Version Date: April 18, 2025

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Network Operations Center (protocols@swog.org)

RE: **S2212**, "Shorter Anthracycline-Free Chemo Immunotherapy Adapted to Pathological Response in Early Triple Negative Breast Cancer (SCARLET), A Randomized Phase III Study"

REVISION # 4

Study Chair: Priyanka Sharma, M.D.
Phone number: 913/588-6079
E-mail: Psharma2@kumc.edu

Action Codes
(✓) Expedited review allowed
(✓) Patients Must be Informed*
(✓) Consent Must Be Amended*
* See "Patient Notification and Use of Consent Addendum" and "Regulatory Considerations" instructions below.

Key Updates
(✓) Informed Consent changes
(✓) Other: Pembrolizumab (MK-3475, NSC 776864) CAEPR update

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of distribution of this notice through the CTSU Bi-Monthly Broadcast email.

Sites not using the NCI CIRB*:* Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice through the CTSU Bi-Monthly Broadcast email.

REVISION # 4

This revision has been prepared in response to a Request for Rapid Amendment (RRA) for Pembrolizumab (MK-3475, NSC 776864) from Dr. Brian Ko, M.D. (brian.ko@nih.gov), Dr. Steven Gore, M.D. (steven.gore@nih.gov), and Dr. Meg Mooney, M.D. (mooneym@ctep.nci.nih.gov) dated, April 11, 2025. The associated Action Letter is attached. The above referenced protocol has been revised as follows:

Protocol Changes

1. The version date has been updated.

2. Throughout the protocol, formatting, typographical errors, pagination, and cross-references have been corrected as needed.

3. **Section 3.6.c**: This section has been updated with the most recent CAEPR for Pembrolizumab (MK-3475, NSC 776864) (Version 2.9, January 31, 2025):

a. SPEER: The section has been updated to remove the SPEER information as it does not apply to this study.
b. Blood and Lymphatic System Disorders: Increased in Attribution:
    i. Changed to Likely from Less Likely: *Anemia*
c. Gastrointestinal Disorders: Increased in Attribution:
    i. Changed to Less Likely from Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution: *Constipation*
d. Respiratory, Thoracic And Mediastinal Disorders: Increase in Attribution:
    i. Changed to Less Likely from Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution: *Cough; Dyspnea*
e. Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution:
    i. Deleted Risk: *Alopecia; Dry Skin*

Model Consent Form Change

1. The version date has been updated.

2. Possible side effects of **Pembrolizumab MK-3475:** The risk profile date has been updated to Table Version 2.9, January 31, 2025.

3. **"What possible risks…":** The following changes have been made to the Pembrolizumab MK-3475 Risk Section:

    a. Increase in Risk Attribution:
        i. Changed to Common from Occasional: *Anemia which may require blood transfusion*
        ii. Changed to Occasional from Rare: *Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath*
        iii. 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*

    b. Provided Further Clarification:
        i. Occasional: *Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives* is now reported as *Skin: itching; acne; rash (can be severe); blisters and peeling on the skin; skin changes; hives*.

Patient Notification and use of Consent Addendum:

Please note that the information provided below regarding patient notification and amendments to local consent forms reflects SWOG's minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements.

SWOG has determined that the changes above that are **bolded** may affect a patient's willingness to participate in the study; therefore, SWOG requires that patients be notified of these changes.

Who must be informed?

- All patients currently on study treatment with Pembrolizumab (MK-3475, NSC 776864) or who may receive treatment with Pembrolizumab (MK-3475, NSC 776864) on the study in the future.

How must patients be notified?

- For patients currently receiving Pembrolizumab (MK-3475, NSC 776864) or who may receive treatment with Pembrolizumab (MK-3475, NSC 776864) on the study in the future: Notification must take place either via the attached Consent Addendum or via amended consent form by next study visit. After the change has been discussed with the patient, the patient must sign and date either the Consent Addendum or the 04/18/2025 version of the consent form.

What is the notification deadline and process?

- For patients currently receiving treatment with Pembrolizumab (MK-3475, NSC 776864) who may receive treatment with Pembrolizumab (MK-3475, NSC 776864) on the study in the future: Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner.
- Sites using the NCI CIRB as their IRB of record: CIRB has approved the attached Consent Addendum; therefore, the Consent Addendum may be utilized immediately to notify patients of these changes.
- Sites not using the NCI CIRB as their IRB of record: If local IRB approval of the Consent Addendum is required before sites may utilize it, the site must still notify patients verbally prior to the notification deadline and notification must be documented in the patient chart. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved.

Regulatory Considerations:

Do local consent forms need to be updated?

- Yes, local consent forms must be updated to include all the changes in this revision.

Can accrual continue until local implementation of the 03/11/2025 version of the consent form?

- Unless otherwise noted in the Action Letter, accrual may continue; however:
  - Patients enrolled after the notification deadline must be enrolled under the 04/18/2025 version of the consent form.
  - Sites using the NCI CIRB as their IRB of record: Patients enrolled prior to the notification deadline but before the 04/18/2025 version is implemented locally may be consented by signing the previous version of the consent form 03/11/2025 together with signing the attached Consent Addendum.
  - Sites not using the NCI CIRB as their IRB of record: Patients enrolled prior to the notification deadline but before the 04/18/25 version is implemented locally may be consented by signing the previous version of the consent form 03/11/25 together with being notified of the updated information verbally at the time of consent. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved.

PLEASE NOTE: If the Action Letter requires suspension of accrual until the updated consent is implemented locally, the Action Letter instructions supersede this memo.

The updated protocol, model informed consent form, and consent addendum can be accessed from the CTSU website (www.ctsu.org). Please discard any previous versions of the documents and replace them with the updated versions. Please contact breastquestion@crab.org or 206/652-2267 with any questions.

This study has been reviewed and approved by the NCI's Central Institutional Review Board (CIRB).

NOTE: Spanish informed consent form documents will be posted by the CTSU at a later date.

This memorandum serves to notify the NCI, CIRB, and SWOG Statistics and Data Management Center.

cc: Protocol & Information Office
Janice M. Mehnert, M.D.
Rita Nanda, M.D. – Alliance Champion
Natalie Klar, M.D. – ECOG-ACRIN Champion
Karen Daily, D.O. – NRG Champion

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

SWOG CANCER RESEARCH NETWORK

S2212, SHORTER ANTHRACYCLINE-FREE CHEMO IMMUNOTHERAPY ADAPTED TO PATHOLOGICAL RESPONSE IN EARLY TRIPLE NEGATIVE BREAST CANCER (SCARLET), A RANDOMIZED PHASE III STUDY

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by SWOG with the participation of the network of NCTN organizations: Alliance for Clinical Trials in Oncology; ECOG-ACRIN Cancer Research Group; and NRG.

NCT# 05929768
Study Exempt from IND Requirements per 21 CFR 312.2(b)

STUDY CHAIRS:

Priyanka Sharma, M.D.
University of Kansas Medical Center
2330 Shawnee Mission Parkway, MS 5003
Westwood, KS 66205
Phone: 913/588-6079
FAX: 913/588-4085
E-mail: Psharma2@kumc.edu

Zahi Mitri, M.D.
British Columbia Cancer Agency, Vancouver
600 West 10th Ave
Vancouver, BC, V5Z 4E6
Phone: 604-217-6002
E-mail: zahi.mitri@bccancer.bc.ca

TRANSLATIONAL MEDICINE CHAIR:

David L. Rimm, M.D., Ph.D.
Institution: Yale Univ School of Medicine,
Dept of Pathology
310 Cedar St.
New Haven, CT 06520
Phone: 203/737-4204
E-mail: david.rimm@yale.edu

QOL CHAIRS:

Michelle Loch, M.D.
LSUHSC-New Orleans Stanley S. Scott Cancer Ctr
1700 Tulane Ave
5th Floor Room 506
New Orleans, LA 70112
Phone: 504/568-3235
FAX: 504/568-3421
E-mail: mloch@lsuhsc.edu

AGENTS:

Commercially Available Agents:
Carboplatin (NSC – 241240)
Cyclophosphamide (NSC – 26271)
Docetaxel (NSC – 628503)
Doxorubicin (NSC – 123127)
Paclitaxel (NSC – 673089)
Pembrolizumab (NSC – 776864)

BIOSTATISTICIANS:

Allison Meisner, Ph.D.
Danika Lew, M.A.
Shay Bellasea, M.S.
SWOG Statistics and Data Management Center
Fred Hutchinson Cancer Center
1100 Fairview Avenue North, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: ameisner@fredhutch.org
E-mail: dlew@fredhutch.org
E-mail: sbellasea@fredhutch.org

Dr. Lynn Henry M.D., Ph.D.
University of Michigan Rogel Cancer Center
1500 E. Medical Center Dr, Rm 7322
Ann Arbor, MI 48109
Phone: 734/936-9868
E-mail: norahh@med.umich.edu

ALLIANCE CHAMPION:

Rita Nanda, M.D.
Section of Hematology/Oncology, Department of Medicine
University of Chicago Comprehensive Cancer Center
900 E. 57th Street
Suite 8118
Chicago, IL 60637
E-mail: rnanda@medicine.bsd.uchicago.edu

ECOG-ACRIN CHAMPION:

Natalie Klar, M.D.
NYU Langone Department of Neurosurgery
530 1st Avenue
New York, NY 10016
E-mail: Natalie.Klar@nyulangone.org

NRG CHAMPION:

Karen Daily, D.O.
University of Florida Health Medical Oncology – Davis Cancer Pavilion
1535 Gale Lemerand Drive
Gainesville, FL 32610
E-mail: karen.daily@medicine.ufl.edu

PARTICIPANTS

U.S. and International Participants:

ALLIANCE/Alliance for Clinical Trials in Oncology
CCTG/Canadian Cancer Trials Group
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG Cancer Research Network

TABLE OF CONTENTS

PROTOCOL CONTACT INFORMATION

Eligibility, RAVE, Data Submission	SWOG Statistics and Data Management Center E-mail: breastquestion@crab.org or Phone: 206/652-2267
Regulatory, Protocol, Informed Consent	SWOG Operations Office E-mail: protocols@swog.org or Phone: 210/614-8808
Medical Queries (treatment or toxicity related questions)	E-mail: S2212question@swog.org or by phone: Dr. Priyanka Sharma at: 913/588-6079 or Dr. Zahi Mitri at: 604-217-6002.
Patient Advocate	Ginny Mason, R.N., B.S.N. via Email: masonvirginia@msn.com Roberta Albany via Email: Roberta.albany@outlook.com
QOL/PRO questions	E-mail: mloch@lsuhsc.edu or call Dr. Michelle Loch at 504/568-3235 Email: norahh@med.umich.edu or call Dr. Lynn Henry at 734/936-9868
Specimen collection/submission questions	Email: david.rimm@yale.edu or call Dr. David L. Rimm at 203/737-4204
Requests for Investigator's Brochures	See Protocol Section 3.0
Specimen Tracking System Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench	technicalquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) (e.g., new account requests, reset password)	https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave or Delegation of Task Log (DTL)	See Protocol Section 14.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Oncology Patient Enrollment Network (OPEN)	See Protocol Section 13.5 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Participant Transfers	patienttransfer@crab.org
Serious Adverse Event Reporting questions	See Protocol Section 8.7 Email: adr@swog.org

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.

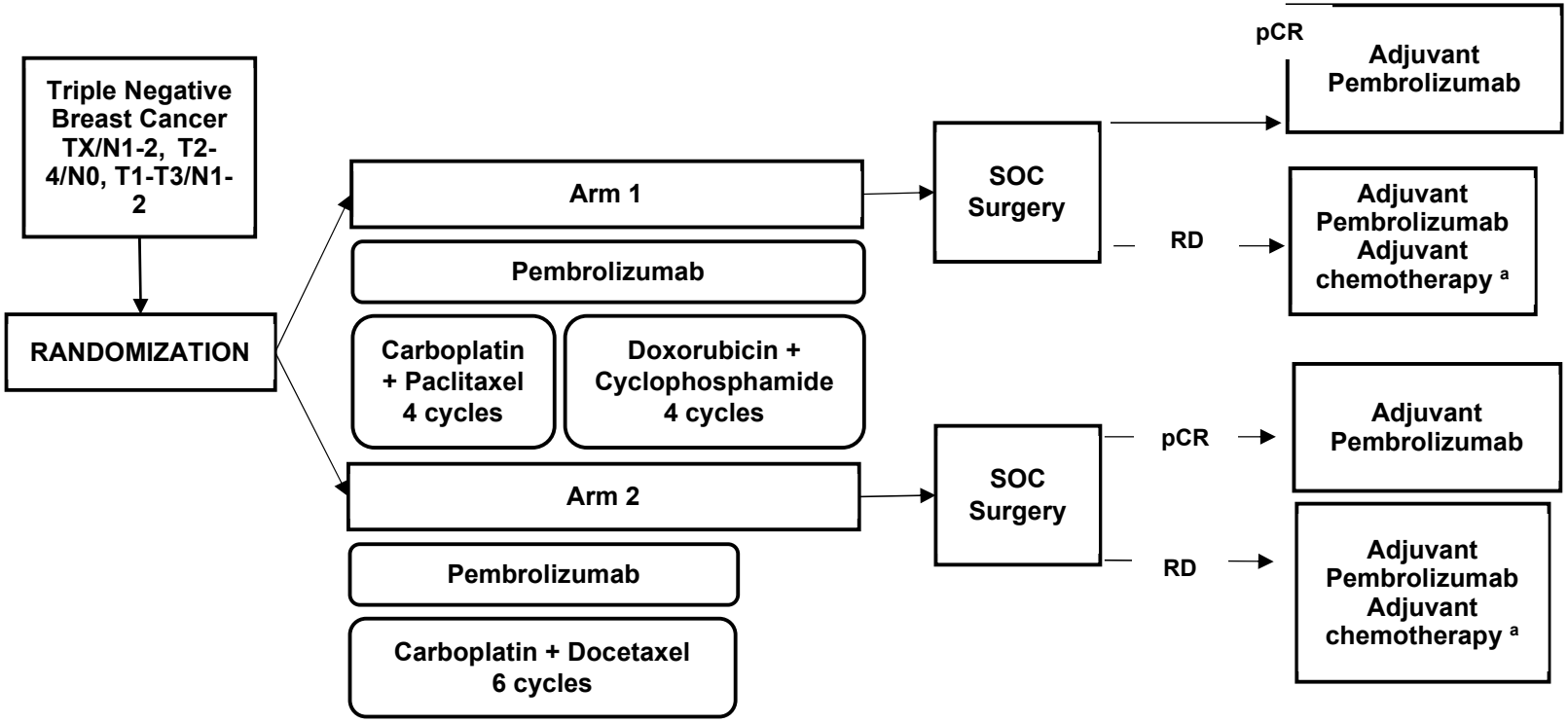
For participant eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone (206/652-2267) or email breastquestion@crab.org.

For treatment or toxicity related questions contact:
E-mail: S2212question@swog.org

or by phone:
Dr. Priyanka Sharma at: 913/588-6079 or
Dr. Zahi Mitri at: 604-217-6002.

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.

SCHEMA



[a] Treating investigator discretion. See Section 7.4b.

1.0 OBJECTIVES

1.1 Primary Objective

a. To assess whether participants with early stage TNBC randomized to receive anthracycline-free, taxane-platinum neoadjuvant chemotherapy with pembrolizumab have non-inferior breast cancer event-free survival (BC-EFS) compared to participants randomized to taxane-platinum-anthracycline neoadjuvant chemotherapy with pembrolizumab.

1.2 Secondary Objectives

a. To compare pathological complete response (pCR) and residual cancer burden (RCB) rates by randomized arm.

b. To compare pCR and RCB rates between randomized arms by tumor infiltrating lymphocytes (TIL) status.

c. To compare BC-EFS between randomized arms in the TIL-enriched and non-TIL enriched subgroups.

d. To compare distant relapse-free survival and overall survival by randomized arm.

e. To compare invasive breast cancer-free survival after surgery between randomized arms in pCR and residual disease groups.

f. To compare the safety and tolerability by randomized arm among those that initiate therapy.

1.3 Translational Medicine Objective

a. To evaluate concordance and accuracy of an Automated stromal TIL (sTIL) algorithm vs. Central pathologist assessed sTILs quantification.

1.4 PRO Objectives

a. Quality of Life:

1. Primary: To compare patient-reported fatigue at 3 weeks after the last neoadjuvant systemic therapy (NAST) dose and, separately, at 18 months after randomization, using the PROMIS Fatigue-7a in participants undergoing NAST with taxane-platinum-anthracycline chemo-immunotherapy vs taxane-platinum chemo-immunotherapy.

2. Secondary: To compare physical function experienced by participants undergoing neoadjuvant systemic chemotherapy (NAST) with taxane-platinum-anthracycline chemo-immunotherapy vs taxane-platinum chemo-immunotherapy, within 3-5 weeks post last neoadjuvant systemic therapy dose using the PROMIS-29 Profile physical function subscale score.

3. Secondary: To compare physical function experienced by participants undergoing NAST taxane-platinum-anthracycline chemo-immunotherapy vs taxane-platinum chemo-immunotherapy at 18 months post registration using the PROMIS-29 Profile physical function subscale score.

4. Exploratory: To compare other PROMIS-29 Profile subscale scores (sleep disturbance, depression, anxiety, social, pain interference, and pain

sensitivity) and GP5 question response by arm within 3-5 weeks post last neoadjuvant systemic therapy dose and at 18 months post registration.

5. Exploratory: To compare the GP-5 item scores by arm within 3-5 weeks post last neoadjuvant systemic therapy dose and at 18 months post registration.

b. Patient-Reported Symptoms of Treatment: To compare select patient-reported outcomes using the Common Terminology Criteria for Adverse Events (PRO-CTCAE) by arm.

1.5 Banking Objectives

a. To bank physical specimens and digital slides for future correlative studies.

2.0 BACKGROUND

2.1 Background and Rationale

Triple negative breast cancer (TNBC) represents 15-20% of all breast cancers and has worse survival stage by stage compared to other breast cancer subtypes *(1).* Chemotherapy is a recommended part of treatment of early stage TNBC to reduce the substantial risk of developing distant metastasis. In recent years chemotherapy for early stage TNBC is increasingly being applied in the neoadjuvant setting. Neoadjuvant systemic therapy (NAST) allows for monitoring of disease response and the opportunity to personalize adjuvant treatment based on response to therapy *(2)*. Personalized de-escalation of treatment in TNBC patients with chemosensitive disease achieving a complete pathological response to NAST offers an opportunity to decrease toxicity of care while maintaining the benefit of systemic therapy. Meta-analyses of prospective trials have demonstrated that achievement of complete pathological response (pCR) following NAST in TNBC is associated with excellent prognosis with ~90% likelihood of cure *(3)*. Additionally, recent evidence suggests that the good prognosis associated with pCR seem to be independent of the NAST regimens that lead to the achievement of pCR *(4,5,6)*. Furthermore, emerging data now suggests that further cytotoxic chemotherapy after achievement of pCR does not improve outcomes *(7)*. Thus, pCR identifies patients at low risk of recurrence who can safely avoid additional systemic chemotherapy and the associated toxicities.

2.2 Current State of NAST for TNBC

Anthracycline/cyclophosphamide (AC) followed by taxanes has historically been considered standard NAST for patients with stage I-III TNBC. Most patients with stage II-III TNBC now receive systemic therapy in the neoadjuvant setting, as this approach allows tailoring of adjuvant therapy based on pathological response. The phase III KEYNOTE-522 trial has established new standard of care neoadjuvant regimen for the treatment of stage II and III TNBC. In that study, the addition of pembrolizumab to a paclitaxel/carboplatin followed by AC based neoadjuvant chemotherapy significantly increased the pCR rates in patients with stage II and III TNBC, with a pCR of 69.7% in the pembrolizumab group and 55.3% in the placebo group. This translated into an improvement in 3-year event-free survival rate to 84.5% with pembrolizumab/chemotherapy compared with 76.8% with chemotherapy alone (HR=0.63, P=0.00031) *(8,9)*.

Other promising data regarding the role of neoadjuvant immune checkpoint blockade in combination with chemotherapy for early stage TNBC has also emerged, indicating that this class of drug/s is going to be part of standard of care for early stage TNBC. The phase II GeparNuevo study of neoadjuvant durvalumab in combination with anthracycline/taxane-based chemotherapy showed only a numeric trend towards improvement in pCR rates with addition of durvalumab to chemotherapy *(10)*. However, a recent update of the GeparNuevo study demonstrated a statistically significant improvement in 3-year invasive disease-free

survival (secondary end point) (77.2% to 85.6%; HR=0.48, P=0.0398), and overall survival (83.5% to 95.2% HR=0.24, P=0.0108) with the addition of durvalumab to neoadjuvant chemotherapy *(11)*. Additionally, the phase III Impassion031 study randomized patients with stage II-III TNBC to receive neoadjuvant chemotherapy (AC-Taxane) with placebo or atezolizumab, and demonstrated an increase in pCR with addition of atezolizumab to chemotherapy (pCR rate 58%% vs 41% P=0.0044) *(12)*. Long-term outcomes from Impassion031 are awaited. The phase III NSABP B-59 which is evaluating addition of atezolizumab to paclitaxel/carboplatin followed by AC chemotherapy has completed accrual and results are awaited.

The addition of carboplatin to anthracyclines/taxane based chemotherapy has been shown to increase pCR in many trials. However, definitive survival data had been lacking. Recent update from the randomized phase III BrighTNess study demonstrated that the addition of carboplatin to paclitaxel (followed by AC) in patients with stage II-III TNBC improved EFS compared to Paclitaxel (followed by AC) (4-year EFS 68.5% vs 79.3% p=0.02, HR=0.57) *(13)*. Given these recent paradigm shifts, most TNBC patients with stage II-III TNBC now receive 6 months of NAST with a regimen that includes 4 cytotoxic chemotherapy drugs (doxorubicin, cyclophosphamide, paclitaxel, carboplatin) plus pembrolizumab (or another checkpoint inhibitor if approved by FDA). The KN-522 regimen of paclitaxel/carboplatin/pembrolizumab followed by anthracycline/cyclophosphamide (AC)/pembrolizumab and adjuvant pembrolizumab has become the de-facto standard of care for patients with stage II-III TNBC. Thus, strategies to de-intensify NAST appropriately in patients with highly chemosensitive disease without compromising clinical benefit are desired.

