative model forms[53].

Running all of the patients in the QoL substudy through this model, and adding in the patient's measured totals from the initial 27 week period and their modelled totals from the 28th week to year 5 period, generates a projection of lifetime costs and QALYs for each patient. With this, mean costs and QALYs of each treatment arm and the incremental cost-utility ratio using a lifetime time horizon will be calculated. Statistical uncertainty around these parameters will be generated by the model, propagating through the stochastic uncertainty around the model's input parameters -- the transition probabilities, cost and utility parameters included in the model. Confidence intervals will be used to represent this uncertainty for costs and QALYs, while probabilistic sensitivity analysis and a cost-effectiveness acceptability curve will be used to reflect uncertainty around the cost-utility ratio.

14.2 Correlative Science (mandatory)

An amendment for any correlative science studies to be performed on biological samples that are biobanked will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include detail regarding the integrated biomarker proposal including the appropriate background, experimental plans with assay details, and a detailed statistical section. Investigators will also note how the assays have been funded. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

14.2.1 Optional Biobanking for Future Correlative Science Studies

In addition to the mandatory specimen collection on this trial, there is an optional biobanking component for future research. The additional 30 mL of blood collected in

EDTA tubes at the time of recurrence is optional for patients. In addition, the leftover tissue and blood will be used for potential genomics and proteomics studies, etc. Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies. The specimens requested for optional submission for biobanking in Section 6.2 will be collected for banking only at this time.

15.0 General Regulatory Considerations and Credentialing

There are no credentialing requirements for this trial.

15.1 Early Study Closure at Sites

Institutions may not close this trial without discussion and approval by the Alliance Regulatory team (regulatory@alliancenctn.org). Before contacting the Alliance regulatory team, please confirm this study does not appear on the list of trials terminated by the Alliance or on a study-specific termination memo (located on the "Study Terminations of Patient Follow-up" page of the Alliance website or on the study-specific page of the CTSU website).

15.2 Continuity of Care

Continuity of Care Provided by Non-Research Staff: The Responsible Investigator for a patient already enrolled on a clinical trial may make appropriate arrangements with a Local Healthcare Provider to provide certain study activities in order to provide continuity of care and follow-up study visits when the patient cannot travel to the site location of the Responsible Investigator. In this situation, the Local Healthcare Provider is providing intermittent/short-term care and the Responsible Investigator believes it is in the patient's best interest to continue study activities. The activities provided by the Local Healthcare Provider must be conducted under the oversight of the Responsible Investigator in accordance with the protocol and with assurances that processes are in place to report all required information to the Responsible Investigator who is responsible for ensuring that the data is entered into the data management system for the trial. These activities include the following:

- Protocol required physical exam(s) and assessment of the patient's vital signs, temperature, weight, performance status, and other standard assessments may be conducted by the Local Healthcare Provider. All clinical findings and information must be conveyed to the Responsible Investigator overseeing the patient's care in the trial. All decisions must continue to reside with the Responsible Investigator for the patient's care within the trial.
- Protocol specified clinical laboratory tests may be performed by the Local Healthcare Provider/Local Laboratory with results sent to the Responsible Investigator.
- Protocol required blood collections necessary for patient assessment within the clinical trial that require evaluation in a central research laboratory may also be collected by the Local Healthcare Provider and shipped to the designated central laboratory under the Responsible Investigator's oversight. The Responsible Investigator needs to ensure that the Local Healthcare Provider can make these collections depending on the protocol requirements.
- Protocol required standard parameters such as ECHO and radiologic imaging may be performed locally with results sent to the Responsible Investigator for review (report and image, if applicable).
- Drug therapy with non-investigational agents may be administered by the Local Healthcare Provider (this includes therapy on treatment arms that do not include investigational agents on IND trials) with appropriate reporting of study therapy administration data and adverse event information to the Responsible Investigator. Standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing may also be performed by the Local Healthcare Provider with oversight by the Responsible Investigator. In such cases, for this activity, the Responsible Investigator must inform the IRB of record for the trial that a Local Healthcare Provider is providing study therapy under his/her oversight. For trials under the NCI CIRB, the Responsible Investigator can send a simple email notification to the NCI CIRB at ncicirbcontact@emmes.com. For trials not under the

NCI CIRB, the Responsible Investigator should follow the appropriate local IRB notification policy.

These activities performed locally are part of usual oncology care and are being provided only on an intermittent/short-term basis with direct oversight by the Responsible Investigator with respect to protocol requirements. All decisions on care within the clinical trial are made by the Responsible Investigator. In this situation, these activities are not considered protocol deviations simply because they are being performed locally and not directly by the Responsible Investigator. The Responsible Investigator is still required to report any protocol deviations and unanticipated problems that occurs (e.g., non-compliance with protocol therapy) per standard procedures.

New Patient Enrollment: Patients can only be enrolled on a clinical trial at an active site that is participating in the study. The active participating sites for a trial can be found on the members' side of the CTSU website at: https://www.ctsu.org/public/default_login.aspx.

16.0 MONITORING PLAN

Standard Alliance monitoring procedures will be used for this study.

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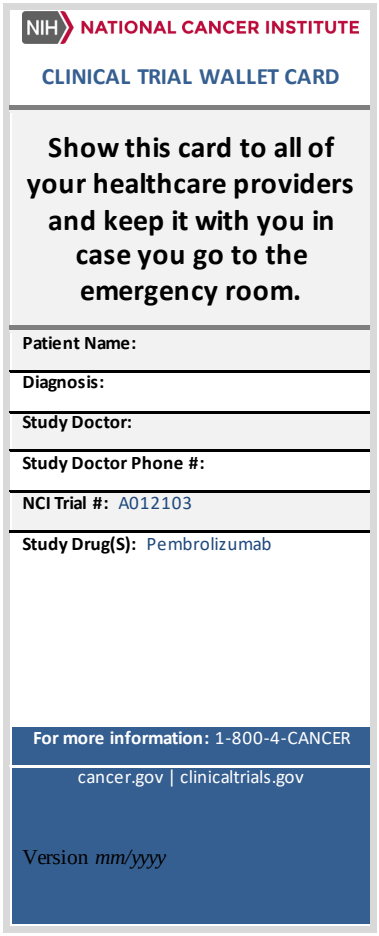
APPENDIX I PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: A012103

Study Drug(S): Pembrolizumab

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

Version *mm/yyyy*

APPENDIX II TRIAL PARTICIPANT THANK YOU LETTER

Trial Participant Thank You Letter

We ask that the physician use the template to prepare a letter thanking the participant for enrolling in this Alliance trial. The template is intended as a guide and can be downloaded from the study page on the Alliance website at www.AllianceNCTN.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by Alliance and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through.

We appreciate your help in this effort.

Sample Template

[PARTICIPANT NAME] [DATE] [PARTICIPANT ADDRESS]

Dear [PARTICIPANT SALUTATION],

Thank you for agreeing to take part in this important research study. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

There are many reasons why individuals choose to participate in a clinical trial. Sometimes it is because they want access to a specific medication or because they want to do whatever they can to help someone else with cancer. Whatever your reason for participating, you are making a contribution towards finding better treatments and ultimately eliminating this disease for future patients.

You will receive high quality care while participating in this clinical trial. My research staff and I will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other participants.

On behalf of [INSTITUTION] and the Alliance for Clinical Trials in Oncology, we thank you again for your participation in this clinical trial and look forward to partnering with you.

Sincerely, [PHYSICIAN NAME]