2.3 Chemotherapy de-escalation for TNBC

Like anthracyclines, platinum agents damage DNA and have shown synergistic activity when given in combination with taxanes in both pre-clinical models and increased pCR when combined with anthracyclines/taxanes in TNBC clinical trials *(14,15,16)*. Efficacy of anthracycline-devoid neoadjuvant carboplatin/taxane chemotherapy regimens (CbT) in TNBC has been evaluated with reported pCR rates of 46-55% with 12-18 weeks of CbT *(17,18,19,20)*. A recent small randomized study *(21)*, demonstrates that 18 weeks of CbT yields pCR rates similar to T+ Carbo→AC but with a more favorable toxicity profile *(22)* Grade 3/4 adverse events were more common with T+ Carbo→AC compared with CbT and mean treatment cost was lower for CbT compared with T+ Carbo→AC. Although not powered for long term survival analysis, event-free and overall survival were also similar between the two treatment arms in NeoSTOP *(23)*. Long term follow up of WGS-ADAPT and Sharma et al neoadjuvant studies also show that patients who achieved pCR with carboplatin/taxane regimens have an excellent 3-year RFS (> 90%) and overall survival (> 94%) without adjuvant anthracyclines, suggesting that pCR accurately identified patients at low risk of recurrence who can avoid anthracyclines and the associated toxicities *(24,25,26,27,28)*.

The CbT chemotherapy regimens are well tolerated with favorable safety profile as 90% of patients can complete prescribed NAST and a very small proportion of patients demonstrate disease progression during NAST (<5%). Furthermore, assessment of patient-reported toxicities during various chemotherapy regimens has noted that longer chemotherapy regimens, such as anthracycline-based regimens followed by paclitaxel, had higher proportions of symptoms rated major toxicities *(29)*.

Additionally, safety and efficacy data for combination of neoadjuvant CbT with pembrolizumab come from the phase II NeoPACT study *(30)*. In this single arm phase II study (n=120), pCR and RCB0+1 rates were 58% and 69% respectively. Treatment completion rate was 86% and 3-year EFS was 86% in all patients; 98% in pCR group and 68% in no-pCR group. Further, the NeoPACT trial used 6 cycles of every 3-week docetaxel and carboplatin as the chemotherapy backbone. Weekly carboplatin was not included in NeoPACT due to the known concern for hypersensitivity reactions with repeated Carboplatin exposure. In patients receiving carboplatin, the number of prior carboplatin

treatments and weekly vs every 3–4-week treatment are risk factors for hypersensitivity reactions with cumulative incidence of carboplatin hypersensitivity reactions increasing with the number of infusions. *(31) (32)* The risk of hypersensitivity with carboplatin is <7% with first 6 exposures but rises sharply to 27% or more after the 7th cycle (exposure). *(32) (33) (34) (35)* Due to this risk of hypersensitivity reactions, 18 weekly doses of carboplatin is challenging to deliver safely to patients.

Taken together these data support the role of CbT in combination with immune checkpoint blockade NAST as treatment de-escalation strategy in TNBC. Testing the administration of shorter, non-anthracycline based CbT regimen (in combination with immune checkpoint inhibitor) is logical for several reasons. First, administration of 6 cycles of CbT is shorter (18 weeks) compared to the 24-week KN-522 regimen CbT/AC/. Second, the long-term toxicity profile of 18 weeks of CbT is likely to be more favorable to AC/CbT due to a lower incidence of heart damage and secondary leukemia. Finally, shorter less intense regimen may have lower negative impact on immediate quality of life and physical functioning compared to conventional anthracycline based regimens.

2.4 Tumor infiltrating lymphocytes (TILs) predict chemosensitivity, pCR and long-term outcomes in TNBC

In TNBC, a tumor's immune microenvironment plays an important role in prognosis and response to NAST and overall prognosis. Stromal and intratumoral lymphocytes (sTIL and iTIL) are a reproducible prognostic biomarker and multiple studies have shown that high TIL counts are associated with better outcomes in TNBC *(36,37,38,39)*. A pooled analysis of nine adjuvant clinical trials (including 2148 TNBC patients) demonstrated the robust the prognostic role of sTIL in early-stage TNBC patients where each 10% increment in sTIL translated to a 17% improvement in disease free survival (DFS) and 16% improvement in overall survival (OS). This pooled analysis demonstrated better survival outcomes for TNBC patients who received adjuvant chemotherapy and had ≥ 30% sTIL compared to those with <30% sTILs. 3-year invasive disease-free survival (iDFS) and distant disease free survival for patients with sTILS ≥ 30% and sTILs <30% were 84% and 75% (p< 0.001), and 88% and 80% (p<0.001), respectively *(40)*.

The association between increasing TIL in pre-treatment tumor tissue and higher pCR has been observed with different NAST chemotherapy regimens and appears to be independent of the type or duration of NAST (*41,42)*. In the NeoPACT trial *(43)* using Carboplatin/Taxotere/Pembrolizumab NAST, 48% of participants had sTIL≥30% and 52% had sTILs<30%. pCR rates were 76% (39/51 participants) and 41% (23/56 participants) in tumors with sTIL≥30% and <30%, respectively (OR 4.66, p<0.001).

Importantly, sTIL assessment uses standard Hematoxylin and Eosin (H&E) slides and the International Immuno-Oncology Biomarker Working Group guidelines provide standardization guidance on the quantification making sTILs an attractive biomarker for patient selection and stratification in prospective trials (https://www.tilsinbreastcancer.org). Given that several published retrospective analyses have indicated an excellent prognosis or higher rates of pCR in patients with sTIL≥ 30%, this cutoff has been chosen as cutoff for defining the TIL-enriched group in this study.

While sTIL is an attractive marker it is still subjective. A new objective method for assessment of TIL using open source QuPath software has been described *(44)*. Using this method could allow more uniform assessment of TIL, even in under-resourced settings without access to trained pathologists. A secondary objective of this study is to determine if this tool is equivalent to pathologist assessment.

2.5 Study Design

This study is an open label randomized non-inferiority phase III study with primary endpoint of event free survival aiming to compare an anthracycline based regimen to a platinum/taxane anthracycline-free NAST regimen in early stage TNBC, when both arms

receive concurrent pembrolizumab. This trial tests whether shorter chemotherapy regimen therapy can be administered without compromising survival in patients with early stage TNBC. If the anthracycline-free regimen of CbT are found to be non-inferior, assessment of differences in patient- reported outcomes and QOL will provide important information when patients and providers are making decisions regarding treatment.

2.6 Rationale for central TIL assessment

To ensure that the chemotherapy de-escalation approach utilized in SCARLET is optimized for all patients, we propose assessment of central TILs. We expect that approximately 60% of TNBC enrolled on SCARLET will have low TILs (sTILs < 30%) and 40% will have high TILs (>/=30%). TILs assessment in this study will serve two purposes:

1) Enable futility analysis to ensure that patients with non-TIL enriched TNBC (sTILs <30%) are not being undertreated in the de-escalated experimental Arm B. One of the goals of the de-escalated regimen is to spare patients who achieve a pCR anthracycline based therapy.

2) When the first 300 participants have the surgical outcome evaluated and classified we will assess the pCR rates in each treatment arm in each sTIL group. . If patients with non-TIL enriched TNBC (~180) demonstrate a very low absolute pCR rate in Arm B (absolute pCR < 20%), the study will be evaluated for futility particularly in the non-TIL enriched patients. In that setting, many patients with non-TIL enriched TNBC would require adjuvant anthracycline for residual disease and thus ultimately not spared that therapy. Furthermore, in the setting of a low pCR rate, long-term outcomes are also likely to be less than desirable thus diminishing enthusiasm for systemic therapy de-escalation for non-TIL enriched TNBC. Thus, futility analysis based on TILs in the non-TIL enriched group seems an appropriate safeguard measure for the study and sTILs density assessment is integral to the study.

3) The final analysis will be stratified by TIL-enrichment or not. Additionally, effect modification of treatment efficacy will be tested with an interaction of treatment and TIL-enrichment. There will also be separate comparisons of BC-EFS between the two treatment arms by TIL-enrichment to determine the nature of any interaction. This is a secondary objective of the study. Central TIL assessment will allow the assessment of pathological response and long-term outcomes in response to neoadjuvant chemo-immunotherapy in TIL subgroups. Assessment of long-term outcomes by TIL status will inform future trial design for further treatment de-escalation in TNBC.

2.7 Rationale for Inclusion of QOL/Patient Reported Outcomes:

Chemotherapy for breast cancer has several known toxicities. Anthracycline-based chemotherapy is known to cause irreversible cardiomyopathy and poor prognosis secondary hematologic malignancies among other toxicities. Trials for biomarker-based tailoring of therapy are needed to test whether regimens associated with fewer serious late effects of chemotherapy can be administered without compromising survival. In the curative treatment of cancer, if two regimens are found to have similar efficacy, assessment of differences in patient- reported outcomes and QOL may provide important information when patients and providers are making decisions regarding treatment.

The proposed trial compares an anthracycline based chemotherapy regimen (AC followed by paclitaxel/carboplatin) vs. carboplatin and docetaxel. These regimens cause short- and long-term effects on QOL and neuropathy, although patient reported differences between the two regimens have not previously been fully assessed. The objective of this PRO study is to compare patient-reported QOL, symptoms such as neuropathy, fatigue, physical function, anxiety, depression, nausea, vomiting, and joint pain between treatment arms.

The tools to be utilized have been validated and used in previous assessments and are available in multiple languages. The PROMIS Fatigue 7a and PROMIS-29 Profile have been used in clinical trials for breast cancer *(45)* and other malignancies *(46,47)* and covers a

range of symptoms and quality of life assessments that are relevant for assessing both short- and long-term effects of chemotherapy, including fatigue. The PRO CTCAE for several symptoms is a well-known and validated tool for assessment of patient-reported adverse events over the prior 7 days in clinical trials and will be used to assess symptoms not captured by the PROMIS-29 Profile including numbness and tingling (severity, interference), fatigue (severity, interference), nausea (severity, interference), vomiting (severity), and joint pain (severity). These instruments will be used at baseline to capture pre-existing symptoms, 3 weeks post neoadjuvant systemic therapy to assess acute chemotherapy toxicity, and 18 months after registration to examine persistence of toxicity after completion of therapy.

2.8 Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	9	0	1	0	10
Asian	75	0	5	0	80
Native Hawaiian or Other Pacific Islander	9	0	1	0	10
Black or African American	396	0	44	0	440
White	1479	5	165	1	1650
More Than One Race	9	0	1	0	10
Total	1977	5	217	1	2200

INTERNATIONAL PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	0	0	0	1
Asian	5	0	0	0	5
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	11	0	1	0	12
White	100	1	79	0	180
More Than One Race	1	0	0	0	1
Total	119	1	80	0	200

3.0 DRUG INFORMATION

IND Exemption

All drugs are commercially available; therefore, this study is IND exempt. This exemption has been determined by attestation that neither the investigator nor sponsor intend to seek a new indication for use or to support any other significant change in the labeling or product advertising for these drugs. These drugs will use an approved route of administration and dosage and have no factors that increase the risk of the drug products. These investigations will be in compliance with 21CFR parts 56, 50, and 312.7.

3.1 Carboplatin (CBDCA, NSC-241240)

a. PHARMACOLOGY

Mechanism of Action: Carboplatin (CBDCA) is a hydrophilic platinum coordination

b. PHARMACOKINETICS

Distribution: Vd = 16 L

Protein Binding: Carboplatin is not bound to plasma proteins.

Elimination: The initial half-life is 1.1 - 2.0 hours and the post-distributional half-life is 2.6 - 5.9 hours. Sixty-five percent of the dose is excreted in the urine within twelve hours.

c. ADVERSE EFFECTS

Possible Side Effects of Carboplatin:

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Pregnancy and Lactation: Pregnancy Category D. Carboplatin may cause fetal harm, therefore women of childbearing potential should be advised to avoid becoming pregnant.

Drug Interactions: Due to potential drug interactions, a complete patient medication list, including Carboplatin, should be screened prior to initiation of and during treatment with Carboplatin. See Section 8.0 Toxicities to be Monitored and Dosage Modifications."

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Carboplatin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.2 Cyclophosphamide (Cytoxan ®) (NSC-26271)

a. PHARMACOLOGY

Mechanism of Action: The mechanism of action is thought to involve cross-linking of tumor cell DNA. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites which are thought to cross-link to tumor cell DNA.

These metabolites interfere with the growth of rapidly proliferating susceptible malignant cells.

b. PHARMACOKINETICS

Absorption: Area under the curve ratio for the drug after IV administration (AUCpo: AUCiv) ranged from 0.87 to 0.96.

Distribution: Approximately 20% of cyclophosphamide is protein bound, with no dose dependent changes. Some metabolites are protein bound to an extent greater than 60%. Volume of distribution approximates total body water (30 to 50 L)

Metabolism: The liver is the major site of cyclophosphamide activation. Approximately 75% of the administered dose of cyclophosphamide is activated by hepatic microsomal cytochrome P450s including CYP2A6, 2B6, 3A4, 3A5, 2C9, 2C18 and 2C19, with 2B6 displaying the highest 4-hydroxylase activity.. Less than 5% of cyclophosphamide may be directly detoxified by side chain oxidation, leading to the formation of inactive metabolites 2-dechloroethylcyclophosphamide. Cyclophosphamide appears to induce its own metabolism. Auto-induction results in an increase in the total clearance, increased formation of 4-hydroxyl metabolites and shortened t1/2 values following repeated administration at 12- to 24-hour interval.

Elimination: Cyclophosphamide is primarily excreted as metabolites unchanged in the urine (10 to 20%) and in the bile (4%) following IV administration. Following IV administration, elimination half-life (t ½) ranges from 3 to 12 hours with total body clearance (CL) values of 4 to 5.6 L/h. Pharmacokinetics are linear over the dose range used clinically. When cyclophosphamide was administered at 4.0 g/m2 over a 90 minutes infusion, saturable elimination in parallel with first-order renal elimination describe the kinetics of the drug.

c. ADVERSE EFFECTS

Possible Side Effects of cyclophosphamide: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in > 20% of subjects treated with cyclophosphamide include infection (especially when white blood cell count is low), blood in urine, nausea, vomiting, diarrhea, loss of appetite, abdominal pain, sores in mouth, amenorrhea, alopecia, skin changes, rash, nail changes.

Adverse effects reported in 4% to 20% of subjects include cardio toxicity, pulmonary toxicity, hematologic toxicity (myelosupression, immunosuppression, bone marrow failure), hepatotoxicity, anaphylaxis, azoospermia, nasal congestion.

Serious adverse effects reported in ≤ 3% of subjects include cardiomyophathy, heart failure, encephalopathy, impaired cognition, secondary malignancies, Stevens-Johnson syndrome, toxic epidermal necrolysis, veno-occlusive disease of the liver.

Pregnancy and Lactation: Cyclophosphamide can cause fetal harm when administered to pregnant women. Exposure to cyclophosphamide during pregnancy may cause fetal malformations, miscarriage, fetal growth retardation, and toxic effects in the newborn.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) cyclophosphamide, the patient should be informed of the potential hazard to the fetus. Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception during

treatment and for up to 1 year after completion of therapy. Cyclophosphamide is present in breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhea have been reported in infants breast fed by women treated with cyclophosphamide. Advise nursing mothers treated with cyclophosphamide to discontinue nursing or discontinue cyclophosphamide, taking into account the importance of the drug to the mother.

Drug Interactions: Cyclophosphamide is a pro-drug that is activated by cytochrome P450s therefore creating potential for interactions based on competitive metabolism with relevant enzymes including CYP2A6, 2B6, 3A4, 3A5, 2C9, 2C18 and 2C19, and 2B6. In addition, combined or sequential use of cyclophosphamide and other agents with similar toxicities can potentiate toxicities.

Due to potential drug interactions, a complete patient medication list, including cyclophosphamide, should be screened prior to initiation of and during treatment with cyclophosphamide. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. STORAGE & STABILITY

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Cyclophosphamide is commercially available and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

3.3 Docetaxel (Taxotere®) (NSC-628503)

a. PHARMACOLOGY

Mechanism of Action: Docetaxel promotes the assembly of microtubules and stabilizes their formation by inhibiting depolymerization. This stabilization creates a microtubule which is non-functional. Cell death is promoted by the disruption of normal cell shape, motility, attachment, and intracellular transport. Docetaxel is cytotoxic predominately in the s-phase of the cell cycle.

b. PHARMACOKINETICS

Absorption: Intravenous administration of docetaxel results in 100% bioavailability. Area under the curve (AUC) of docetaxel was dose proportional following doses of 70 mg/m2 to 115 mg/m2 with infusion times of 1 to 2 hours.

Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins.

Metabolism: Docetaxel is primarily metabolized in the liver by cytochrome P450 3A4 (CYP3A4).

Elimination: Docetaxel elimination follows a three compartment model with an initial distribution half-life of 3 to 5 minutes, an intermediate elimination half-life of

36 to 60 minutes, and a terminal half-life of 10 to 18 hours. Mean total body clearance was 21 L/h/m2.Approximately 6% of unchanged drug is eliminated by the kidney in 24 hours, with the majority (80%) of excretion occurring in feces at 7 days.

c. ADVERSE EFFECTS

Possible Side Effects of Docetaxel: The most common adverse effects occurring in > 20% of people receiving docetaxel include: fluid retention, alopecia, nail disorders, skin reactions (rash, pruritis), nausea, vomiting, diarrhea, constipation, mucositis, infections, anemia, asthenia, neutropenia, neuropathy, fever, amenorrhea, erythema of the extremities with edema, pain and lacrimation with or without conjunctivitis, pleural effusion, weight gain.

Adverse effects occurring in ≤ 20% of people receiving docetaxel include: cutaneous skin reactions, abdominal pain, thrombocytopenia, febrile neutropenia, hepatotoxicity, venous thromboembolism, pulmonary embolism, myalgia, anorexia, dysgeusia, dyspnea, and cardiac dysrhythmias, hypertension , epistaxis, cough, joint pain.

Rare (< 3%) but potentially serious adverse effects include: hypersensitivity reactions (rash/erythema, hypotension, wheezing, shortness of breath, swelling of the face or throat), acute myeloid leukemia, and interstitial lung disease or pneumonia, syncope, phlebitis, hearing loss, confusion, seizures, visual disturbances (flashes, scotomata).

Patients receiving docetaxel infusions may experience alcohol intoxication from the ethanol included in the formulation.

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Pregnancy and Lactation: Pregnancy Category D. Excretion in breast milk is unknown and breast feeding is not recommended during treatment.

Drug Interactions: Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A inhibitor cannot be avoided. The alcohol content in a dose of Docetaxel Injection may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in Docetaxel Injection on the ability to drive or use machines immediately after the infusion. In addition, some medications, such as pain relievers and sleep aids, may interact with the alcohol in the Docetaxel infusion and worsen the intoxicating effects. Due to potential drug interactions, a complete patient medication list, including docetaxel, should be screened prior to initiation of and during treatment with docetaxel. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See treatment plan in Section 7.0.

e. HOW SUPPLIED

Docetaxel is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.4 Doxorubicin (Adriamycin) (NSC-123127)

a. PHARMACOLOGY

Mechanism of Action: Doxorubicin is an anthracycline, topoisomerase II inhibitor. It is isolated from cultures of Streptomyces peucetius var. caesius. The cytotoxic effect of doxorubicin is related to nucleotide base intercalation and cell membrane lipid binding activities. It blocks nucleotide replication and the action of DNA and RNA polymerases. The interaction between doxorubicin and topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of its cytocidal activity.

b. PHARMACOKINETICS

1. Absorption: Doxorubicin is given via intravenous infusion. With intravenous administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, administration should be immediately terminated and managed per standard local practice.

2. Distribution: Steady-state volume of distribution: 809-1214 L/m2; protein binding: 74-76%; doxorubicin does not cross the blood brain barrier. Half-life for distribution is approximately 5 minutes.

3. Metabolism: Primarily hepatic. Enzymatic reduction and cleavage of the daunosamine sugar results in aglycones and free radicals. Local production of free radicals contributes to the cardiotoxicity of doxorubicin.

4. Elimination: Excretion is predominantly by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Plasma clearance is in the range of 324 to 809 mL/min/m^2. The terminal half-life is 20-48 hours.

c. ADVERSE EFFECTS

1. Possible Side Effects of Doxorubicin:

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in > 20% of subjects treated with doxorubicin include: vomiting, red colored urine, saliva, or sweat, and hair loss.

Adverse effects reported in 4% to 20% of subjects include: heart failure or heart attack which may cause shortness of breath, swelling of ankles, cough, or tiredness which may occur years after the dose, abnormal heartbeat, cancer of the bone marrow caused by chemotherapy, damage to the lungs which may cause shortness of breath when combined with

radiation, infection (especially when white blood cell count is low), bruising, bleeding, anemia which may cause tiredness or may require transfusion, hepatitis or damage to the liver which may cause yellowing of eyes and skin swelling, kidney damage which may require dialysis, sores in the mouth or throat, belly pain, nausea, diarrhea, allergic reactions which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat, damage to the skin which may cause pain, swelling and redness at the site of the medication injection or area of previous radiation, loss of nails, and darkening of the nail beds or skin or hands and feet.

Serious adverse effects reported in ≤ 3% of subjects include severe blood infection.

2. Pregnancy and Lactation: Pregnancy Category D. Doxorubicin HCl can cause fetal harm when administered to a pregnant woman. Doxorubicin HCl was teratogenic and embryotoxic in rats and rabbits at doses approximately 0.07 times (based on body surface area) the recommended human dose of 60 mg/m2. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

   Doxorubicin has been detected in the milk of at least one lactating patient. Nursing is not recommended while receiving doxorubicin therapy because of the potential for adverse events in a nursing child.

3. Drug Interactions: Doxorubicin is a major substrate of cytochrome P450 CYP 3A4, CYP 2D6, and P-glycoprotein (P-gp). Avoid concurrent use of doxorubicin with inhibitors and inducers of CYP 3A4, CYP 2D6, or P-gp. Do not administer doxorubicin in combination with Trastuzumab due to increased risk of cardiac dysfunction.

   Due to potential drug interactions, a complete patient medication list, including doxorubicin, should be screened prior to initiation of and during treatment with doxorubicin. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

   See Section 7.0 Treatment Plan

e. STORAGE & STABILITY

   Doxorubicin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

f. HOW SUPPLIED

   Doxorubicin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.5 Paclitaxel (Taxol®, NSC-673089)

a. PHARMACOLOGY

Mechanism of Action: Paclitaxel is a diterpene plant product found in the needles and bark of the western yew, Taxus brevifolia. The marketed formulation is prepared in a semi-synthetic process. Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This results in the inhibition of the normal dynamic reorganization of the microtubule network that is required for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle which interrupt mitosis and subsequently result in apoptosis.

b. PHARMACOKINETICS

Absorption: Paclitaxel is given via intravenous infusion.

Distribution: Following intravenous administration of paclitaxel, the drug, plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is a result, in part, of a relatively slow efflux of paclitaxel from the peripheral compartment. In vitro studies of paclitaxel binding to human serum proteins using concentrations from 0.1 to 50 microgram/mL indicated that between 89%-98% of paclitaxel is protein bound. The mean apparent volume of distribution at steady state, with the 24-hour infusion of paclitaxel, ranged from 227 to 688 L/m2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

Metabolism: Paclitaxel is metabolized via the cytochrome P450 isoenzyme CYP2C8 to one major inactive metabolite (6-alpha-hydroxypaclitaxel), and via the cytochrome P450 isoenzyme CYP3A4 to two minor inactive metabolites (3-p-hydroxypaclitaxel and 6-α, 3-p-dihydroxypaclitaxel).

Elimination: Following the administration paclitaxel, the cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. Use of radiolabeled paclitaxel infusion showed that 71% of paclitaxel dose was excreted in feces, with 5% as unchanged drug. The elimination half-life of paclitaxel ranged between 13.1 and 52.7 hours.

c. ADVERSE EFFECTS

Possible Side Effects of Paclitaxel: Refer to the current FDA-approved paclitaxel package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in >20% of subjects treated with paclitaxel include alopecia, anemia, arthralgia, asthenia, cytopenia, diarrhea, flushing, hypersensitivity reactions, infection, increased serum alkaline phosphatase, nausea, mucositis, myalgia, paresthesia, peripheral neuropathy, pneumonitis, thrombosis, and vomiting.

Adverse effects reported in 4% to 20% of subjects treated with paclitaxel include: ECG abnormalities, pneumonitis, and thrombosis

Serious adverse effects reported in ≤3% of subjects treated with paclitaxel include: anaphylaxis; gastrointestinal ischemia or perforation; myocardial infarction; severe hypersensitivity reactions characterized by dyspnea, hypotension requiring treatment, angioedema, and generalized urticaria; Stevens-Johnson syndrome; and toxic epidermal necrolysis.

Pregnancy and Lactation: Paclitaxel may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryo- and fetotoxic in rats and rabbits and to decrease fertility in rats. In these studies, paclitaxel was shown to result in abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased resorption and embryo-fetal deaths. Paclitaxel is present in breast milk. A pharmacokinetic breastfeeding study indicated that the relative infant dose of paclitaxel is ~17% of the maternal dose. Due to the potential for serious adverse events in a breastfeeding infant, nursing is not recommended.

Drug Interactions: Concomitant administration of paclitaxel with inhibitors/inducers/substrates of CYP3A4 and CYP2C8 may alter the pharmacokinetic or pharmacodynamic properties of paclitaxel and/or concurrent medications. See section 7.X for details.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Paclitaxel is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.6 MK-3475 (pembrolizumab, KEYTRUDA ®) (NSC-776864)

a. PHARMACOLOGY

Mechanism of Action: Pembrolizumab (MK-3475) is a humanized MAb of the IgG4/kappa isotype. The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells expressing PD-1 ligands to suppress immune control. Pembrolizumab (MK-3475) blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands and thereby promoting the host immune system to recognize tumor cells as foreign bodies to be eliminated.

b. PHARMACOKINETICS

1. Absorption: Pembrolizumab is administered via intravenous infusion.

2. Distribution: The geometric mean value for volume of distribution at steady state is 6.0 L. In a population PK analysis, 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.

3. Metabolism: Pembrolizumab follows general protein degradation pathways in the body. Cytochrome p450 enzymes are not involved in metabolism.

4. Elimination: Clearance is approximately 23% lower (195 mL/day) at steady state than that after the first dose (252 mL/day); this decrease in clearance with time is not considered clinically significant. The terminal half-life (t1/2) is 22 days.

c. ADVERSE EVENTS

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 systemRefer 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)
		Uveitits[2]
GASTROINTESTINAL DISORDERS		

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Abdominal pain	
	Colitis[2]	
	Constipation	
	Diarrhea[2]	
		Entercolitis[2]
		Gastritis[2]
		Gastrointestinal distorders – Other (exocrine pancreatic insufficiency)
	Mucositis oral[2]	
	Nausea	
	Pancreatitis[2]	
	Small intestinal mucositis[2]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills[2]	
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]	

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 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	
	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)

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		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 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.

1. Pregnancy and Lactation:
Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. There are no available human data informing the risk of embryo-fetal toxicity. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Females of reproductive potential should use effective contraception during treatment with pembrolizumab and for at least 4 months following the final dose.
There are no data on the presence of pembrolizumab in either animal or human milk or its effects on the breastfed child or on milk production. Women should not breastfeed during treatment and for 4 months after the final dose.

2. Drug Interactions: There are no reported enzyme or transporter drug interactions that may alter the pharmacokinetic or pharmacodynamics properties of pembrolizumab.

c. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

d. HOW SUPPLIED

Pembrolizumab is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

4.0 STAGING CRITERIA

All staging will be based on the American Joint Committee on Cancer (AJCC) 2017 Staging System, 8th Edition.

Primary Tumor (T)

TX Main tumor cannot be measured
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm in greatest dimension
T4 Tumor of any size with direct extension to the chest wall and/or to the skin

Regional Lymph Nodes (N)

N0 No regional lymph node metastasis
N1 Metastasis to movable ipsilateral axillary lymph node(s)
N2 Metastasis in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis

Distant Metastasis (M)

M0 No distant metastasis

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a participant to be considered eligible for registration in OPEN. Section 5 may be printed and used to by the site, but is not to be uploaded in RAVE (unless specially stated). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG SDMC in Seattle at 206/652-2267 or breastquestion@crab.org prior to registration.
NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient participant scheduling without exceeding the guidelines. **If Day 7, 14, 28, 30 or 49 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Participants must have histologically confirmed ER-negative, PR-negative, and HER2-negative breast cancer (TNBC) defined as ER<5%, PR<5%, and HER2 negative (per 2020 ASCO CAP guidelines).

NOTE: Participants with weakly ER or PR positive disease, defined as ER and/or PR between 1-4% by immunohistochemistry, are eligible if adjuvant endocrine therapy is not recommended/planned by the treating physician.

NOTE: Participants with bilateral invasive breast cancer are eligible if both breast cancers are ER-negative, PR-negative, and HER2-negative provided they meet the other eligibility criteria.

NOTE: Participants with concurrent DCIS (ipsilateral or contralateral) are eligible provided endocrine therapy is not planned for DCIS treatment and they meet other eligibility criteria.

NOTE: Participants with multifocal or multicentric disease are eligible provided they meet the other eligibility criteria.

b. Participants must have AJCC 8 anatomic tumor clinical stage (determined by physical examination and/or imaging) either

- T2-T4, N0, M0
- T1-T3, N1-2, M0 or
- TX N1-2, M0

NOTE: All participants with clinically suspicious nodes must undergo core needle biopsy or fine needle biopsy per standard clinical practice to pathologically confirm nodal status, unless biopsy/FNA is not safe or feasibe.

c. Participants must have breast and axillary imaging (on the affected side) with mammogram and/or ultrasound and/or MRI within 49 days prior to randomization.

NOTE: Participants with Tx N1-2 disease are eligible provided they meet other eligibility criteria.

d. Participants must not have T4/N+, any N3, or inflammatory breast cancer.

e. Participants must not have metastatic disease (M1).

5.2 Prior/Concurrent Therapy Criteria

a. Participants must not have received prior systemic therapy or radiation therapy with curative intent for the current breast cancer

b. Participants must not have had previous definitive ipsilateral breast surgery for the current breast cancer

c. Participants must not have current or anticipated use of other investigational agents during the protocol directed neoadjuvant therapy.

d. Participants must not have history of allergic reactions attributed to compounds of similar chemical or biologic composition as study agents

e. Participants must not have severe hypersensitivity (≥ grade 3) to pembrolizumab or any of its excipients.

f. Participants must not have received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).

g. Participants must not be currently participating in or have participated in a study of an investigational agent or used an investigational device within 28 days prior to randomization.

5.3 Clinical/Laboratory Criteria

a. Participants must be ≥ 18 years old.

b. Participants must have Zubrod Performance Status of 0-2 (see Section 10.11).

c. Participants with evidence of peripheral neuropathy must have it at ≤ Grade 1, by CTCAE v. 5.0, within 28 days prior to randomization.

d. Participants must have a complete medical history and physical exam within 28 days prior to randomization.

e. Participants must have adequate organ and marrow function as defined below within 28 days prior to randomization:

– Hemoglobin	≥9.0 g/dL or ≥ 5.6 mol/L (Criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within last 2 weeks)
– leukocytes	≥3 x 10^3/uL
– absolute neutrophil count*	≥1.5 x 10^3/uL
– platelets	≥100 x 10^3/uL
– total bilirubin	≤ 1.5x institutional upper limit of normal (IULN), OR direct bilirubin ≤ IULN for participants with total bilirubin >1.5x IULN (unless history of Gilbert's disease. Participants with history of Gilbert's disease must have total bilirubin ≤ 5 x institutional IULN).
– AST and ALT	≤ 3 × institutional ULN

* Participants with documented Fy(A-/B-) immunophenotype must have an absolute neutrophil count ≥ 1.2 x 10^3/uL *(48, 49)*

f. Participants must have a serum creatinine ≤ the IULN OR calculated creatinine clearance ≥ 50 mL/min/1.73m2 using the Cockcroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to registration For creatinine clearance formula see the tools on the CRA Workbench https://txwb.crab.org/TXWB/Tools.aspx.

Note: If weight is greater than 140% of IBW, IBW x 1.4 must be used in the Calculated Creatinine Clearance formula. IBW is to be calculated as per SWOG Policy 38. If creatinine < 0.7 mg/dL, a creatinine value of 0.7 mg/dL must be used in the Calculated Creatinine Clearance formula.

g. Participants must have adequate cardiac function. Participants must have left ventricular ejection fraction ≥50% as assessed by either ECHO or MUGA assessed within 28 days prior to registration. Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (see Section 18.1) and must be class 2B or better.

h. Participants with known human immunodeficiency virus (HIV)-infection must be on effective anti-retroviral therapy at randomization and have undetectable viral load test on the most recent test results obtained within 6 months prior to randomization.

i. Participants with evidence of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load while on suppressive therapy on the most recent test results obtained within 6 months prior to randomization, if indicated.

NOTE: No testing for Hepatitis B is required unless mandated by local health authority.

j. Participants with a history of hepatitis C virus (HCV) infection must have been treated and cured. Participants currently being treated for HCV infection must have undetectable HCV viral load test on the most recent test results obtained within 6 months prior to randomization, if indicated.

NOTE: No testing for Hepatitis C is required unless mandated by local health authority.

k. Participants with history of diabetes must not have uncontrolled diabetes in the opinion of the treating investigator.

l. Participants must not have uncontrolled hypertension in the opinion of the treating investigator.

m. Participants must not have had a major surgery within 14 days prior to randomization. Participants must have fully recovered from the effects of prior major surgery in the opinion of the treating investigator.

n. Participants must not have severe or active infections within 14 days prior to Randomization, including but not limited to hospitalization for infection, bacteremia, or severe pneumonia.

o. Participants must not have a diagnosis of immunodeficiency and be receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization.

p. Participants must not have active autoimmune disease that has required systemic treatment in 2 years prior to randomization (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

q. Participants must not have a history of (non-infectious) pneumonitis that required steroids, or has current (non-infectious) pneumonitis.

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

s. Participants must not have a prior or concurrent malignancy whose natural history or treatment (in the opinion of the treating physician) has the potential to interfere with the safety or efficacy assessment of the treatment regimen.

t. Participants must not be pregnant or nursing. Individuals who are of reproductive potential must have agreed to use an effective contraceptive method with details provided as a part of the consent process. A person who has had menses at any time in the preceding 12 consecutive months or who has semen likely to contain sperm is considered to be of "reproductive potential." In addition to routine contraceptive methods, "effective contraception" also includes refraining from sexual activity that might result in pregnancy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) including hysterectomy, bilateral oophorectomy, bilateral tubal ligation/occlusion, and vasectomy with testing showing no sperm in the semen.

5.4 Additional Criteria

a. Participants must have one (1) physical 4–5-micron single H&E slide from the archival pretreatment diagnostic biopsy available for submission, as outlined in Section 15.2.

b. Participants registered by sites located in the United States must be offered the opportunity to participate in specimen banking as outlined in Section 15.3. With participant consent, specimens must be collected and submitted via the SWOG Specimen Tracking System as outlined in Section 15.4.

c. Participants who can complete the questionnaires in English, Spanish, or French must be offered the opportunity to participate in the Quality of Life studies as outlines in Section 15.6.

5.5 Regulatory Criteria

NOTE: As a part of the OPEN registration process (see Section 13.5 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

a. Participants ***must*** be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines. Documentation of informed consent via remote consent is allowed, as indicated in Section 18.5. See Section 18.5 for remote consenting procedures.

For participants with impaired decision-making capabilities, legally authorized representatives may sign and give informed consent on behalf of study participants in accordance with applicable federal, local, and CIRB regulations.

As part of the registration process the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION AND DESCRIPTIVE FACTORS

Participants will be randomized between the two treatment arms according to a dynamic balancing scheme, with the randomization stratified by nodal status (negative vs. positive). After randomization TIL status will be determined and used as a stratification factor in the analysis.

7.0 TREATMENT PLAN

See Section 18.5 for remote consenting procedures.

Initiation of treatment must be planned to start no more than 21 calendar days after registration.

- For treatment or dose modification questions, please contact:

  E-mail: S2212question@swog.org

  or by phone:
  Dr. Priyanka Sharma at: 913-588-6079 or
  Dr. Zahi Mitri at: 604-217-6002.

- For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Participants on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2021-10/Policy38_1.pdf.

  Note: Unless otherwise indicated, scheduled procedures and assessments must follow the established SWOG guidelines as outlined in the "Best Practices" document located at https://www.swog.org/clinical-trials/protocol-workbench.

7.1 Pre-Medication and Concomitant Therapy

a. Pre-medication: Pre-medication associated with standard drug administration and supportive care (including anti-emetics, anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines and per institutional guidelines.

b. Concomitant Therapy

1. Enzyme Drug Interactions: Docetaxel and Paclitaxel (Taxol®) are a substrate of enzyme CYP3A4 and CYP2C8. Concurrent administration of the strong/moderate inhibitors or inducers of these enzymes should be avoided or monitored closely during study participation to avoid increased or decreased systemic exposure of the paclitaxel and the concurrent medication.

2. Lists of CYP inhibitors or inducers are accessible from: https://drug-interactions.medicine.iu.edu/MainTable.aspx OR consult local institutional pharmacists.

3. Transporter Drug Interactions: Examples of clinical substrates and inhibitors of transporters [e.g. P-gp, BCRP, OATP1B1 or 3, OAT1 or 3, MATE1 or 2K, OCT2] are accessible from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers OR consult local institutional pharmacists.

4. QT Prolongation: Docetaxel and Paclitaxel have been associated with QTc interval prolongation and bradycardia on rare occasions. Docetaxel and Paclitaxel can also increase QT/QTc interval prolongation risk of concomitant drugs. Concurrent administration of these agents should be avoided or monitored closely during study participation.

5. Lists of drugs known to have QT prolongation risk are accessible from (requires free registration): https://www.crediblemeds.org/ OR consult local institutional pharmacists.

6. Due to potential drug interactions, a complete patient medication list, including paclitaxel, should be screened prior to initiation of and during treatment with paclitaxel. Counseling local institutional pharmacists is also recommended.

7. Vaccines (Live)

   Immunosuppressants may result in enhanced viral replication and increased risk of disseminated disease. Administration of live vaccines should be avoided during treatment with paclitaxel and for at least 3 months after immunosuppression.

7.2 Treatment

For treatment or dose modification questions, please contact:

E-mail: S2212question@swog.org

or by phone:
Dr. Priyanka Sharma at: 913/588-6079 or
Dr. Zahi Mitri at: 604-217-6002.

The standard of care protocol-specified therapy may be administered by a local healthcare professional (HCP) with appropriate reporting of therapy administration data and adverse event information to the Responsible Investigator (RI). See Section 18.5 for details.

a. **Arm 1: Neoadjuvant Carboplatin/Paclitaxel/Pembrolizumab followed by AC/Pembrolizumab**

Growth factor support can be used per MD discretion during all parts of the treatment

AGENT [i]	**DOSE**	**ROUTE**	**DAY**	**Cycles**	**SCHEDULE** [a]
Paclitaxel[j]	80 mg/m2	IV (over 60 minutes)	Days 1, 8, 15	1-4	Every 21 days [b,d]
Carboplatin [c]	AUC 1.5	IV	Days 1, 8, 15	1-4	Every 21 days [b,d]
	OR				
	AUC 5	IV	Day 1	1-4	Every 21 days [b]
Pembrolizumab	200 mg	IV	Day 1	1-4	Every 21 days [b]
Followed by					
AGENT [i]	**DOSE**	**ROUTE**	**DAY**	**Cycles**	**SCHEDULE**[e]
Doxorubicin [f,g]	60 mg/m2	IV push (over 3-5 min)	Day 1	5-8	Every 21 days [f] ***OR*** Every 14 days [f]
Cyclophosphamide [f,g]	600mg/m2	IV (over 30 min)	Day 1	5-8	
Pembrolizumab	200 mg	IV	Day 1 [h]	5-8 [h]	Every 21 days [h]

[a] One cycle = 21days

[b] +/- 1 day

[c] The SWOG guidelines must be followed for carboplatin dose calculation: 1) Use of Modified Cockcroft-Gault formula for calculating renal function, 2) Calculating Modified Cockcroft-Gault with serum creatinine set to 0.7 mg/dL if actual serum creatinine < 0.7 mg/dL, 3) Maximum GFR is 125 mL/min, 4) Limiting weight to 140% of ideal body weight for calculation of creatinine clearance. There are freely available calculators to assist with calculations: https://txwb.crab.org/TXWB/CreatinineClearanceCalculator.aspx.

[d] Any missed doses of weekly paclitaxel and/or carboplatin (cycles 1-4) can be made up prior to starting doxorubicin plus cyclophosphamide as long total duration of paclitaxel plus carboplatin treatment does not exceed 16 weeks.

[e] One cycle = 21days ***OR*** 14 days, determined by doxorubicin and cyclophosphamide (AC) schedule.

[f] Doxorubicin and cyclophosphamide to be given on same schedule either every 21 days (+/- 3 days) ***OR*** every 14 days (+/- 2 days).

[g] Myeloid Growth factor support with pegfilgrastim or equivalent is required for every 14 days schedule, and can be used per MD discretion for every 21 days schedule.

[h] On the 14 day cycle AC schedule, the pembrolizumab doses would correspond to C5D1, C6D8, C8D1, and C8D22. All four (4) doses of pembrolizumab should be given. The last dose of pembrolizumab will count as the last neoadjuvant systemic therapy.

[i] Sites should follow standard protocols for administration and sequencing of drugs.

[j] Nab-paclitaxel may be substituted for participants with hypersensitivity reaction to paclitaxel (see Section 8.3a.5).

NOTE: No more than eight Neoadjuvant Pembrolizumab doses should be given in ARM 1. Adjuvant pembrolizumab can be administered in the adjuvant post-surgery setting per Section 7.4a.

b. **Arm 2: Neoadjuvant Carboplatin/Docetaxel/Pembrolizumab**

AGENT [c]	DOSE	ROUTE	DAY	Cycles	SCHEDULE
Docetaxel [a]	75 mg/m2	IV over 60 min	Day 1	1-6	Every 21 days [b]
Carboplatin [a, d]	AUC 6	IV	Day 1	1-6	Every 21 days [b]
Pembrolizumab	200 mg	IV	Day 1	1-6	Every 21 days [b]

[a] Myeloid Growth factor support with pegfilgrastim or equivalent is required with every cycle

[b] +/- 3 days

[c] Sites should follow standard protocols for administration and sequencing of drugs.

[d] The SWOG guidelines must be followed for carboplatin dose calculation: 1) Use of Modified Cockcroft-Gault formula for calculating renal function, 2) Calculating Modified Cockcroft-Gault with serum creatinine set to 0.7 mg/dL if actual serum creatinine < 0.7 mg/dL, 3) Maximum GFR is 125 mL/min, 4) Limiting weight to 140% of ideal body weight for calculation of creatinine clearance. There are freely available calculators to assist with calculations: https://txwb.crab.org/TXWB/CreatinineClearanceCalculator.aspx.

NOTE: No more than six Neoadjuvant Pembrolizumab doses should be given in ARM 2. Adjuvant pembrolizumab can be administered in the adjuvant post-surgery setting per Section 7.4a.

7.3 Post-Chemotherapy Surgery

After completion of NAST, participants will proceed with definitive surgery (appropriate surgery type to be determined by treating physician/s). It is recommended that surgery should take place between 3 and 10 weeks after the last NAST dose.

Histopathological examination of the surgical specimen will be done to determine the extent of residual disease. pCR will be defined as no evidence of invasive disease in the breast and axilla at the time of pathology review. Participants with only residual DCIS in breast and/or ITCs in axillary Lymph nodes will be defined as having pCR.

7.4 Adjuvant Therapy

a. ***Adjuvant Pembrolizumab***

Adjuvant pembrolizumab is recommended for all participants. For both groups, the overall duration of pembrolizumab is no more than 55 weeks, regardless of how many cycles are administered during the 55-week period. For participants achieving pCR, co-enrollment on de-escalation trials (e.g. OptimICE-pCR (A012103) is allowed.

Adjuvant pembrolizumab should be resumed after surgery as standard of care at the timepoint considered appropriate by treating provider. Adjuvant pembrolizumab can be given at an every 6 week dose/schedule at physician's discretion for a total of 55 weeks of therapy (neoadjuvant plus adjuvant pembrolizumab therapy.

b. ***Adjuvant Chemotherapy***

1. Participants achieving pCR: No further adjuvant chemotherapy is recommended regardless of the randomized arm. Participants will be followed for primary and secondary study endpoints.

2. Participants with residual disease:

i. Arm 1: Adjuvant capecitabine recommendations will be per the discretion of treating physician. Adjuvant capecitabine if recommended can be given concurrently or sequentially with pembrolizumab.

ii. Arm 2: Adjuvant chemotherapy with AC (4 cycles) can be given per physician discretion. Adjuvant pembrolizumab should be given concurrently with AC in this setting. Adjuvant capecitabine can be given after AC per physician preference/recommendation. Adjuvant capecitabine if recommended can be given concurrently or sequentially with pembrolizumab.

iii. Arms 1 and 2: For participants with germline BRCA mutations, adjuvant Olaparib is allowed. Adjuvant Olaparib can be given per treating physican's discretion.

c. ***Adjuvant Radiotherapy***

Adjuvant radiation therapy should follow standard guidelines.

7.5 Disease Assessment

a. Participants will be assessed by physical examination each cycle while on neoadjuvant therapy. Follow-up assessment date is calculated from the date of surgery, or if the participant does not go on to surgery, calculated from the date of last dose of neoadjuvant systemic therapy.

b. Participants will have annual breast cancer screening as standard of care with mammography with or without supplemental ultrasonogram or MRI at the discretion of the treating physician. All other imaging studies are at the discretion of the treating physician.

Post neoadjuvant systemic treatment (NAST)/pre-surgical breast imaging (MRI or ultrasound) is recommended at the end of the planned NAST or at any time point if there is suspected clinical progression. This is standard of care. Patients with clinical disease progression or disease progression confirmed by imaging will be considered as non-pCR and can undergo additional NAST prior to surgical resection at the discretion of the treating physician.

7.6 Central Tumor Infiltrating Lymphocyte Assessment

A scanned full-face H&E slide will be used for TIL assessment. After a new participant is registered for the trial, a full-face H&E slide will be shipped to SWOG Biospecimen Bank where it will be scanned. The scanned slide will subsequently be uploaded on VIPER platform to enable central pathologist TIL reading. TIL scoring will follow the guidelines and recommendation by international TIL working group (Salgado, Denkert et al. 2015). The TILs are assessed proportionally to the stromal compartment of the cancer area, considering exclusion-criteria like TILs present in areas of necrosis and normal breast tissue. Further details regarding TIL assessment recommendations are available on the TIL working group website (Breast Cancer Research Foundation International TILs Working Group 2019) and also described in the Salgado et al 2014 Annals of oncology publication. sTILs can be reported at a range of 1%-100%. sTILs scoring will be reported as quantitative data as continuous values in 10% increments. The 10% increments are typically used for continuous reporting to minimize categories and variance. TIL read and results will not be required for randomization but will be performed in a batched fashion during the course of the study.

7.7 Criteria for Removal from Protocol Treatment

a. Completion of neoadjuvant therapy followed by surgery.

b. Progression of disease (as defined in Section 10.3).

c. Unacceptable toxicity.

d. Treatment delay for any reason > 42 days.

e. The participants may withdraw from the protocol treatment at any time for any reason.

7.8 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.9 Follow-Up Period

All participants will be followed until death or 5 years after registration, whichever occurs first. All participants continue to be followed after neoadjuvant therapy and surgery regardless of whether pCR is achieved or not.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 General Considerations

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

a. The maximum dose delay for any reason is 42 days (6 weeks).

b. Any missed doses of weekly paclitaxel or carboplatin can be made up prior to starting Doxorubicin plus cyclophosphamide as long as total duration of paclitaxel plus carboplatin treatment duration does not exceed 16 weeks.

c. Dose interruptions and discontinuations are allowed to manage toxicity.

d. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

e. Reductions are based on the dose being given at the end of the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.

8.3 Chemotherapy Dose Adjustments / Modifications

a. **Arm 1: Neoadjuvant Carboplatin/Paclitaxel/Pembrolizumab followed by AC/Pembrolizumab**

1. Tables 1 and 2 outline dose level modifications for Arm 1 agents.

2. Paclitaxel dose reductions beyond 70 mg/m2 are allowed per institutional guidelines.

3. During the first part of the combination therapy, if one or more component(s) must be discontinued due to toxicity, the investigator should select one of the following options at his/her discretion for the participant:

a. If only paclitaxel is discontinued due to toxicity related to paclitaxel:

Continue with first part of the neoadjuvant chemotherapy (pembrolizumab + carboplatin); start and complete the AC + pembrolizumab regimen as per protocol, then proceed with surgery.

b. If only carboplatin is discontinued due to toxicity related to carboplatin:

Continue with the first part of the neoadjuvant chemotherapy (pembrolizumab + paclitaxel); start and complete the AC + pembrolizumab regimen as per protocol, then proceed with surgery.

c. If both carboplatin and paclitaxel have to be discontinued due to toxicity:

Participants should proceed to the AC part of the regimen.

d. If only pembrolizumab is discontinued due to toxicity related to pembrolizumab:

Continue with the first part of the neoadjuvant chemotherapy (carboplatin+ paclitaxel); start and complete the AC regimen (without pembrolizumab) as per protocol, then proceed with surgery. Participants will not resume pembrolizumab in the adjuvant phase.

4. During the second part of the combination therapy, if one or more component(s) must be discontinued due to toxicity, the investigator should select one of the following options at his/her discretion.

a. If only doxorubicin is discontinued due to toxicity related to doxorubicin:

Discontinue all study treatment including pembrolizumab and proceed with surgery. Participants can resume pembrolizumab in the adjuvant phase.

b. If pembrolizumab is discontinued due to pembrolizumab related toxicity:

Continue AC for the remaining cycles as planned per protocol, and proceed with surgery. Participants will not resume pembrolizumab in the adjuvant phase.

c. If Cyclophosphamide is discontinued due to toxicity related to cyclophosphamide:

Continue doxorubicin + pembrolizumab for the remaining cycles as planned per protocol, and proceed with surgery

5. Hypersensitivity reactions to chemotherapeutic agents (paclitaxel, carboplatin, doxorubicin, cyclophosphamide) should be managed per institutional guidelines

6. Nab-paclitaxel can be substituted for paclitaxel per institutional guidelines in participants who have a hypersensitivity reaction to paclitaxel.

b. **Arm 2: Neoadjuvant Carboplatin/Docetaxel/Pembrolizumab**

1. Tables 3-6 outline dose level modifications for Arm 2 agents

2. If pembrolizumab is discontinued due to toxicity related to pembrolizumab:

Continue with neoadjuvant chemotherapy (carboplatin+ docetaxel) as per protocol, then proceed with surgery. Participants will not resume pembrolizumab in the adjuvant phase.

3. If carboplatin or docetaxel is discontinued due to toxicity related to the respective drug the investigator can select one of the following options at his/her discretion for the participant:

Docetaxel and Carboplatin dose levels provided in Table 3.

a. Stop neoadjuvant treatment and proceed to surgery, or
b. Switch treatment to another regimen that includes pembrolizumab, at which point the participant will be considered off protocol treatment, or
c. Continue with neoadjuvant treatment with pembrolizumab + Docetaxel (if carboplatin needs to be stopped for drug related toxicity) or continue treatment with pembrolizumab + carboplatin (if docetaxel needs to be stopped for drug related toxicity) per protocol. Then proceed with surgery.

4. Dose modifications for hematological toxicities (Table 4)

5. Dose modifications for non-hematological toxicities (Table 5)

6. Dose modifications for hepatic dysfunction (Table 6). Dose modifications based on day 1 liver function testing.

7. Hypersensitivity reactions to carboplatin or docetaxel should be managed per institutional guidelines

8. Management of edema/fluid retention related to docetaxel:

No dose reduction is required. Participants developing new onset edema, progression of existing edema, or another sign of fluid retention (e.g. pound weight gain) can be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below:

- Hydrochlorothiazide/Triamterene one capsule 25/37.5 mg PO up to three times per day per the discretion of the treating physician

- Furosemide 40 mg PO daily if edema progresses despite hydrochlorothiazide/triamterene therapy. Potassium supplementation should be given as needed.

- If after a two week trial, furosemide 40 mg PO daily is ineffective, the participant may be treated with furosemide 20 mg PO daily plus metolazone 2.5 mg PO daily, with potassium supplementation as needed.

- Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the participant, the overall tumor response, and the medical judgment of the investigator will determine if it is in the participant's best interest to continue or discontinue treatment.

Table 1. Dose Modifications for Paclitaxel and/or Carboplatin (Arm 1)

Toxicities	Grade or Actual Value	Paclitaxel / Carboplatin
Hematological		
Neutropenia	≥1000/mm^3 (Grade 1-2)	No change to paclitaxel and/or carboplatin

	<1000/mm^3 (Grade 3-4)	- Hold paclitaxel and/or carboplatin until ANC ≥1000/mm^3. Administer G-CSF until ANC ≥1000/ mm^3<. - Resume paclitaxel and/or carboplatin based on timing of recovery: < 1 week: Resume paclitaxel and carboplatin at current dose. > 1 week but <3 weeks: Dose reduce paclitaxel to 70 mg/m2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent cycles ≥3 weeks: discontinue paclitaxel and/or carboplatin
Febrile Neutropenia	ANC ≤1000/mm^3 , Fever ≥ 38.5ºC (Grade 3 and 4)	Hold paclitaxel and/or carboplatin until resolved (ANC >1000/mm3, fever <38.5ºC, and resolution of any signs of infection). Administer G-CSF until ANC ≥1000/ mm3. Resume paclitaxel and/or carboplatin according to number of episodes - First episode: Reduce paclitaxel to 70 mg/m2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent cycles - Second episode: discontinue paclitaxel and/or carboplatin
Thrombocytopenia	75-<100,000/mm^3 (Grade 1)	Hold paclitaxel and/or carboplatin until ≥100,000/mm^3, resume treatment based on timing of recovery: - ≤1 week — no change to paclitaxel and carboplatin. - >1 but <3 weeks — Reduce paclitaxel to 70 mg/m2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent doses. - ≥3 weeks: Discontinue paclitaxel and/or carboplatin
	<75,000/mm^3 (≥Grade 2)	Hold paclitaxel and/or carboplatin until ≥100,000/mm3. - Reduce paclitaxel to 70 mg/m2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent doses. - Stop paclitaxel and/or carboplatin if held for ≥3 weeks in a row
Anemia	All grades	No change to paclitaxel and carboplatin - Iron studies can be done and iron replaced at the investigator discretion. Red blood cell transfusions can be given at the investigator's discretion.
Non-Hematological		
Nausea / vomiting	Grade 1 or 2	No change to paclitaxel and/or carboplatin

	≥Grade 3	Hold paclitaxel and/or carboplatin until resolved to ≤Grade 1. - Resume paclitaxel and/or carboplatin at previous dose with modification of premedication - Second episode ≥Grade 3 despite with maximum supportive care, reduce paclitaxel to 70 mg/m2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent cycles
Mucositis / Stomatitis	Grade 1 or 2	No change to paclitaxel and/or carboplatin
	≥Grade 3	Hold paclitaxel and /or carboplatin until resolved to ≤Grade 1. - Resume paclitaxel and /or carboplatin at previous dose with modification of premedication - Second episode ≥Grade 3 despite with maximum supportive care, reduce paclitaxel to 70 mg/m2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent cycles
Neurotoxicity	Grade 1	Continue treatment
	Grade 2	Decrease the dose of paclitaxel by one dose level for all subsequent doses. The dose of carboplatin is not reduced.
	Grade 3	Hold paclitaxel and carboplatin. When neuropathy improves to ≤ grade 2, resume treatment with one dose level reduction of both paclitaxel and carboplatin. If grade 3 peripheral neuropathy does not improve within 3 weeks, discontinue paclitaxel and carboplatin. For grade 3 neuropathy that has recurred after recovery to ≤ grade 2, discontinue paclitaxel and carboplatin.
	Grade 4	Discontinue paclitaxel and carboplatin
Hepatic	Grade 1	No change to paclitaxel and/or carboplatin
	Grade 2 or 3	- Bilirubin fractionation should be performed if total bilirubin >1.5xULN. Dose may continue if isolated bilirubinemia is mostly indirect such as in subject with Gilbert - Hold paclitaxel and/or carboplatin until resolve to Grade 1 and resume the dose at previous level - Discontinue paclitaxel and/or carboplatin if held for ≥3 weeks in a row
	Grade 4	- Discontinue paclitaxel and/or carboplatin - Note all concurrent ALT/AST >3×ULN and Total bilirubin >2×ULN should be discontinued

		and evaluated for potential Hy's law
Anaphylaxis / Hypersensitivity	Mild	Complete paclitaxel or carboplatin infusion, observe until symptom resolved
	Moderate	- Stop infusion and treat per standard practice - Resume infusion at half of the infusion speed if symptoms resolve - Stop if symptoms recur
	Severe	Stop infusion immediately and discontinue treatment
Other significant toxicities excluding fatigue, alopecia and leukopenia	Grade 2	- Hold paclitaxel and/or carboplatin until resolve to ≤Grade 1 - Resume at the previous dose and increase supportive care measure, if available
	≥Grade 3	- Hold paclitaxel and/or carboplatin, and discuss with sponsor medical monitor for further instructions - If ≥Grade 3 toxicity recurs upon rechallenge, discontinue treatment permanently

Table 2. Dose Modifications for AC (Arm 1)

Toxicities	Grade or Actual Value	Doxorubicin and Cyclophosphamide (AC)
Hematological		
Neutropenia	≥1000/mm^3 (Grade 1-2)	No change to AC
	<1000/mm^3 (Grade 3-4)	- Hold AC until ANC ≥1000/mm^3. Administer G-CSF until ANC ≥1000/ mm3. - Resume AC based on timing of recovery: <3 weeks: Dose reduce AC by 20% for all subsequent cycles ≥3 weeks: discontinue AC
Febrile Neutropenia	ANC ≤1000/mm^3 , Fever ≥ 38.5^{o}C (Grade 3 and 4)	Hold AC until resolved (ANC >1000/mm3 , fever <38.5^{o}C, and resolution of any signs of infection). Administer G-CSF until ANC ≥1000/ mm3 . Resume AC according to number of episodes - First episode: Reduce AC by 20% for all subsequent cycles - Second episode: discontinue AC
Thrombocytopenia	75-<100,000/mm^3 (Grade 1)	Hold AC until ≥100,000/mm^3, resume treatment based on timing of recovery: - ≤1 week — no change AC - >1 but <3 weeks — Reduce AC by 20% for all subsequent doses. - ≥3 weeks: Discontinue AC
	<75,000/mm^3 (≥Grade 2)	Hold AC until ≥100,000/mm3. - Reduce AC by 20% for all subsequent cycles - Discontinue AC if held for ≥3 weeks in a row

Anemia	All grades	No change to AC - Iron studies should be done and iron should be replaced as indicated. - Red blood cell transfusions can be given at the investigator's discretion.
Non-Hematological		
Nausea / vomiting	Grade 1 or 2	No change to AC
	≥Grade 3	Hold AC until resolved to ≤Grade 1. - Resume AC at previous dose with modification of premedication - Second episode ≥Grade 3 despite with maximum supportive care, reduce AC by 20% for all subsequent cycles
Mucositis / Stomatitis	Grade 1 or 2	No change to AC
	≥Grade 3	Hold AC until resolved to ≤Grade 1. - Resume AC at previous dose with modification of premedication - Second episode ≥Grade 3 despite with maximum supportive care, reduce AC by 20% for all subsequent cycles
Hepatic	Grade 1	No change to AC
	Grade 2 or 3	- Hold AC until resolve to Grade 1 and resume the dose at previous level - Discontinue AC if held for ≥3 weeks in a row
	Grade 4	- Discontinue AC - Note all concurrent ALT/AST >3×ULN and Total bilirubin >2×ULN should be discontinued and evaluated for potential Hy's law
Cardiac	Grade 1 or 2	No change to AC
	≥Grade 3	Discontinue AC
Anaphylaxis / Hypersensitivity	Mild	Complete AC infusion, observe until symptom resolved
	Moderate	- Stop infusion and treat per standard practice - Resume infusion at half of the infusion speed if symptoms resolve - Stop if symptoms recur
	Severe	Stop infusion immediately and discontinue treatment
Other significant toxicities excluding fatigue, alopecia and leukopenia	Grade 2	- Hold AC until resolve to ≤Grade 1 - Resume at the previous dose and increase supportive care measure, if available
	≥Grade 3	- Hold AC, and discuss with sponsor medical monitor for further instructions - If ≥Grade 3 toxicity recurs upon rechallenge, discontinue treatment permanently

Table 3. Dose Levels for Carboplatin and Docetaxel (Arm 2)

DOSE LEVEL [a] / AGENT	Carboplatin (AUC)	Docetaxel (mg/m2)
Level 0	6	75
Level -1	5	60
Level -2	4	50

[a] There are no dose reductions below level -2 for carboplatin or docetaxel. If dose reduction below level -2 is required, discontinue the respective drug.

Table 4. Dose Adjustment for Hematological Toxicities (Arm 2)

ANC[a] < 1000/uL (day 1 of cycle)	Delay docetaxel and carboplatin until ANC ≥1,000/uL. If counts recover to ≥ 1,000/uL in ≤ 1 week, resume at current dose. If docetaxel and carboplatin are delayed for 2 consecutive weeks for ANC < 1000/uL, reduce docetaxel and carboplatin by one dose level for all subsequent cycles. If docetaxel and carboplatin are delayed for 3 consecutive weeks for ANC < 1000/uL, discontinue docetaxel and carboplatin.
ANC < 100/uL or febrile neutropenia[a] (at any time)	Reduce docetaxel and carboplatin by one dose level for all subsequent cycles.
Platelets < 50,000/uL (day 1 of cycle)	Hold docetaxel and carboplatin until platelets ≥ 75,000/uL, then resume docetaxel and carboplatin with one dose level reduction for both drugs for all subsequent doses. If docetaxel and carboplatin are held for 3 consecutive weeks for platelets < 75,000/uL, discontinue treatment.
Platelets ≥ 50,000/uL and < 75,000/uL (day 1 of cycle)	Hold both docetaxel and carboplatin until platelets ≥ 75,000/uL and resume docetaxel at previous dose and carboplatin with one dose level reduction for all subsequent doses. If docetaxel and carboplatin are held for 3 consecutive weeks for platelets < 75,000/uL, discontinue treatment.

[a] There will be no dose modifications for grade 1-4 anemia. If the ANC is < 1,000/uL or platelet count is
< 50,000/uL when drawn more than 24 h prior to the scheduled treatment, CBC should be re-checked on the day of treatment to see if the blood counts have recovered sufficiently to allow the schedule treatment to be given.

[b] Febrile neutropenia: a single temperature ≥ 38.3 ˚C or a sustained temperature of ≥ 38˚C for more than an hour in presence of ANC < 1,000/uL.

Table 5. Dose Adjustment for non-Hematological Toxicities (Arm 2)

Peripheral neuropathy	Grade 1: Continue treatment Grade 2: Decrease the dose of docetaxel by one dose level for all subsequent doses. The dose of carboplatin is not reduced. Grade 3: Hold docetaxel and carboplatin. When neuropathy improves to ≤ grade 2, resume treatment with one dose level reduction of both docetaxel and carboplatin. If grade 3 peripheral neuropathy does not improve within 3 weeks, discontinue docetaxel and carboplatin. For grade 3 neuropathy that has recurred after recovery to ≤ grade 2, discontinue docetaxel and carboplatin. Grade 4: Discontinue docetaxel and carboplatin	
Nausea/Vomiting	Grade 1 or 2	No change to docetaxel and/or carboplatin
	≥Grade 3	Hold docetaxel and/or carboplatinuntil resolved to ≤Grade 1. - Resume docetaxell and/or carboplatin at previous dose with modification of premedication - Second episode ≥Grade 3 despite with maximum supportive care, reduce docetaxel and/or carboplatin one dose level for all subsequent cycles
Hypersensitivity reactions	See below for management.	
Fluid retention	There are no dose reductions for fluid retention (see below for management).	
Hepatic dysfunction (day 1 LFTs)	Refer to Table 6 for management of hepatic dysfunction on Arm 2.	
Other non-hematologic toxicities	For any other grade 3 or 4 toxicity (except for fatigue, nausea or vomiting), delay docetaxel and carboplatin until toxicity improves to ≤ grade 2. When treatment is resumed, reduce the doses of docetaxel and carboplatin by one dose level. If toxicity does not improve to ≤ grade 2 within 3 weeks, discontinue docetaxel and carboplatin and proceed to surgery when feasible.	

Table 6. Dose Adjustments for Hepatic Dysfunction (Arm 2)

Liver Function Tests	Dose Modification
Total bilirubin > 1.5x IULN AND alkaline phosphatase > 2.5x IULN	Hold docetaxel. If not resolved in one week, subject should be removed from protocol treatment.
AST/ALT >2.5x IULN but ≤ 5x IULN AND Alkaline phosphatase > IULN but ≤ 2.5x IULN	Docetaxel one dose level reduction
AST/ALT >1.5x IULN and ≤ 5x IULN AND Alkaline phosphatase > 2.5x IULN but ≤5x IULN	Docetaxel one dose level reduction
AST/ALT > 5x IULN AND/OR Alkaline phosphatase > 5x IULN	Hold docetaxel. If not resolved in one week, subject should be removed from protocol treatment.

8.4 Arms 1 and 2: Pembrolizumab Dose Adjustments / Modifications

a. Table 7 outlines management of Pembrolizumab immune related adverse events (irAEs).

b. Table 8 outlines management of Pembrolizumab infusion reactions.

c. Table 9 outlines management of Pembrolizumab neurological toxicities.

d. There are no dose reductions for pembrolizumab.

e. Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 6 weeks of the schedule interruption, unless otherwise discussed with the principal investigator. The reason for interruption should be documented in the participant's study record.

f. If pembrolizumab is discontinued during the neoadjuvant treatment phase due to toxicity, pembrolizumab should not be resumed after surgery.

g. Immune-related toxicities management

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as described in Section 8.4.i.

h. Supportive Care Guidelines

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in the table in Section 8.4.i. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note

that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

i. Dose Modification and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 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.

Table 7. Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions Associated with Pembrolizumab

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, abdominal pain, blood or mucus in stool with

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**
	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	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)

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**
	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.

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**
	New onset T1DM (evidence of b-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]		

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**
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 carbimazole as needed	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue [d]		
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		

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**
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

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**
	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
	Suspected SJS, TEN, or DRESS	Withhold		Ensure adequate evaluation to

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**
Exfoliative Dermatologic Conditions	Confirmed SJS, TEN, or DRESS	Permanently discontinue	Based on severity of AE administer corticosteroids	confirm etiology or exclude other causes Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology
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		

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).

Table 8. Management of Pembrolizumab Infusion Reactions

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	• 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.	
<u>Grade 4:</u> Life-threatening; pressor or ventilator support indicated	• 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
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Table 9. Management of Pembrolizumab 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-	• Permanently discontinue pembrolizumab.

Event	Management
mediated myelitis, Grade 2	• 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).

8.5 White blood Cell Growth Factors

Growth factor support recommended after every cycle with every 21-day carboplatin/docetaxel regimen in Arm 2 and for every 14 days AC for arm 1

If used, white blood cell growth factors, including biosimilars, must be used per ASCO guidelines (http://jco.ascopubs.org/content/24/19/3187.full) and NCCN Guidelines® Myeloid Growth Factors (http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf).

8.6 Dose Modification Contacts

For treatment or dose modification questions, please contact:

E-mail: S2212question@swog.org

or by phone:
Dr. Priyanka Sharma at: 913/588-6079 or
Dr. Zahi Mitri at: 604-217-6002.

8.7 Adverse Event/Serious Adverse Event Reporting Guidance

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box Send All AEs for Evaluation and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctephelpdesk@nih.gov if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301/897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols* > *Documents* > *Protocol Related Documents* > *Adverse Event Reporting*; and
- Additional resources: *Resources* > *CTSU Operations Information*> *User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

If you have questions about this process, please contact the SWOG SAE Team at 210-614-8808 or email adr@swog.org.

8.8 Serious Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of participants enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of participant safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

Clinician graded CTCAE is the AE (adverse event) 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.

b. Reporting method

This study requires that expedited adverse events be reported to SWOG Operations Office using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

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

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event as specified in Table 8.9e.

In the rare event when Internet connectivity is disrupted notification is made to SWOG by telephone at 210-614-8808 or by email adr@swog.org. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the participant must be reported according to local policy and procedures.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 8.9e. The

commercial agent(s) used in arms 1 and 2 of this study are all commercial agents. If there is any question about the reportability of an adverse event or if Internet connectivity is disrupted please telephone or email the SWOG SAE Team at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will suggest whether or not the adverse event requires expedited reporting. Although RAVE may recommend an SAE report, sites should confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 8.9e.

Table 8.9e Expedited reporting requirements for adverse events experienced by participants on study arms 1 and 2 within 30 days of the last administration of the commercial agent(s). All of the agents used in the study are commercial agents.

Attribution	**Grade 4**		**Grade 5[a]**	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by uploading CTSU Source Document Portal through CTEP-AERS.

f. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC**.**

   Additionally, the pregnancy outcome for participants on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as "Death in utero." 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-AER recognizes this event as a participant death.

3. **Death Neonatal** "Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth." A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal" under the General disorders and administration SOC.**

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a participant death.

   NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.
   The Pregnancy Information Form is available at: http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

g. PRO-CTCAE

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 study-specific **S2212** PRO-CTCAE items can be found on the forms section of the CTSU **S2212** protocol webpage.

9.0 STUDY CALENDAR

9.1 Arm 1

	Pre Reg	Neoadjuvant Systemic Therapy (NAST) [M, S,Y,AA] (Cycles 1-4 are 21 days long, Cycles 5-8 can be 14 or 21 days long)																Surgery [D]	Adjuvant Therapy	F/U [F]
		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 [J]	Cycle 6 [J]	Cycle 7 [J]	Cycle 8 [J]	3-5 weeks Post NAST			
		D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15	D1	D1	D1	D1				
PHYSICAL																					
History, Physical Exam & Zubrod Performance Status	X [A]	X			X			X			X			X	X	X	X				
Adverse Events					X			X			X			X	X	X	X	X			X
Disease Assessment		X			X			X			X			X	X	X	X				X
Surgical Pathology																			X		
LABORATORY[BB]																					
Hematology [G]	X [B]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Serum Chemistries [R]	X [A]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
TSH, free T4		X												X							
ACTH and AM cortisol	X [A, B]																				
HIV, and Hepatitis B and C testing	X [C]																				
Pregnancy Test [L]	X																				
IMAGING																					
Breast and Axillary Imaging	X [E]																		X [O]		
ECHO or MUGA	X [A]																				
SPECIMEN SUBMISSION																					
FFPE Tissue H&E slide	X [V]																				
FFPE Tissue Biobanking	X																		X [I]		
Blood		X						X										X [K]			X [H]

	Pre Reg	Neoadjuvant Systemic Therapy (NAST) [M, S, Y,AA] (Cycles 1-4 are 21 days long, Cycles 5-8 can be 14 or 21 days long)																	Surgery [D]	Adjuvant Therapy	F/U [F]
		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 [J]	Cycle 6 [J]	Cycle 7 [J]	Cycle 8 [J]	3-5 weeks Post NAST			
		D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15	D1	D1	D1	D1				
Treatment																					
Carboplatin (Q3 week) [N, S]		X			X			X			X										
Paclitaxel [N]		X	X	X	X	X	X	X	X	X	X	X	X								
Doxorubicin [U]														X	X	X	X				
Cyclophosphamide [U]														X	X	X	X				
Pembrolizumab [S]		X			X			X			X			X	X	X	X			X	
Myeloid Growth Factor														X [Q]	X [Q]	X [Q]	X [Q]				
OR																					
Carboplatin (Weekly) [N]		X	X	X	X	X	X	X	X	X	X	X	X								
Paclitaxel [N]		X	X	X	X	X	X	X	X	X	X	X	X								
Doxorubicin [U]														X	X	X	X				
Cyclophosphamide [U]														X	X	X	X				
Pembrolizumab		X			X			X			X			X [P]	X [P]	X [P]	X [P]			X	
Myeloid Growth Factor														X [Q]	X [Q]	X [Q]	X [Q]				
PARTICIPANT-COMPLETED QUESTIONNAIRES [X]																					
PROMIS Fatigue-7a		X [W]																X [K]			X (Month 18)
PROMIS-29 Profile		X [W]																X [K]			X (Month 18)
FACT-G GP5																		X [K]			X (Month 18)
PRO-CTCAE		X			X			X			X			X	X	X	X				

NOTE: Forms are found on the protocol-specific page on the CTSU website (www.ctsu.org) and on the CTSU website (www.ctsu.org). Forms submission guidelines are found in Section 14.0.

Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection, and follow up activities) must follow the guidelines established in the SWOG Best Practices document which is accessible from the Protocol Workbench at https://www.swog.org/clinical-trials/protocol-workbench.

A	Within **28** days prior to registration
B	ACTH should be drawn at the same time as AM cortisol
C	This is only required in patients with known history of HIV or Hepatitis (B or C). Patients with known history of HIV or Hepatitis (B or C) must have an undetectable viral load within 6 months prior to registration.
D	After completion of NAST, participants will proceed with definitive surgery (appropriate surgery type to be determined by treating physician/s). It is recommended that surgery should take place between 3 and 10 weeks after the last NAST dose.
E	Within **49** days prior to registration
F	After surgery (or after off NAST for participants who do not go on to surgery), participants will be seen every 6 months for first 2 years, then annually until 5 years from registration.
G	CBC must include hemoglobin, leukocytes, ANC, platelets
H	**6 and 12-**months post-surgery
I	Upon completion of definitive surgery. If participant has residual disease, please submit surgical FFPE slides at time of surgery. See Section 15.3a.1
J	Doxorubicin and cyclophosphamide can be given every 14 or 21 days per treating physician discretion
K	3-5 weeks after last neoadjuvant systemic therapy dose
L	Pregnancy testing should be performed as clinically indicated, per institutional standards within 49 days prior to registration.
M	+/- 2 days if cycle is 14 days and +/- 1 day for weekly treatments.
N	Any missed doses of weekly paclitaxel or carboplatin can be made up prior to starting doxorubicin plus cyclophosphamide as long total duration of paclitaxel plus carboplatin treatment duration does not exceed 16 weeks.
O	Post neoadjuvant systemic therapy / pre-surgical standard of care imaging is recommended at the end of the planned neoadjuvant systemic therapy.
P	Pembrolizumab to be given every 21 days during cycle 5-8 regardless of the AC schedule. All 8 doses should be completed prior to definitive surgery
Q	Myeloid growth factor support with pegfilgrastim or equivalent is required with every cycle if doxorubicin and cyclophosphamide given every 2 weeks. Myeloid growth factor support will be given from Day 2 of each cycle and not on day one unless using the on-body formulation.
R	Full list includes: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine or GFR, sodium, potassium, calcium, chloride, bicarbonate, glucose, bilirubin, and total protein.
S	(+/- 3 days) if cycle is 21 days
U	Doxorubicin and cyclophosphamide to be given on same schedule either every 21 days (+/- 3 days) OR every 14 days (+/- 2 day).
V	This tissue is mandatory. Tissue is not submitted until after registration. See Section 15.2 for more details
W	Any time prior to treatment on Cycle 1, Day 1
X	See Section 15.6b for timepoints.
Y	Labs, H&P, and disease assessments completed within 14 days prior to C1D1 do not need to be repeated prior to start of protocol treatment.
Z	Tissue is not submitted until after registration. See Section 15.3 for more details.
AA	The Responsible Investigator (RI) at the clinical trial site may make arrangements with a local Healthcare Professional (HCP) to administrer the study treatment for a participant. See Section 18.5 for details.
BB	Laboratory tests may be performed by a local lab. See Section 18.5 for details.

9.2 Arm 2

	Pre Reg	Neoadjuvant Systemic Therapy (NAST)[S, T] (Each cycle is 21 days long)							Surgery [D]	Adjuvant Therapy	Follow up [F]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	3-5 weeks Post NAST			
		D1 [M]	D1 [M]	D1 [M]	D1 [M]	D1 [M]	D1 [M]				
PHYSICAL											
History, Physical Exam & Zubrod Performance Status	X [A]	X	X	X	X	X	X				
Adverse Events			X	X	X	X	X	X			X
Disease Assessment		X	X	X	X	X	X				X
Surgical Pathology									X		
LABORATORY[U]											
Hematology [G]	X [B]	X	X	X	X	X	X				
Serum Chemistries [N]	X [A]	X	X	X	X	X	X				
TSH, free T4		X			X						
ACTH and AM cortisol	X [A, B]										
HIV, and Hepatitis B and C testing	X [C]										
Pregnancy Test [L]	X										
IMAGING											
Breast and Axillary Imaging	X [E]								X [O]		
ECHO or MUGA	X [A]										
SPECIMEN SUBMISSION											
FFPE Tissue H/E slide	X [P]										
FFPE Tissue Biobanking	X [P]								X [I]		
Blood		X		X				X [K]			X [H]

	Pre Reg	Treatment[S, T]	Surgery [D]		Follow up [F]

		(Each cycle is 21 days long)									
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	3-5 weeks Post NAST		Adjuvant Therapy	
		D1 [M]	D1 [M]	D1 [M]	D1 [M]	D1 [M]	D1 [M]				
TREATMENT											
Docetaxel		X	X	X	X	X	X				
Carboplatin		X	X	X	X	X	X				
Pembrolizumab		X	X	X	X	X	X			X	
Myeloid Growth Factor [J]		X	X	X	X	X	X				
PARTICIPANT-COMPLETED QUESTIONNAIRES [R]											
PROMIS Fatigue-7a		X [Q]						X [K]			X (Month 18)
PROMIS-29 Profile		X [Q]						X [K]			X (Month 18)
FACT-G GP5								X [K]			X (Month 18)
PRO-CTCAE		X	X	X	X	X	X				

NOTE: Forms are found on the protocol-specific page on the CTSU website (www.ctsu.org) and on the CTSU website (www.ctsu.org). Forms submission guidelines are found in Section 14.0.

Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection, and follow up activities) must follow the guidelines established in the SWOG Best Practices document which is accessible from the Protocol Workbench at https://www.swog.org/clinical-trials/protocol-workbench.

A	Within **28** days prior to registration
B	ACTH should be drawn at the same time as AM cortisol
C	This is only required in patients with known history of HIV or Hepatitis (B or C). Patients with known history of HIV or Hepatitis (B or C) must have an undetectable viral load within 6 months prior to registration.
D	After completion of NAST, participants will proceed with definitive surgery (appropriate surgery type to be determined by treating physician/s). It is recommended that surgery should take place between 3 and 10 weeks after the last NAST dose.
E	Within **49** days prior to registration
F	After surgery (or after off NAST for participants who do not go on to surgery), participants will be seen every 6 months for first 2 years, then annually until 5 years from registration.
G	CBC must include hemoglobin, leukocytes, ANC, platelets
H	**6 and 12-**months post surgery
I	Upon completion of definitive surgery. If participant has residual disease, please submit surgical FFPE slides at time of surgery. See Section 15.3a.1
J	Myeloid growth factor support with pegfilgrastim or equivalent is required with every cycle. Myeloid growth factor support will be given from Day 2 of each cycle and not on day one unless using the on-body formulation.
K	3-5 weeks after last neoadjuvant systemic therapy dose
L	Pregnancy testing should be performed as clinically indicated, per institutional standards within 49 days prior to registration.
M	(+/- 3 day)
N	Full list includes: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine or GFR, sodium, potassium, calcium, chloride, bicarbonate, glucose, bilirubin, and total protein.
O	Post neoadjuvant systemic therapy / pre-surgical standard of care imaging is recommended at the end of the planned neoadjuvant systemic therapy.
P	Tissue is not submitted until after registration. See Section 15.2 and Section 15.3 for more details
Q	Any time prior to treatment on Cycle 1, Day 1
R	See Section 15.6b for timepoints.
S	Labs, H&P, and disease assessments completed within 14 days prior to C!D1 do not need to be repeated prior to start of protocol treatment.
T	The Responsible Investigator (RI) at the clinical trial site may make arrangements with a local Healthcare Professional (HCP) to administrer the study treatment for a participant. See Section 18.5 for details.
U	Laboratory tests may be performed by a local lab. See Section 18.5 for details.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Pathologic complete response (pCR)

Defined as no viable invasive cancer in the breast and lymph nodes (ypT0 ypN0 or ypT0/is ypN0). DCIS is not invasive cancer and should not be considered as not pCR. All other outcomes are defined as "not pCR" including 1) residual disease (RD) defined as viable invasive cancer in the breast and/or lymph nodes, or 2) not going to surgery. Participants who have bilateral breast cancer must have pCR in both breasts to be considered to have had pCR.

10.2 Residual Cancer Burden (RCB)

Residual Cancer Burden is a continuous measure of the extent of residual cancer after neoadjuvant chemotherapy that combines the largest diameter of the cancer in the breast, the tumor cell cellularity of the cancer, and the largest diameter and number of involved axillary lymph nodes into a single RCB score. The RCB score can be computed using the free online tool; http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3 .

RCB class is an ordinal measure with four levels using defined cutpoints of RCB: RCB-0; RCB-I; RCB-II; RCB-III. Participants not undergoing surgery will be classified as RCB-II/RCB-III in the analysis.

10.3 Progression prior to Surgery

Clear increase in disease sites present at registration or development of new sites of disease.

10.4 Invasive Recurrence after Surgery

Appearance of any new invasive lesion(s) during or after protocol treatment. Whenever possible, recurrences should be documented histologically. Invasive recurrence includes local, regional, or distant breast cancer recurrence with an invasive component. A new diagnosis of ipsilateral DCIS without an invasive component is not considered to be a recurrence.

10.5 Sites of First Invasive Recurrence

All sites of invasive disease documented within 30 days of first documentation of invasive recurrence.

10.6 Breast Cancer-Free Survival (BC-EFS)

Time from date of randomization to date of the earliest occurrence of any of the following events: progression prior to surgery, invasive recurrence after surgery, new contralateral breast cancer, or death due to any cause. New non-breast primaries are not included as events. Participants last known to be alive who have not experienced any of these events are censored at their last contact date.

10.7 Distant Relapse-Free Survival

Time from date of randomization to date of invasive distant disease recurrence or death due to any cause. Participants last known to be alive who have not experienced distant recurrence or death are censored at their last contact date.

10.8 Overall Survival

Time from date of randomization to date of death due to any cause. Participants last known to be alive are censored at their last contact date.

10.9 Invasive Breast Cancer-free Survival (IBCFS)

Time from date of surgery to date of first invasive recurrence (local, regional, or distant), new contralateral breast cancer, or death due to any cause. Participants last known to be alive who have not experienced recurrence are censored at their last contact date.

10.10 Distant Relapse-Free Interval (DRFI)

Time from date of randomization to date of invasive distant disease recurrence or death due to breast cancer or its treatment. Participants last known to be alive who have not experienced distant recurrence are censored at their last contact date. Participants who die from other causes are considered censored by a competing risk.

10.11 Performance Status

Participants will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Overview

This is a randomized Phase III trial comparing a standard neoadjuvant chemotherapy regimen to an experimental neoadjuvant chemotherapy regimen that omits AC therapy. Both arms receive pembrolizumab for one year. If participants in the experimental arm have residual disease after neoadjuvant therapy, then they may receive adjuvant therapy post-surgery at physician discretion. This is a parallel randomization open-label design with equal allocation to the two treatment groups: (1) standard neoadjuvant chemotherapy and (2) neoadjuvant chemotherapy without AC. Randomization will be stratified by nodal status (negative or positive). Post-randomization sTILs will be evaluated and we expect that approximately 60% of participants will have low TILs (sTILs < 30%) and 40% will have high sTILs (≥30%). The primary outcome breast cancer event-free survival (BC-EFS) will be compared in a noninferiority analysis by Cox regression testing of the association of EFS and randomized treatment arm with covariate adjustment of nodal status and TIL status. A secondary comparison of pCR rates and residual cancer burden (RCB) outcomes between the two arms will be conducted. Secondary survival outcomes include comparison of distant relapse-free survival (DRFS), distant relapse-free interval (DRFI), and overall survival (OS) measured from randomization. After determination of pCR status, separate analyses of IBCFS measured from surgery will be compared by treatment arm in those with a pCR and those without pCR. QOL measures include PROMIS measures at designated timepoints. All analyses are intent-to-treat (ITT) by randomized assignment of eligible participants. Toxicity and serious adverse events will be compared between the two arms for those starting assigned therapy.

11.2 Sample size with power justification

This is a randomized open label Phase III trial with a single primary endpoint, BC-EFS and a noninferiority design. Randomization is stratified by nodal status (node-negative vs. pathological or clinical node-positive). We expect Arm 2 (experimental) to be noninferior to

Arm 1 (control) with respect to BC-EFS. We assume power of 80% and 1-sided α=0.05 since we are only interested in whether Arm 2 is inferior to Arm 1. We expect a 3-year BC-EFS of 88.6% with chemotherapy and pembrolizumab in the node-negative population and 80.4% in the node-positive population. We weight the node-negative (~65%) and node-positive (~35%) hazard rates to get an expected overall hazard rate based on an exponential model. Then the expected 3-year BC-EFS for Arm 1 (standard treatment of chemotherapy plus immunotherapy) is anticipated to be 85.6%, thus the expected hazard rate is 0.052 (weighted by subgroups). We expect the true hazard ratio of Arm 2 vs. Arm 1 to be 1.0 but allow the upper limit of the 95% CI on the hazard ratio to be as high as 1.25. We stress that the expected hazard ratio is 1.0 comparing arms, but the upper limit of the confidence interval for that estimate must be less than 1.25. At the very worst Arm 2 could have a hazard rate of 0.065 which would translate to 82.4% BC-EFS. However, the expectation is that both will be similar. We assume that accrual will take four years with three additional years of follow-up. Then the computed sample size is 2,183. Allowing for dropout or ineligibility, we increased the sample size by 10%, and we will plan to accrue 2,400 patients.

11.3 Primary analyses

The final analysis will be Cox regression of assigned treatment with adjustment for two covariates: nodal status (positive/negative) and sTIL enrichment (determined post-randomization from baseline tissue slides). STIL enrichment will be categorized as (<30%; ≥ 30%; and not determined) for the analysis. The upper limit of the hazard ratio will be computed using likelihood bounds. The expected number of events under the assumption of noninferiority would be 496 events overall which will be used to trigger the final analysis. If that number of events is not reached within four years of the last enrollment (one year later than expected) then the final analysis will be conducted with the observed number of events. The primary analysis is intent-to-treat (ITT). An exploratory analysis limited to those who accept their randomized assignment (per protocol) will also be conducted.

11.4 Sensitivity analyses

The following variations of the primary analysis will also be conducted for BC-EFS:

a. Per protocol: An analysis limited to those who accept their randomized assignment will also be conducted with treatment, nodal status, and sTIL status as included variables in the multivariable analysis.

b. Test of interaction between treatment and sTIL status. The interaction of treatment and sTIL status (low/high) will be tested in the ITT Cox model. Additionally, separate Cox models will be fit separately by sTIL status to determine if the treatment hazard ratio in each sTIL group is similar to the overall hazard ratio.

c. Test of interaction between treatment and nodal status. The interaction of treatment and nodal status (negative/positive) will be tested in the ITT Cox model. Additionally, separate Cox models will be fit separately by nodal status to determine if the treatment hazard ratio in each nodal group is similar to the overall hazard ratio.

11.5 Secondary outcomes

a. PCR rates by assigned treatment arm will be compared using a difference of two proportions overall and by sTIL group. Additionally, a multivariable logistic regression model will estimate the odds ratio for treatment adjusting for nodal status and sTIL group.

b. RCB 0/I rates (i.e., RCB-0 and RCB-I combined) by assigned treatment arm will be compared using a difference of two proportions overall and by sTIL group. Additionally, a multivariable logistic regression model will estimate the odds ratio for treatment adjusting for nodal status and sTIL group.

c. Both DRFS and OS will be compared by treatment arms using Cox regression for treatment adjusted by nodal status and sTIL status.

d. DRFI will be compared by treatment arms using Cox regression for treatment adjusted by nodal status and sTIL status. Deaths not due to breast cancer will be considered competing risks in this analysis. Cumulative incidence curves will describe the two arms over the follow-up period from randomization.

e. RFS measured from time of surgery will compare treatment arms in a Cox regression for patients who had pCR. Nodal status and sTIL status will be included as covariates if there are sufficient numbers of events for the analysis. The expectation is that IBCFS after pCR should not differ by treatment assignment.

f. RFS measured from time of surgery will compare treatment arms in a Cox regression for patients who did not have a pCR. Nodal status and sTIL status will be included as covariates.

g. Rates of adverse events will be compared between treatment arms for those initiating the assigned therapy.

h. Analysis of PROMIS measures and PRO-CTCAE are described in Section 18.1. Note that the accrual goal of the PRO studies is 750 so new participants will not be asked to join the QOL studies when that accrual goal is reached. The protocol will be amended at that time and those already enrolled in the QOL studies will continue to complete the patient reported outcomes at the designated follow-up points.

i. Comparison of central vs. automated TIL assessment. For the concordance of central read to automated values this will be conducted in the first 700 pairs. We will round down the automated reads to the nearest 10% to correspond to the central read so as to not introduce discordance just due to the unit of measurement. With 700 pairs of continuous sTILs scores we would have 89% power with 2-sided α=0.05 to show that our expected correlation of 0.82 is superior to the null hypothesis that states the correlation is 0.75. Again, we would also form the 2x2 comparison and calculate the kappa.

11.6 Interim analyses

The purpose of this study is to assess whether patients can be safely spared the toxicity of multi-drug chemotherapy regimens, particularly anthracyclines. Patients achieving a pCR on the experimental non-anthracyline regimen will not receive adjuvant chemotherapy, whereas patients not achieving a pCR with the experimental non-anthracycline regimen will be allowed to take anthracycline therapy post-surgery and are therefore not at risk of undertreatment or harm. We propose to evaluate the percentage of patients achieving pCR in an interim feasibility analysis which will be conducted after 300 patients have completed surgery. pCR rate in the experimental arm will define the proportion of patients who would be able to avoid anthracycline. If the pCR rate in a specific group is very low, then a small fraction of patients in this group would potentially be able to avoid anthracycline and this may impact the overall feasibility of the study. Baseline sTILs density is positively associated with pCR independent of type of chemotherapy regimens as this positive association has been noted with both anthracycline based and non-anthracycline based chemotherapies *(50, 51, 52, 53)*. Generally lower pCR rates are noted in lower TIL tumors with both anthracycline and non-anthracycline neoadjuvant therapy. In NeoPACT (anthracycline-free chemoimmunotherapy) the pCR in low and high TIL patients was 41% (95% CI of 28-54%) and 74% respectively. In KN-173 study (anthracycline-based neoadjuvant chemoimmunotherapy) the pCR in low and high TIL patients was 38% (95% CI 15%-61%) and 70% respectively *(54, 43)*. In S2212 the 30% pCR rate threshold for the first interim feasibility analysis is chosen for patients with low TILs and not for the entire experimental arm. This threshold was derived based on review of above published data and also keeping in consideration a clinically meaningful patient proportion for avoidance of anthracycline. A threshold that includes both a pCR rate of 30% plus 10%-point absolute difference compared to control arm in the Low TIL group is chosen because if pCR is equally below 30% in both arms no change in protocol would be needed.

a. Interim analysis 1 (feasibility analysis).

After the first 300 surgery outcomes are available, we will assess the pCR rates in each treatment arm in low sTIL group (feasibility analysis). In the experimental arm low sTIL group (~90) if the pCR rate is ≤ 30% and the absolute difference in pCR rates for Low TIL groups of the two arms is greater than 10%, then only less than 30% of the patients in low TIL group will potentially be able to avoid anthracycline. This will trigger a discussion by the DSMC regarding stopping enrollment in the low TIL group with continued enrollment only for high TIL group. In this first interim analysis of feasibility there would be approximately 90 low TIL patients so a 30% pCR rate would have a 95% CI of 20.8% to 40.6%. Decision to stop enrollment in the low TIL group would require a protocol amendment and upfront testing of sTIL. In this scenario we would need to show sufficient power to achieve noninferiority with possibly an increased margin for enrollment to continue only in the high TIL group. A threshold that includes both a pCR rate of 30% plus 10%-point absolute difference compared to control arm in the Low TIL group is chosen because if pCR is equally below 30% in both arms no change in protocol would be needed.

b. Interim analysis 2.

The second interim futility analysis will be at 25% of the BC-EFS events when about 77% of the accrual goal has been completed. If the hazard ratio for treatment (over all sTIL groups) exceeds 1.25 by a statistically significant margin using a 1-sided α=0.05 test, i.e. the 1-sided lower bound (α=0.05) of the confidence interval exceeds 1.25, then futility will be declared and it will be recommended that enrollment be stopped. pCR rates will also be assessed at this analysis.

c. Interim analysis 3.

The third interim futility analysis will be at 50% of the BC-EFS events when enrollment has been completed. If the observed hazard ratio for treatment (over all sTIL groups) exceeds 1.25 and the 1-sided lower bound (α=0.05) of the confidence interval exceeds 1.0, then it will be recommended that futility be declared. pCR rates will also be assessed at this analysis. Declaring futility at this point will hasten sharing of results, rather than waiting until 100% of the events have been observed.

11.7 Data Safety and Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG Cancer Research Network, three SWOG members, three non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every six months from the SWOG Statistics and Data Management Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

Discipline review is not necessary for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Participants must be registered prior to the initiation of treatment (no more than 21 calendar days prior to planned start of treatment).

See Section 18.5 for remote consenting procedures.

13.2 Investigator/Site Registration

Prior to the recruitment of a participant for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

13.3 CTEP Registration Procedures

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 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.

- 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; and

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 (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.

13.4 CTSU Registration Procedures

This study is supported by the NCI CTSU.

a. 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 calling 1-888-651-CTSU (2878).

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.

b. 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 protocol-specific requirements (PSRs).

c. Protocol-Specific Requirements (PSR) for S2212 Site Registration

There are no Protocol-Specific Requirements for **S2212**.

d. 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 the 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 **SWOG**, and protocol number **S2212**.
- 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.)

e. 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.

f. Checking Your 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 sites 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.

13.5 Oncology Patient Enrollment Network (OPEN) Registration Requirements

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 the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- 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.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Participant Initials

g. Participant's Date of Birth

h. Country of Residence

i. ZIP Code

j. Sex (select one):
- Female
- Male

k. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

l. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

m. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.6 Exceptions to SWOG registration policies will not be permitted.

a. Participants must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for ALL participants registered, whether or not assigned treatment is administered, including participants deemed to be ineligible. Participants for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol page on the CTSU website (www.ctsu.org).

14.3 Data Submission / Data Reporting Procedures

a. Medidata Rave is a 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 Associates (A) registration type.

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

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.

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. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave Resources > Medidata Account Activation and Study Invitation (to activate your iMedidata account). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management Rave Resources section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

d. DMU Demography Reporting Requirement

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.

e. 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.

14.4 Data Submission Overview and Timepoints

Please reference the ORP Manual on the CRA Workbench (www.swog.org) for detailed General Forms and Guidelines, as well as some disease-specific and study-specific forms. There are also many other chapters available in the manual to be used for regular reference of SWOG processes and procedures. Non-SWOG sites can access the Workbench with the credentials necessary to access secure NCI/CTSU IT systems: https://crawb.crab.org/TXWB/ctsulogon.aspx

a. WITHIN 15 DAYS OF REGISTRATION:

Submit the following:

- Vital Status Form
- **S2212** Eligibility Criteria Form
- **S2212** Onstudy Form
- All pre-registration breast cancer pathology reports. *

*__Note__: Upload reports via the Source Documentation: Baseline form in Rave. Pathology report(s) documenting TNBC as defined in Section 5.1 must be uploaded to Rave to confirm eligibility.

b. WITHIN 30 DAYS OF REGISTRATION:

Submit specimens for sTILs assay as specified in Section 15.2.

c. SPECIMENS AT ALL TIME POINTS OUTLINED IN SECTION 15.0:

Submit specimens for participants who have consented to biobanking.

d. WITHIN 30 DAYS AFTER EACH CYCLE OF NEOADJUVANT TREATMENT:

Submit the following:

- Vital Status Form
- **S2212** Neoadjuvant Treatment Form
- **S2212** Supplemental Treatment Form
- **S2212** Adverse Event Form
- **S2212** PRO-CTCAE Form

e. WITHIN 30 DAYS AFTER SURGERY:

Submit the following:

- Vital Status Form
- Breast Surgery Form
- Off Treatment Notice
- All breast cancer surgical pathology and operative reports. *

*__NOTE__: Upload reports via the Source Documentation: Follow Up form in Rave.

f. (For participants who do not go on to surgery) WITHIN 30 DAYS OF DISCONTINUATION OF NEOADJUVANT TREATMENT:

Submit the following:

- Vital Status Form
- Off Treatment Notice
- Final **S2212** Neoadjuvant Treatment Form if patient didn't go on to surgery
- Final **S2212** Supplemental Treatment Form
- Final **S2212** Adverse Event Form
- Final **S2212** PRO-CTCAE Form

g. WITHIN 60 DAYS AFTER DISCONTINUATION OF ADJUVANT TREATMENT:

Submit the following:

- Vital Status Form
- **S2212** Adjuvant Treatment Summary Form

h. (For participants participating in the Quality of Life studies) WITHIN 15 DAYS AFTER BASELINE QOL ASSESSMENT:

Submit the following:

- Vital Status Form
- **S2212** Cover Sheet for Participant-Reported Questionnaires
- PROMIS Fatigue-7a
- PROMIS-29 Profile v2.1

i. (For participants participating in the Quality of Life studies) WITHIN 30 DAYS AFTER QOL ASSESSMENTS, 3-5 WEEKS AFTER NEOADJUVANT THERAPY, AND 18 MONTHS FROM REGISTRATION:

Submit the following:

- Vital Status Form
- **S2212** Cover Sheet for Participant-Reported Questionnaires
- PROMIS Fatigue-7a
- PROMIS-29 Profile v2.1
- FACT-G GP5

j. WITHIN 30 DAYS AFTER ONE YEAR FROM REGISTRATION:

Submit the following:

- Vital Status Form
- Breast Radiation Therapy Form

k. WITHIN 30 DAYS OF PROGRESSION/RELAPSE:

Submit the following:
- Vital Status Form
- Breast Follow Up Form documenting date, site, and method for determining progression/relapse.

If participant was still on protocol treatment, also submit the forms listed in Section 14.4f.

l. AFTER OFF PROTOCOL TREATMENT, WITHIN 60 DAYS AFTER EACH FOLLOW-UP VISIT (EVERY 6 MONTHS UNTIL 2 YEARS AFTER RANDOMIZATION, THEN ANNUALLY UNTIL 5 YEARS AFTER RANDOMIZATION):

Submit the following:

- Vital Status Form
- Breast Follow Up Form
- Late Adverse Events (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the participant experiences any severe [Grade ≥ 3] adverse event that is possibly, probably, or definitely related to protocol treatment, or a Serious Adverse Event [SAE] of any grade/attribution, that has not been previously reported).

m. WITHIN 30 DAYS AFTER KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information and the forms listed in Section 14.4f (if the participant was still on protocol treatment) or Breast Follow Up Form (if the participant was off protocol treatment).

15.0 SPECIAL INSTRUCTIONS

15.1 Specimen Submission Summary Table

- **M = Mandatory; R = Required, if participant consents**

Purpose	Specimen	Timepoint	Required	ShipTo
sTILs assay	**FFPE Archival Tissue** • One (1) representative full face 4–5-micron single H&E slide	– after participant registration	**M**	Ship to SWOG Biospecimen Bank (Lab #201)
Biobanking	**FFPE Tissue** • one FFPE Tissue block (preferred) • If a block cannot be submitted, then provide Ten (10) 4-to-5-micron unstained charged slides	– after participant registration – Upon completion of definitive surgery if participant has residual disease	**R**	
Biobanking	**Blood** • 20 mL in Streck cfDNA tubes • 10 mL in red top tubes	– Cycle 1 Day 1 – Cycle 3 day 1 – Within 3-5 weeks after last NAST dose – 6-months post-surgery – 12months post-surgery	**R**	

15.2 Specimen for sTIL Assay ***(MANDATORY)***

a. Specimens must be submitted at the time points listed below.

1. After registration:

One (1) physical 4–5-micron single H&E slide from the archival pre-treatment diagnostic biopsy.

b. Specimen Collection and Submission Instructions

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. Complete specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures). If collection/submission instructions differ from those in the protocol, the protocol instructions should be followed; otherwise, the website instructions should be followed.

Note: Any leftover tissue not consumed by testing will be banked for future use according to the patient's selection on the "Optional Biobanking for Possible Future Studies" section of the consent form.

c. Tissue specimen collection kits are not being provided for this submission; sites will use institutional supplies.

d. See Section 15.4 for Specimen Labelling and Shipping Instructions.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of diagnostic tissue samples for SWOG Biospecimen Submission and Pathology review is identified as follows:

Lab #201: SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division
Phone: 614/722-2865
E-mail: bpcbank@nationwidechildrens.org

15.3 Specimen Submission for Banking (***REQUIRED FOR PARTICIPANTS REGISTERED BY SITES IN THE UNITED STATES, IF PARTICIPANT CONSENTS***)

a. With participant's consent, specimens must be submitted at the following times (see Section 9.0)

1. Formalin-fixed paraffin embedded (FFPE) tumor tissue

a. Archived FFPE specimen after participant registration: one FFPE tissue block (preferred). If a block cannot be provided, then submit ten (10) 4–5-micron unstained charged FFPE slides.

b. Residual Disease surgical FFPE sample collected upon completion of definitive surgery: one FFPE tissue block (preferred). If a block cannot be provided, then submit ten (10) 4–5-micron unstained charged FFPE slides.

2. 30 mL blood – Two (2) 10 mL cell-free DNA Streck tubes and one (1) 10 mL red-top Vacutainer® tube

a. Cycle 1 Day 1

b. Cycle 3 Day 1

c. 3-5 weeks post last neoadjuvant systemic therapy (NAST) dose

d. 6-months post-surgery (+/- 30 days)

e. 12-months post-surgery (+/- 30 days)

b. Specimen Collection and Submission Instructions

1. Streck cfDNA tubes for peripheral blood submission may be ordered by using the SWOG Biospecimen Bank KitManagement Application at https://kits.bpc-apps.nchri.org. Sites must order collection kits in advance of each collection timepoint; A single collection kit will be provided for each collection timepoint. Allow at 5-7 days for shipment of collection kits.

2. Specimen collection kits are not being provided for tissue submission and blood collection in red-top Vacutainer® tube; sites will use institutional supplies. See Section 15.4 for specimen labelling and shipping instructions.

3. See Section 15.4 for Specimen Labelling and Required Documents. See section 15.5 for Shipping Specimens to the SWOG Biospecimen Bank.

   In the online specimen tracking system, the appropriate SWOG laboratory for submission of diagnostic tissue samples for SWOG Biospecimen Submission and Pathology review is identified as follows:

   Lab #201: SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division
   Phone: 614/722-2865
   E-mail: bpcbank@nationwidechildrens.org

4. **Whole Blood in red-top tube Collection Guidelines**

   • After collection, gently invert blood to mix.
   • Allow blood to clot upright for 30 minutes. Do not process. Do not freeze.
   • If blood in red top tube cannot be shipped the day of collection, then refrigerate and ship on the next day to the SWOG Biospecimen Bank (Lab #201).
   • If shipping blood in red top tube with the blood in Streck cfDNA tubes, then allow the blood in red top tube to come to room temperature before packaging. Ship blood at ambient temperature.

5. **Streck Cell-Free DNA Collection Tube Collection Guidelines**

   • Fill tube completely (10 mL)
   • Immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in an inadequate specimen.
   • **After collection, blood in cfDNA Streck tubes should never be refrigerated**, as this will compromise the specimen. Blood collected in Streck cfDNA tubes is stable at room temperature.

If blood in Streck cfDNA tubes cannot be shipped the day of collection, then it must be kept at **room temperature** and shipped on the next working day to the SWOG Biospecimen Bank (Lab #201). Do not process.

6. **Formalin-fixed Paraffin Embedded (FFPE) Tissue Collection Guidelines**

Standard Processing of Slides

a. Although an FFPE tissue block is preferred, ten unstained charged slides may be submitted if the institution cannot release an FFPE tissue block long term.

b. All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. Complete specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/member-resources/biospecimen-resources). If collection/submission instructions differ from those in the protocol, the protocol instructions should be followed; otherwise, the website instructions should be followed.

15.4 SPECIMEN LABELING AND REQUIRED DOCUMENTATION

a. Label blood tubes with the following:

- SWOG patient number
- Patient initials (write as Last, First Middle)
- Collection date (date the specimen was collected from the patient)
- Specimen type (i.e., blood)

b. Include the following on FFPE tissue labels:

- SWOG patient number
- Patient initials (write as Las, First Middle)
- Collection date (date the specimen was collected from the patient)
- Tissue type (P for primary or M for metastatic)
- The Surgical Pathology ID # (Accession#) and block number (e.g., A2, 3E, 2-1, B, etc.) must be on both the specimen label and the pathology report in order for the Bank to adequately match the specimen with any findings in the pathology report.

c. Required Documentation

- The STS Shipping List is required for all shipments.
- For FFPE blocks and slides, a partially redacted pathology report corresponding to the tissue submitted is required. **Label each page of the pathology report with the SWOG patient ID#.**
    i. Remove participant identifiers such as name, date of birth, medical record number, and insurance information form the report.
    ii. The date of procedure, surgical pathology ID (SPID) number, block number, and diagnosis must be left on the report.

15.5 SHIPPING SPECIMENS TO THE SWOG BIOSPECIMEN BANK

a. SWOG Specimen Tracking System

All specimen submissions for this study must be submitted using the SWOG Specimen Tracking system accessible either via the SWOG CRA Workbench on www.swog.org (Login at www.swog.org (with CTEP IAM ID), then go to: Member Resources >> CRA Workbench) or at https://spectrack.crab.org.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

Label the sample with the label type specific for the sample and as specified on the system-generated packing list. Specimen labelling instructions are available on swog.org and at: https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures#Specimen%20Labeling%20Notes.

The Shipment Packing List produced by Specimen Tracking must be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The SWOG patient ID must be included on any source documentation (e.g., pathology report) included with the shipment.

If the specimen was not collected, you still must use the Specimen Tracking System to indicate as such using the "Notify that Specimen Cannot be Submitted" link.

If limited tissue is available or fewer than the required number of tubes of blood were collected, document the reason for incomplete specimen submission in the SWOG Specimen Tracking System under "Comments" on the "Verify Shipment" page.

Specimen Tracking instructions are available after signing into Specimen Tracking. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the SWOG Statistics and Data Management Center at 206/652-2267.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of diagnostic tissue samples for SWOG Biospecimen Submission and Banking review is identified as follows:

Lab #201: SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division
Phone: 614/722-2865
E-mail: bpcbank@nationwidechildrens.org

b. Complete instructions for packaging and shipping specimens are located on the SWOG Specimen submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

15.6 Quality of Life Submission Requirements **and** Patient-Reported Outcome Common Toxicity Criteria for Adverse Events (PRO-CTCAE) (***REQUIRED IF PARTICIPANT CONSENTS***)

a. Instrument

- PROMIS Fatigue-7a
- PROMIS-29 Profile v2.1
- FACT-G GP5
- PRO-CTCAE

b. Administration Timepoints

1. PROMIS Fatigue-7a, PROMIS-29 Profile v2.1, and GP5

- Baseline assessment any time prior to treatment start on C1D1 (PROMIS instruments only)
- Within 3-5 weeks post last neoadjuvant systemic therapy dose
- 18 months after date of registration, +/- 28 days

2. PRO- CTCAE

- Day 1 of each cycle of neoadjuvant therapy

Each assessment should take the participant about 5 – 12 minutes to complete.
Notes about assessment time points:

- Follow-up assessments for PRO-CTCAE are conducted in conjunction with the investigator Adverse Event assessments.
- If a participant goes off protocol treatment, continue to administer questionnaires according to the protocol-defined assessment schedule.
- Questionnaires should be administered regardless of eligibility or treatment status according to the protocol-defined assessment schedule.
- If a participant refuses or cannot complete the patient questionnaires at one time point, he/she should be asked to do so at the next scheduled administration time.
- The Expectation Report and the MediData RAVE system provide reminders of upcoming patient-reported outcomes/quality of life assessments for a patient.
- The scheduled follow-up PRO assessments must be completed even if the participant has a treatment delay, goes off treatment early for any reason; or if a participant is deemed ineligible for any reason.

c. Instructions for administration

- Anyone involved in the collection of patient-reported outcomes/quality of life data in SWOG trials should review the Patient Reported Outcome Questionnaires training program available on the SWOG website (under the CRA workbench). The training program is a narrated set of slides designed to standardize the way patient-reported outcomes/quality of life data is collected from participants. Questions regarding the patient-reported outcomes/quality of life assessments can be addressed to the SWOG Statistics and Data Management Center (206/652-2267).

- Paper administration of questionnaires will be used for this study.

- The first time the patient completes the questionnaires: Please read to the patient the instructions attached to each section. Explain the specific administration times for this protocol. Patients should be directed to report all symptoms and limitations whether or not they are related to the cancer or its treatment.

- It is permissible to assist patients with completing the questionnaires by reading the questions to them (for patients with visual deficits) or writing their answers (for patients with motor deficits), being careful not to influence the patient's response. Note what assistance was required and indicate the reason in the Comments section. Discourage family members from: 1) being present while the patient completes the questionnaire and/or 2) influencing patient responses to the questions.

- It is very important to review the questionnaires after completion by the patient to be sure all of the questions have been answered and that only one answer is marked per question. If the patient has marked more than one answer per question, ask the patient which answer reflects how he/she is feeling. If the patient skipped a question, tell the patient that a question was not answered and ask if he/she would like to answer the question. Always give the patient the option to refuse. Indicate on the form by the question that the patient did not want to answer this question, if applicable.

- If a patient misses an appointment or is too sick to complete the questionnaires on the scheduled date, the questionnaire can be mailed to the patient or sent home with him/her. A telephone interview must be scheduled and completed within one week of the originally scheduled timepoint. Patient responses to questionnaire items are to be obtained during the telephone interview while the patient is looking at a copy of the questionnaire.

- If the patient appointment is conducted via a telehealth visit within one week of the originally scheduled timepoint, and the toxicity assessment is also conducted via the telehealth visit, then, the PRO-CTCAE questionnaire may also be administered via telephone (or videoconference) at the same timepoint. A copy of the PRO-CTCAE questionnaire must be provided to the patient (e.g. via e-mail or mail), and a telephone (or videoconference) interview may completed at the same telehealth visit as the toxicity assessment or may be scheduled separately as close to possible (and within the assessment window depending on the timepoint of the original assessment timepoint) to the physician-directed toxicity assessment. Patient responses to questionnaire items are to be obtained during the telephone (videoconference) interview while the patient is looking at a copy of the questionnaire.

d. Administration Quality Control Procedures

When a patient is registered to **S2212**, a calendar should be made with dates of upcoming patient-completed questionnaires noted. A copy of this calendar can be given to the patient with the notation that the questionnaires should be completed before receiving treatment. You may wish to photocopy the Study Calendar, Section 9.0, and include the patient's name and specific dates. A copy of this (if created) should be kept in the patient file.

1. If a patient goes off protocol treatment, continue to administer the patient completed questionnaires according to the protocol-defined assessment schedule (time from registration date).

2. If a patient refuses or cannot complete the patient questionnaires at one time point, he/she should be asked to do so at the next scheduled administration time.

3. The Quality of Life Coordinator will monitor compliance on a regular basis, having been provided with timely reports from the SWOG Statistics and Data Management Center. The Expectation Report and the MediData RAVE system provides reminders of upcoming quality of life assessments for a patient.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent
The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review
This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Confidentiality
Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

17.0 BIBLIOGRAPHY

1. Carey L, Winer E, Viale G, Cameron D, Gianni L. Triple-negative breast cancer: disease entity or title of convenience? Nat Rev Clin Oncol. 2010 Dec;7(12):683-92. doi: 10.1038/nrclinonc.2010.154. Epub 2010 Sep 28. PMID: 20877296.

2. Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, Colleoni M, Denkert C, Piccart-Gebhart M, Regan M, Senn HJ, Winer EP, Thurlimann B; Members of the St. Gallen International Consensus Panel on the Primary Therapy of Early Breast Cancer 2019. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol. 2019 Oct 1;30(10):1541-1557. doi: 10.1093/annonc/mdz235. PMID: 31373601

3. Cortazar P, Geyer CE Jr. Pathological complete response in neoadjuvant treatment of breast cancer. Ann Surg Oncol. 2015 May;22(5):1441-6. doi: 10.1245/s10434-015-4404-8. Epub 2015 Mar 2. PMID: 25727556.

4. Sharma P, López-Tarruella S, García-Saenz JA, Khan QJ, Gómez HL, Prat A, Moreno F, Jerez-Gilarranz Y, Barnadas A, Picornell AC, Monte-Millán MD, González-Rivera M, Massarrah T, Pelaez-Lorenzo B, Palomero MI, González Del Val R, Cortés J, Fuentes-Rivera H, Morales DB, Márquez-Rodas I, Perou CM, Lehn C, Wang YY, Klemp JR, Mammen JV, Wagner JL, Amin AL, O'Dea AP, Heldstab J, Jensen RA, Kimler BF, Godwin AK, Martín M. Pathological Response and Survival in Triple-Negative Breast Cancer Following Neoadjuvant Carboplatin plus Docetaxel. Clin Cancer Res. 2018 Dec 1;24(23):5820-5829. doi: 10.1158/1078-0432.CCR-18-0585. Epub 2018 Jul 30. PMID: 30061361; PMCID: PMC6279513.

5. I-SPY2 Trial Consortium, Yee D, DeMichele AM, Yau C, Isaacs C, Symmans WF, Albain KS, Chen YY, Krings G, Wei S, Harada S, Datnow B, Fadare O, Klein M, Pambuccian S, Chen B, Adamson K, Sams S, Mhawech-Fauceglia P, Magliocco A, Feldman M, Rendi M, Sattar H, Zeck J, Ocal IT, Tawfik O, LeBeau LG, Sahoo S, Vinh T, Chien AJ, Forero-Torres A, Stringer-Reasor E, Wallace AM, Pusztai L, Boughey JC, Ellis ED, Elias AD, Lu J, Lang JE, Han HS, Clark AS, Nanda R, Northfelt DW, Khan QJ, Viscusi RK, Euhus DM, Edmiston KK, Chui SY, Kemmer K, Park JW, Liu MC, Olopade O, Leyland-Jones B, Tripathy D, Moulder SL, Rugo HS, Schwab R, Lo S, Helsten T, Beckwith H, Haugen P, Hylton NM, Van't Veer LJ, Perlmutter J, Melisko ME, Wilson A, Peterson G, Asare AL, Buxton MB, Paoloni M, Clennell JL, Hirst GL, Singhrao R, Steeg K, Matthews JB, Asare SM, Sanil A, Berry SM, Esserman LJ, Berry DA. Association of Event-Free and Distant Recurrence-Free Survival With Individual-Level Pathologic Complete Response in Neoadjuvant Treatment of Stages 2 and 3 Breast Cancer: Three-Year Follow-up Analysis for the I-SPY2 Adaptively Randomized Clinical Trial. JAMA Oncol. 2020 Sep 1;6(9):1355-1362. doi: 10.1001/jamaoncol.2020.2535. PMID: 32701140; PMCID: PMC7378873.

6. Sharma P, Kimler BF, O'Dea A, Nye L, Wang YY, Yoder R, Staley JM, Prochaska L, Wagner J, Amin AL, Larson K, Balanoff C, Elia M, Crane G, Madhusudhana S, Hoffmann M, Sheehan M, Rodriguez R, Finke K, Shah R, Satelli D, Shrestha A, Beck L, McKittrick R, Pluenneke R, Raja V, Beeki V, Corum L, Heldstab J, LaFaver S, Prager M, Phadnis M, Mudaranthakam DP, Jensen RA, Godwin AK, Salgado R, Mehta K, Khan Q. Randomized Phase II Trial of Anthracycline-free and Anthracycline-containing Neoadjuvant Carboplatin Chemotherapy Regimens in Stage I-III Triple-negative Breast Cancer (NeoSTOP). Clin Cancer Res. 2021 Feb 15;27(4):975-982. doi: 10.1158/1078-0432.CCR-20-3646. Epub 2020 Nov 18. PMID: 33208340; PMCID: PMC7887017.

7. Spring LM, Fell G, Arfe A, Sharma C, Greenup R, Reynolds KL, Smith BL, Alexander B, Moy B, Isakoff SJ, Parmigiani G, Trippa L, Bardia A. Pathologic Complete Response after

Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-analysis. Clin Cancer Res. 2020 Jun 15;26(12):2838-2848. doi: 10.1158/1078-0432.CCR-19-3492. Epub 2020 Feb 11. PMID: 32046998; PMCID: PMC7299787.

8. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663.

9. Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Untch M, Fasching PA, Cardoso F, Andersen J, Patt D, Danso M, Ferreira M, Mouret-Reynier MA, Im SA, Ahn JH, Gion M, Baron-Hay S, Boileau JF, Ding Y, Tryfonidis K, Aktan G, Karantza V, O'Shaughnessy J; KEYNOTE-522 Investigators. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med. 2022 Feb 10;386(6):556-567. doi: 10.1056/NEJMoa2112651. PMID: 35139274.

10. Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer JU, Grischke EM, Furlanetto J, Tesch H, Hanusch C, Engels K, Rezai M, Jackisch C, Schmitt WD, von Minckwitz G, Thomalla J, Kümmel S, Rautenberg B, Fasching PA, Weber K, Rhiem K, Denkert C, Schneeweiss A. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019 Aug 1;30(8):1279-1288. doi: 10.1093/annonc/mdz158. Erratum in: Ann Oncol. 2022 Jul;33(7):743-744. PMID: 31095287.

11. Loibl S, Schneeweiss A, Huober JB, Braun M, Rey J, Blohmer JU, Furlanetto J, Zahm DM, Hanusch C, Thomalla J, Jackisch C, Staib P, Link T, Rhiem K, Solbach C, Fasching PA, Burchardi N, Denkert C, Untch M. Durvalumab improves long-term outcome in TNBC: results from the phase II randomized GeparNUEVO study investigating neodjuvant durvalumab in addition to an anthracycline/taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC). Journal of Clinical Oncology [Internet]. 2021 May 20 [cited 2022 Oct 27];39(15_suppl):506. Available from: https://doi.org/10.1200/jco.2021.39.15_suppl.506

12. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, Koehler A, Sohn J, Iwata H, Telli ML, Ferrario C, Punie K, Penault-Llorca F, Patel S, Duc AN, Liste-Hermoso M, Maiya V, Molinero L, Chui SY, Harbeck N. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020 Oct 10;396(10257):1090-1100. doi: 10.1016/S0140-6736(20)31953-X. Epub 2020 Sep 20. PMID: 32966830.

13. Geyer CE, Sikov WM, Huober J, Rugo HS, Wolmark N, O'Shaughnessy J, Maag D, Untch M, Golshan M, Lorenzo JP, Metzger O, Dunbar M, Symmans WF, Rastogi P, Sohn JH, Young R, Wright GS, Harkness C, McIntyre K, Yardley D, Loibl S. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022 Apr;33(4):384-394. doi: 10.1016/j.annonc.2022.01.009. Epub 2022 Jan 31. PMID: 35093516.

14. Von Minckwitz, G., Schneeweiss, A., Loibl, S., Salat, C., Denkert, C., Rezai, M., Blohmer, J. U., Jackisch, C., Paepke, S., Gerber, B., Zahm, D. M., Kümmel, S., Eidtmann, H., Klare, P., Huober, J., Costa, S., Tesch, H., Hanusch, C., Hilfrich, J., Untch, M. (2014). Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): A randomised phase 2 trial. The lancet oncology, [cited 2022 Oct 27]15(7), 747-756. Available from: https://doi.org/10.1016/S1470-2045(14)70160-3.

15. Sikov WM, Berry DA, Perou CM, Singh B, Cirrincione CT, Tolaney SM, Kuzma CS, Pluard TJ, Somlo G, Port ER, Golshan M, Bellon JR, Collyar D, Hahn OM, Carey LA, Hudis CA, Winer EP. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol. 2015 Jan 1;33(1):13-21. doi: 10.1200/JCO.2014.57.0572. Epub 2014 Aug 4. PMID: 25092775; PMCID: PMC4268249.

16. Loibl S, O'Shaughnessy J, Untch M, Sikov WM, Rugo HS, McKee MD, Huober J, Golshan M, von Minckwitz G, Maag D, Sullivan D, Wolmark N, McIntyre K, Ponce Lorenzo JJ, Metzger Filho O, Rastogi P, Symmans WF, Liu X, Geyer CE. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. The Lancet Oncology [Internet]. 2018 Apr [cited 2022 Oct 27];19(4):497-509. Available from: https://doi.org/10.1016/s1470-2045(18)30111-6

17. Sharma, P., et al. (2016). "Efficacy of neoadjuvant carboplatin plus docetaxel in triple negative breast cancer: Combined analysis of two cohorts." Clinical Cancer Research: clincanres.0162.2016.

18. Sharma P, López-Tarruella S, García-Saenz JA, Khan QJ, Gómez HL, Prat A, Moreno F, Jerez-Gilarranz Y, Barnadas A, Picornell AC, Monte-Millán MD, González-Rivera M, Massarrah T, Pelaez-Lorenzo B, Palomero MI, González Del Val R, Cortés J, Fuentes-Rivera H, Morales DB, Márquez-Rodas I, Perou CM, Lehn C, Wang YY, Klemp JR, Mammen JV, Wagner JL, Amin AL, O'Dea AP, Heldstab J, Jensen RA, Kimler BF, Godwin AK, Martín M. Pathological Response and Survival in Triple-Negative Breast Cancer Following Neoadjuvant Carboplatin plus Docetaxel. Clin Cancer Res. 2018 Dec 1;24(23):5820-5829. doi: 10.1158/1078-0432.CCR-18-0585. Epub 2018 Jul 30. PMID: 30061361; PMCID: PMC6279513.

19. Gluz, O., et al. (2019). "Abstract GS5-06: No survival benefit of chemotherapy escalation in patients with pCR and “high-immune” triple-negative early breast cancer in the neoadjuvant WSG-ADAPT-TN trial." Cancer Research 79(4 Supplement): GS5-06-GS05-06.

20. Shen, Yuanyuan & Shyu, Chi-Ren & Mitchem, Jonathan & Ding, F & Shajahan-Haq, Ayesha. (2019). Abstract P2-09-14: Immunogenomic pathway and survival analysis in breast cancers based on tumor location and molecular subtypes. Cancer Research. 79. P2-09. 10.1158/1538-7445.SABCS18-P2-09-14.

21. Sharma P, Kimler BF, O'Dea A, Nye L, Wang YY, Yoder R, Staley JM, Prochaska L, Wagner J, Amin AL, Larson K, Balanoff C, Elia M, Crane G, Madhusudhana S, Hoffmann M, Sheehan M, Rodriguez R, Finke K, Shah R, Satelli D, Shrestha A, Beck L, McKittrick R, Pluenneke R, Raja V, Beeki V, Corum L, Heldstab J, LaFaver S, Prager M, Phadnis M, Mudaranthakam DP, Jensen RA, Godwin AK, Salgado R, Mehta K, Khan Q. Randomized Phase II Trial of Anthracycline-free and Anthracycline-containing Neoadjuvant Carboplatin

Chemotherapy Regimens in Stage I-III Triple-negative Breast Cancer (NeoSTOP). Clin Cancer Res. 2021 Feb 15;27(4):975-982. doi: 10.1158/1078-0432.CCR-20-3646. Epub 2020 Nov 18. PMID: 33208340; PMCID: PMC7887017.

22. Sharma P, Kimler BF, O'Dea A, Nye L, Wang YY, Yoder R, Staley JM, Prochaska L, Wagner J, Amin AL, Larson K, Balanoff C, Elia M, Crane G, Madhusudhana S, Hoffmann M, Sheehan M, Rodriguez R, Finke K, Shah R, Satelli D, Shrestha A, Beck L, McKittrick R, Pluenneke R, Raja V, Beeki V, Corum L, Heldstab J, LaFaver S, Prager M, Phadnis M, Mudaranthakam DP, Jensen RA, Godwin AK, Salgado R, Mehta K, Khan Q. Randomized Phase II Trial of Anthracycline-free and Anthracycline-containing Neoadjuvant Carboplatin Chemotherapy Regimens in Stage I-III Triple-negative Breast Cancer (NeoSTOP). Clin Cancer Res. 2021 Feb 15;27(4):975-982. doi: 10.1158/1078-0432.CCR-20-3646. Epub 2020 Nov 18. PMID: 33208340; PMCID: PMC7887017.

23. Sharma P, Kimler BF, O'Dea A, Nye L, Wang YY, Yoder R, Staley JM, Prochaska L, Wagner J, Amin AL, Larson K, Balanoff C, Elia M, Crane G, Madhusudhana S, Hoffmann M, Sheehan M, Rodriguez R, Finke K, Shah R, Satelli D, Shrestha A, Beck L, McKittrick R, Pluenneke R, Raja V, Beeki V, Corum L, Heldstab J, LaFaver S, Prager M, Phadnis M, Mudaranthakam DP, Jensen RA, Godwin AK, Salgado R, Mehta K, Khan Q. Randomized Phase II Trial of Anthracycline-free and Anthracycline-containing Neoadjuvant Carboplatin Chemotherapy Regimens in Stage I-III Triple-negative Breast Cancer (NeoSTOP). Clin Cancer Res. 2021 Feb 15;27(4):975-982. doi: 10.1158/1078-0432.CCR-20-3646. Epub 2020 Nov 18. PMID: 33208340; PMCID: PMC7887017.

24. Sharma P, Kimler BF, O'Dea A, Nye L, Wang YY, Yoder R, Staley JM, Prochaska L, Wagner J, Amin AL, Larson K, Balanoff C, Elia M, Crane G, Madhusudhana S, Hoffmann M, Sheehan M, Rodriguez R, Finke K, Shah R, Satelli D, Shrestha A, Beck L, McKittrick R, Pluenneke R, Raja V, Beeki V, Corum L, Heldstab J, LaFaver S, Prager M, Phadnis M, Mudaranthakam DP, Jensen RA, Godwin AK, Salgado R, Mehta K, Khan Q. Randomized Phase II Trial of Anthracycline-free and Anthracycline-containing Neoadjuvant Carboplatin Chemotherapy Regimens in Stage I-III Triple-negative Breast Cancer (NeoSTOP). Clin Cancer Res. 2021 Feb 15;27(4):975-982. doi: 10.1158/1078-0432.CCR-20-3646. Epub 2020 Nov 18. PMID: 33208340; PMCID: PMC7887017.

25. Sharma P, López-Tarruella S, García-Saenz JA, Khan QJ, Gómez HL, Prat A, Moreno F, Jerez-Gilarranz Y, Barnadas A, Picornell AC, Monte-Millán MD, González-Rivera M, Massarrah T, Pelaez-Lorenzo B, Palomero MI, González Del Val R, Cortés J, Fuentes-Rivera H, Morales DB, Márquez-Rodas I, Perou CM, Lehn C, Wang YY, Klemp JR, Mammen JV, Wagner JL, Amin AL, O'Dea AP, Heldstab J, Jensen RA, Kimler BF, Godwin AK, Martín M. Pathological Response and Survival in Triple-Negative Breast Cancer Following Neoadjuvant Carboplatin plus Docetaxel. Clin Cancer Res. 2018 Dec 1;24(23):5820-5829. doi: 10.1158/1078-0432.CCR-18-0585. Epub 2018 Jul 30. PMID: 30061361; PMCID: PMC6279513.

26. Schneeweiss A, Denkert C, Fasching PA, Fremd C, Gluz O, Kolberg-Liedtke C, Loibl S, Lück HJ. Diagnosis and Therapy of Triple-Negative Breast Cancer (TNBC) - Recommendations for Daily Routine Practice. Geburtshilfe Frauenheilkd. 2019 Jun;79(6):605-617. doi: 10.1055/a-0887-0285. Epub 2019 Jun 14. PMID: 31217629; PMCID: PMC6570613.

27. Gluz, O., et al. (2019). "Abstract GS5-06: No survival benefit of chemotherapy escalation in patients with pCR and “high-immune” triple-negative early breast cancer in the neoadjuvant WSG-ADAPT-TN trial." Cancer Research 79(4 Supplement): GS5-06-GS05-06.

28. Sharma, P. (2022). Clinical and biomarker results of neoadjuvant phase II study of pembrolizumab and carboplatin plus docetaxel in triple-negative breast cancer (TNBC) (NeoPACT). ASCO.

29. Nyrop KA, Deal AM, Shachar SS, Basch E, Reeve BB, Choi SK, Lee JT, Wood WA, Anders CK, Carey LA, Dees EC, Jolly TA, Reeder-Hayes KE, Kimmick GG, Karuturi MS, Reinbolt RE, Speca JC, Muss HB. Patient-Reported Toxicities During Chemotherapy Regimens in Current Clinical Practice for Early Breast Cancer. Oncologist. 2019 Jun;24(6):762-771. doi: 10.1634/theoncologist.2018-0590. Epub 2018 Dec 14. PMID: 30552158; PMCID: PMC6656489.

30. Sharma P, Stecklein SR, Yoder R, et al. Clinical and Biomarker Findings of Neoadjuvant Pembrolizumab and Carboplatin Plus Docetaxel in Triple-Negative Breast Cancer: NeoPACT Phase 2 Clinical Trial. JAMA Oncol. Published online November 22, 2023. doi:10.1001/jamaoncol.2023.5033

31. Lafay-Cousin L, Sung L, Carret AS, Hukin J, Wilson B, Johnston DL, Zelcer S, Silva M, Odame I, Mpofu C, Strother D, Bouffet E. Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. Cancer. 2008 Feb 15;112(4):892-9. doi: 10.1002/cncr.23249. PMID: 18098210.

32. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, Belinson J. Clinical features of hypersensitivity reactions to carboplatin. J Clin Oncol. 1999 Apr;17(4):1141. doi: 10.1200/JCO.1999.17.4.1141. PMID: 10561172.

33. Sliesoraitis S, Chikhale PJ. Carboplatin hypersensitivity. Int J Gynecol Cancer. 2005 Jan-Feb;15(1):13-8. doi: 10.1111/j.1048-891x.2005.14401.x. PMID: 15670291.

34. Hoekstra AV, Hurteau JA, Kirschner CV, Rodriguez GC. The combination of monthly carboplatin and weekly paclitaxel is highly active for the treatment of recurrent ovarian cancer. Gynecol Oncol. 2009 Dec;115(3):377-81. doi: 10.1016/j.ygyno.2009.08.021. Epub 2009 Oct 1. PMID: 19800107.

35. Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saif MW. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. Met Based Drugs. 2010;2010:207084. doi: 10.1155/2010/207084. Epub 2010 Sep 20. PMID: 20886011; PMCID: PMC2945654.

36. Denkert C, von Minckwitz G, Brase JC, Sinn BV, Gade S, Kronenwett R, Pfitzner BM, Salat C, Loi S, Schmitt WD, Schem C, Fisch K, Darb-Esfahani S, Mehta K, Sotiriou C, Wienert S, Klare P, André F, Klauschen F, Blohmer JU, Krappmann K, Schmidt M, Tesch H, Kümmel S, Sinn P, Jackisch C, Dietel M, Reimer T, Untch M, Loibl S. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol. 2015 Mar 20;33(9):983-91. doi: 10.1200/JCO.2014.58.1967. Epub 2014 Dec 22. PMID: 25534375.

37. Savas P, Salgado R, Denkert C, Sotiriou C, Darcy PK, Smyth MJ, Loi S. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. Nat Rev Clin Oncol. 2016 Apr;13(4):228-41. doi: 10.1038/nrclinonc.2015.215. Epub 2015 Dec 15. PMID: 26667975.

38. Loi S, Drubay D, Adams S, Pruneri G, Francis PA, Lacroix-Triki M, Joensuu H, Dieci MV, Badve S, Demaria S, Gray R, Munzone E, Lemonnier J, Sotiriou C, Piccart MJ, Kellokumpu-Lehtinen PL, Vingiani A, Gray K, Andre F, Denkert C, Salgado R, Michiels S. Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of

Early-Stage Triple-Negative Breast Cancers. J Clin Oncol. 2019 Mar 1;37(7):559-569. doi: 10.1200/JCO.18.01010. Epub 2019 Jan 16. PMID: 30650045; PMCID: PMC7010425.

39. Luen SJ, Salgado R, Dieci MV, Vingiani A, Curigliano G, Gould RE, Castaneda C, D'Alfonso T, Sanchez J, Cheng E, Andreopoulou E, Castillo M, Adams S, Demaria S, Symmans WF, Michiels S, Loi S. Prognostic implications of residual disease tumor-infiltrating lymphocytes and residual cancer burden in triple-negative breast cancer patients after neoadjuvant chemotherapy. Ann Oncol. 2019 Feb 1;30(2):236-242. doi: 10.1093/annonc/mdy547. PMID: 30590484.

40. Loi S, Drubay D, Adams S, Pruneri G, Francis PA, Lacroix-Triki M, Joensuu H, Dieci MV, Badve S, Demaria S, Gray R, Munzone E, Lemonnier J, Sotiriou C, Piccart MJ, Kellokumpu-Lehtinen PL, Vingiani A, Gray K, Andre F, Denkert C, Salgado R, Michiels S. Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of Early-Stage Triple-Negative Breast Cancers. J Clin Oncol. 2019 Mar 1;37(7):559-569. doi: 10.1200/JCO.18.01010. Epub 2019 Jan 16. PMID: 30650045; PMCID: PMC7010425.

41. Denkert C, Loibl S, Noske A, Roller M, Müller BM, Komor M, Budczies J, Darb-Esfahani S, Kronenwett R, Hanusch C, von Törne C, Weichert W, Engels K, Solbach C, Schrader I, Dietel M, von Minckwitz G. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol. 2010 Jan 1;28(1):105-13. doi: 10.1200/JCO.2009.23.7370. Epub 2009 Nov 16. Erratum in: J Clin Oncol. 2010 Feb 1;28(4):708. PMID: 19917869.

42. Denkert C, von Minckwitz G, Brase JC, Sinn BV, Gade S, Kronenwett R, Pfitzner BM, Salat C, Loi S, Schmitt WD, Schem C, Fisch K, Darb-Esfahani S, Mehta K, Sotiriou C, Wienert S, Klare P, André F, Klauschen F, Blohmer JU, Krappmann K, Schmidt M, Tesch H, Kümmel S, Sinn P, Jackisch C, Dietel M, Reimer T, Untch M, Loibl S. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol. 2015 Mar 20;33(9):983-91. doi: 10.1200/JCO.2014.58.1967. Epub 2014 Dec 22. PMID: 25534375.

43. Sharma, P. (2022). Clinical and biomarker results of neoadjuvant phase II study of pembrolizumab and carboplatin plus docetaxel in triple-negative breast cancer (TNBC) (NeoPACT). ASCO.

44. Bai Y, Cole K, Martinez-Morilla S, Ahmed FS, Zugazagoitia J, Staaf J, Bosch A, Ehinger A, Nimeus E, Hartman J, Acs B, Rimm DL. An Open-Source, Automated Tumor-Infiltrating Lymphocyte Algorithm for Prognosis in Triple-Negative Breast Cancer. Clin Cancer Res. 2021 Oct 15;27(20):5557-5565. doi: 10.1158/1078-0432.CCR-21-0325. Epub 2021 Jun 4. PMID: 34088723; PMCID: PMC8530841.

45. Pusic AL, Matros E, Fine N, Buchel E, Gordillo GM, Hamill JB, Kim HM, Qi J, Albornoz C, Klassen AF, Wilkins EG. Patient-Reported Outcomes 1 Year After Immediate Breast Reconstruction: Results of the Mastectomy Reconstruction Outcomes Consortium Study. J Clin Oncol. 2017 Aug 1;35(22):2499-2506. doi: 10.1200/JCO.2016.69.9561. Epub 2017 Mar 27. PMID: 28346808; PMCID: PMC5536162.

46. Shaw, B., et al. PROMIS measures can be used to assess symptoms and function in long-term hematopoietic cell transplantation survivors. Cancer. 2018 Feb 15;124(4):841-849. doi: 10.1002/cncr.31089. Epub 2017 Oct 26. PMID: 29072787; PMCID: PMC5800994.

47. Cook KF, Jensen SE, Schalet BD, Beaumont JL, Amtmann D, Czajkowski S, Dewalt DA, Fries JF, Pilkonis PA, Reeve BB, Stone AA, Weinfurt KP, Cella D. PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions. J Clin Epidemiol. 2016 May;73:89-102. doi: 10.1016/j.jclinepi.2015.08.038. Epub 2016 Mar 4. PMID: 26952842; PMCID: PMC5131708.

48 Bagheri M, Chung CP, Dickson AL, Van Driest SL, Borinstein SC, Mosley JD. White blood cell ranges and frequency of neutropenia by Duffy genotype status. Blood Adv. 2023 Feb 14;7(3):406-409. doi: 10.1182/bloodadvances.2022007680. PMID: 35895516; PMCID: PMC9979714.

49 Merz LE, Story CM, Osei MA, Jolley K, Ren S, Park HS, Yefidoff Freedman R, Neuberg D, Smeland-Wagman R, Kaufman RM, Achebe MO. Absolute neutrophil count by Duffy status among healthy Black and African American adults. Blood Adv. 2023 Feb 14;7(3):317-320. doi: 10.1182/bloodadvances.2022007679. PMID: 35994632; PMCID: PMC9881043.

50 Denkert, C., von Minckwitz, G., Darb-Esfahani, S., Lederer, B., Heppner, B. I., Weber, K. E., … Loibl, S. (2017). Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: A pooled analysis of 3771 patients treated with neoadjuvant therapy. The Lancet Oncology, 19(1), 40–50. doi:10.1016/s1470-2045(17)30904-x

51 Loi S, Drubay D, Adams S, Pruneri G, Francis PA, Lacroix-Triki M, Joensuu H, Dieci MV, Badve S, Demaria S, Gray R, Munzone E, Lemonnier J, Sotiriou C, Piccart MJ, Kellokumpu-Lehtinen PL, Vingiani A, Gray K, Andre F, Denkert C, Salgado R, Michiels S. Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of Early-Stage Triple-Negative Breast Cancers. J Clin Oncol. 2019 Mar 1;37(7):559-569. doi: 10.1200/JCO.18.01010. Epub 2019 Jan 16. PMID: 30650045; PMCID: PMC7010425.

52 Sharma P, Kimler BF, O'Dea A, Nye L, Wang YY, Yoder R, Staley JM, Prochaska L, Wagner J, Amin AL, Larson K, Balanoff C, Elia M, Crane G, Madhusudhana S, Hoffmann M, Sheehan M, Rodriguez R, Finke K, Shah R, Satelli D, Shrestha A, Beck L, McKittrick R, Pluenneke R, Raja V, Beeki V, Corum L, Heldstab J, LaFaver S, Prager M, Phadnis M, Mudaranthakam DP, Jensen RA, Godwin AK, Salgado R, Mehta K, Khan Q. Randomized Phase II Trial of Anthracycline-free and Anthracycline-containing Neoadjuvant Carboplatin Chemotherapy Regimens in Stage I-III Triple-negative Breast Cancer (NeoSTOP). Clin Cancer Res. 2021 Feb 15;27(4):975-982. doi: 10.1158/1078-0432.CCR-20-3646. Epub 2020 Nov 18. PMID: 33208340; PMCID: PMC7887017.

53 Sharma, P. (2022). Time to optimize deescalation strategies in triple-negative breast cancer? Clinical Cancer Research, 28(22), 4840–4842. doi:10.1158/1078-0432.ccr-22-2140

54 Schmid P, Salgado R, Park YH, Muñoz-Couselo E, Kim SB, Sohn J, Im SA, Foukakis T, Kuemmel S, Dent R, Yin L, Wang A, Tryfonidis K, Karantza V, Cortés J, Loi S. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann Oncol. 2020 May;31(5):569-581. doi: 10.1016/j.annonc.2020.01.072. Epub 2020 Feb 14. PMID: 32278621.

18.0 APPENDIX

18.1 New York Heart Association Criteria

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight or occasional	Usually only slight	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the participant, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

18.2 Instructions the SWOG Biospecimen Bank – Lab #201: Solid Tissue, Myeloma and Lymphoma Division

a. The Bank will receive and process specimens as follows:

The Bank will retain all specimens until CTEP approves use of the specimens for translational medicine studies.

1. Tissue

Upon receipt, the Bank will accession, barcode, and store H&E stained slides at room temperature. The H&E stained slides will be scanned to digital images (at 40x magnification) and sent electronically to a study-designated pathologist for the sTIL review in batches.

FFPE tissue blocks and unstained slides will be accessioned, barcoded, and stored at room temperature for long-term storage.

2. Blood

- Whole blood in red top tube: Upon receipt, the Bank will isolate serum in 1 ml aliquots, accession, barcode, and store in a -80°C freezer.
- Whole blood in Streck cfDNA tube: Upon receipt, the Bank will accession, barcode, and process blood in Streck cfDNA tubes for plasma and buffy coat, using a double-centrifugation protocol. Plasma will be stored in 1-mL aliquots. Buffy coat and plasma aliquots will be stored in a -80°C freezer for long-term storage.

18.3 Integrated Correlative PRO Study

a. Objectives

Primary PRO Objective

To compare fatigue experienced by participants undergoing neoadjuvant systemic chemotherapy (NAST) with taxane-platinum-anthracycline chemo-immunotherapy vs taxane-platinum chemo-immunotherapy within 3-5 weeks post last neoadjuvant systemic therapy dose and at 18 months after registration using the PROMIS Fatigue-7a instrument.

Secondary Objectives

1. To compare physical function experienced by participants undergoing neoadjuvant systemic chemotherapy (NAST) with taxane-platinum-anthracycline chemo-immunotherapy vs taxane-platinum chemo-immunotherapy, within 3-5 weeks post last neoadjuvant systemic therapy dose using the PROMIS-29 Profile physical function subscale score.

2. To compare physical function experienced by participants undergoing NAST taxane-platinum-anthracycline chemo-immunotherapy vs taxane-platinum chemo-immunotherapy at 18 months post registration using the PROMIS-29 Profile physical function subscale score.

Exploratory Objectives:

1. To compare other PROMIS-29 Profile subscale scores (sleep disturbance, depression, anxiety, social, pain interference, and pain sensitivity) and GP5 question response by arm within 3-5 weeks post last neoadjuvant systemic therapy dose and at 18 months post registration.

2. To compare the GP-5 item scores by arm within 3-5 weeks post last neoadjuvant systemic therapy dose and at 18 months post registration.

b. Hypotheses

Primary Hypotheses:

We hypothesize that participants assigned to taxane-platinum-anthracycline chemo-immunotherapy will experience increased fatigue both within 3-5 weeks post last neoadjuvant systemic therapy dose and at 18 months following registration as measured by the PROMIS Fatigue-7a than participants assigned to the non-anthracycline containing regimen.

Secondary Hypotheses:

1. We hypothesize that participants assigned to taxane-platinum-anthracycline chemo-immunotherapy will experience worse physical function as measured by the PROMIS-29 instrument than participants assigned to the non-anthracycline containing regimen.

2. We hypothesize that participants assigned to taxane-platinum-anthracycline chemo-immunotherapy will experience worse physical function at 18 months subsequent to randomization as measured by PROMIS-29 instrument than participants assigned to the non-anthracycline containing regimen.

c. Background

Chemotherapy for breast cancer has a number of known toxicities. Anthracycline-based chemotherapy is known to cause irreversible cardiomyopathy and poor prognosis secondary hematologic malignancies among other toxicities. Trials for biomarker-based tailoring of therapy are needed to test whether regimens associated with fewer serious late effects of chemotherapy can be administered without compromising survival. In the curative treatment of cancer, if two regimens are found to be non-inferior, assessment of differences in patient- reported outcomes and QOL may provide important information when patients and providers are making decisions regarding treatment.

The proposed trial compares an anthracycline based chemotherapy regimen (AC followed by paclitaxel/carboplatin) vs. carboplatin and paclitaxel. These regimens cause short- and long-term effects on QOL and neuropathy, although patient-reported differences between the two regimens have not previously been fully assessed. The objective of this PRO study is to compare patient-reported QOL, symptoms such as neuropathy, fatigue, physical function, anxiety, depression, nausea, vomiting, and joint pain between treatment arms.

The tools to be utilized have been validated and used in previous assessments and are available in multiple languages. The PROMIS-29 Profile and the PROMIS Fatigue 7a have been used in clinical trials for breast cancer (i.e., Pusic et al JCO 2017) and other malignancies (Shaw, et al Cancer 2017). The PROMIS Fatigue 7a is a 7-item questionnaire that is used to obtain a multidimensional assessment of fatigue, a symptom that commonly occurs with chemotherapy and immunotherapy. The PROMIS-29 Profile is a 29-item questionnaire that covers a range of symptoms and quality of life assessments that are relevant for assessing both short- and long-term effects of chemotherapy. The single item GP5, “I am bothered by side effects of treatment,” is derived from the FACT-General (FACT-G) questionnaire, and has been shown to be associated with clinician-reported adverse events in multiple cancer clinical trials (*2*). The PRO CTCAE for a number of symptoms is a well-known and validated tool for assessment of patient-reported adverse events over the prior 7 days in clinical trials and will be used to assess symptoms not captured by the PROMIS-29 Profile and the PROMIS fatigue including numbness and tingling (severity, interference), fatigue (severity, interference), nausea (severity, interference), vomiting (severity), and joint pain (severity). These instruments will be used at baseline to capture pre-existing symptoms, within 3-5 weeks post last neoadjuvant systemic therapy dose to assess acute chemotherapy toxicity, and 18 months after registration to examine persistence of toxicity after completion of therapy.

d. Patient-Reported Outcome Assessment Instruments

Inclusion: Participants who consented to complete the questionnaires in English, Spanish, or French. When 750 participants have been enrolled in the PRO study, further recruitment into the sub study will end.

The PROMIS and FACT -G GP5 questionnaires will be self-administered by the participants, with assistance available from the research staff if required. This is currently planned to be done on paper. When questionnaires are administered by the research staff, they will be done in a private area, where possible.

1. PROMIS-29 Profile v2.1

The PROMIS-29 Profile is a validated 29-item questionnaire that assesses patient-reported symptoms in 9 PROMIS domains (fatigue, sleep disturbance, physical functioning, depression, anxiety, ability to participate in social roles and activities, pain interference, and pain severity) over the past 7 days. Calculated raw scores for each domain are converted to a T-score, with mean 50 and standard deviation 10. Higher T scores represent

more of the concept being measured. *(55)* The questionnaire is available in English, Spanish, and French.

2. PROMIS Short Form v1.0 – Fatigue 7a

The PROMIS Fatigue-7a is a validated 7-item questionnaire that assesses patient-reported fatigue over the past 7 days. Calculated raw scores are converted to a T-score, with mean 50 and standard deviation 10. Higher T scores represent more fatigue *(56)*. The questionnaire is available in English, Spanish, and French.

3. FACT -G GP5 question

The GP5 question is a single item rated on a 5-point Likert scale. It asks about treatment-related symptom bother and is part of the FACT-G questionnaire.

e. Timepoints

The patient-reported outcome assessments are scheduled to occur prior to randomization and within 3-5 weeks post last neoadjuvant systemic therapy dose and 18 months after date of randomization.

f. Endpoints

Fatigue.
Assessed using the PROMIS Fatigue-7a.

Sleep disturbance.
Assessed using the PROMIS-29 Profile 4-item Sleep disturbance subscale

Physical functioning.
Assessed using the PROMIS-29 Profile 4-item Physical functioning subscale

Depression.
Assessed using the PROMIS-29 Profile 4-item Depression subscale

Anxiety.
Assessed using the PROMIS-29 Profile 4-item Anxiety subscale

Ability to participate in social roles and activities.
Assessed using the PROMIS-29 Profile 4-item Ability to participate in social roles and activities subscale

Pain interference.
Assessed using the PROMIS-29 Profile 4-item Pain interference subscale

Pain sensitivity.
Assessed using the PROMIS-29 Profile 1-item pain sensitivity question

Side effect bother.
Assessed using the FACT-G GP5 single item

g. Statistical Considerations

Primary Objectives:

Patient-reported outcome assessments will occur in conjunction with the planned clinical follow-up schedule in order to minimize missing data and to link the clinical assessment with participants' self-reported symptom assessments using the PROMIS Fatigue-7a and the PROMIS-29. This design should also minimize participant and staff burden. The assessment times are scheduled to occur at

baseline prior to registration, within 3-5 weeks post last neoadjuvant systemic therapy dose to assess the acute effects of chemotherapy, and at 18 months after registration to examine persistence of symptoms after completion of therapy.
The primary endpoint is fatigue based on the PROMIS Fatigue-7a. Our primary aim is twofold; to compare fatigue by arm within 3-5 weeks post last neoadjuvant systemic therapy dose, and to compare fatigue by arm at 18 months after registration. We will account for multiple testing using Bonferroni; thus, each assessment will be examined using a two-sided alpha=.025 test. Within 3-5 weeks post last neoadjuvant systemic therapy dose, the design assumes 10% dropout, and at 18 months, 20% dropout is anticipated. The PROMIS system utilizes standardized scoring based on T-scores with a mean of 50 and a standard deviation of 10. Smaller standard deviations have been observed in cancer patients. However, for design purposes a standard deviation of 10 is assumed (conservative assumption). Per Yost et al., minimally important differences using anchor-based approaches for the PROMIS Fatigue-7a range from 3 to 5 points. Our aim is to identify a small effect of 0.3 at each assessment time (3 point difference with 10 point standard deviation implies and effect size=0.3). Accrual of N=750 total evaluable patients to the QOL substudy would provide 95% power to identify an effect size of 0.3 within 3-5 weeks post last neoadjuvant systemic therapy dose (675 evaluable patients, including an additional 10%, or 75 patients, to account for the anticipated 10% dropout). Similarly, this sample size would provide 92% power to detect an effect size of 0.3 at 18 months after registration (600 evaluable patients, including an additional 20%, or 150 patients, to account for the anticipated 20% dropout). Due to expected subset comparisons following the primary objective, including by the stratification factors and sTIL grouping the larger sample size is necessary to show smaller group differences.

The primary analysis will be conducted using linear regression adjusting for the clinical study stratification factor (nodal status) and the baseline fatigue subscale score.

The secondary objectives will be to compare by arm the PROMIS-29 Profile physical function subscale scores within 3-5 weeks post last neoadjuvant systemic therapy dose, and at 18 months after registration. Total type I error contributed to the family of secondary analyses will be α=0.05, split equally between the two tests (two-sided α=.025 for each). Linear regression analysis will be used, adjusting for the stratification factor and the baseline total score

In exploratory analyses, we will compare by arm the other PROMIS-29 Profile subscale scores (sleep disturbance, depression, anxiety, social, pain interference, and pain sensitivity) and the GP5 item response within 3-5 weeks post last neoadjuvant systemic therapy dose and at 18 months post registration. For all exploratory PRO/QOL analyses, we will set alpha=.05; however, any positive results will be considered hypothesis-generating, requiring confirmation in an independent study. This specification of all exploratory analyses as hypothesis-generating, requiring independent confirmation, will be explicitly included in all reporting of PRO/QOL analyses. No further control for type I error of exploratory analyses will be included.

h. References

1 Cella D, Riley W, Stone A, et al. PROMIS Cooperative Group. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010 Nov;63(11):1179-94. doi: 10.1016/j.jclinepi.2010.04.011. Epub 2010 Aug 4. PMID: 20685078; PMCID: PMC2965562.

2. Pearman TP, Beaumont JL, Mroczek D, O'Connor M, Cella D. Validity and usefulness of a single-item measure of patient-reported bother from side effects of cancer therapy. Cancer. 2018 Mar 1;124(5):991-997. doi: 10.1002/cncr.31133. Epub 2017 Nov 13. PMID: 29131323; PMCID: PMC5892190.

18.4 PRO-CTCAE Common Terminology Criteria for Adverse Events (PRO-CTCAE) Instrument

a. General Information:

The PRO-CTCAE instruments will be used to assess Patient-Reported toxicity outcomes.

PRO-CTCAE is intended to enhance the quality of adverse event data reporting in clinical trials, provide data that complements and extends the information provided by clinician reporting using CTCAE, represent the patient perspective of the experience of symptomatic adverse events, and improve detection of potentially serious adverse events.

The selection of PRO-CTCAE should be complementary to the clinician identified AEs for ongoing monitoring.

PRO-CTCAE assessment tools are available in the following languages. Estimated completion time: 5 minutes.

- PRO-CTCAE: Available in English, Spanish, and French

PRO-CTCAE is not currently available on the Medidata Patient Cloud ePRO.

Forms are accessible from the **S2212** protocol abstract page on the CTSU website at www.ctsu.org. Administration instructions are included in Section 15.5.

Please refer to the PRO-CTCAE Terms of Use for more information.

Recall Period for the PRO-CTCAE measures is: 7 days

b. PRO-CTCAE Analyses

The examination of PRO-CTCAE is exploratory, given there are currently no standardized scoring rules for how to combine attributes into a single score or how best to analyze PRO-CTCAE data longitudinally. PRO-CTCAE responses are scored from 0 to 4. For each of the PRO-CTCAE adverse events examined, the scores for each attribute (frequency, severity and/or interference) will be presented descriptively using summary statistics at each assessment time. Additionally, the worst severity and/or interference over the entire course will be summarized.

c. Study-Specific PRO-CTCAE Questions for Adults:

Solicited Adverse Events: The following adverse events are considered expected and their presence/ absence should be solicited and severity graded at timepoints indicated in Section 9.0.

For this study, 5 symptomatic AEs summing to items have been selected as presented below. There is 1 symptomatic AE which is assessed using one item, and 4 symptomatic AEs which are assessed using two items. The types of items in order of prevalence include severity (n=5 symptomatic AEs), interference (n=3 symptomatic AEs), frequency (n=1 symptomatic AEs), present/not present (none), and amount (none).

CTCAE Term – System Organ Class	PRO-CTCAE Symptomatic AE (Attributes)
Nausea - Gastrointestinal disorders	Nausea (FS)
Vomiting – Gastrointestinal disorders	Vomiting (S)
Fatigue – General disorders and administration site conditions	Fatigue (SI)
Peripheral sensory neuropathy – Nervous system disorders	Numbness and tingling (SI)
Arthralgia – Musculoskeletal and connective tissue disorders	Joint pain (SI)

Attribute Acronyms:

F: Frequency, S: Severity, I: Interference, P: Presence/Absence

Symptom AE	Attributes	PRO-CTCAE Items	Response options
Nausea	Frequency	In the last 7 days, how OFTEN did you have NAUSEA?	Never, Rarely, Occasionally, Frequently, Almost constantly
	Severity	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	--	--
Vomiting	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	--	--
Fatigue	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much
Numbness and tingling	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?	None, Mild, Moderate, Severe, Very Severe

Symptom AE	Attributes	PRO-CTCAE Items	Response options
	Interference	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTEFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much
Joint pain	Frequency	--	--
	Severity	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES,SHOULDERS) at their WORST?	None, Mild, Moderate, Severe, Very Severe
	Interference	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES,SHOULDERS) INTERFERE with your usual or daily activities?	Not at all, A little bit, Somewhat, Quite a bit, Very much

d. References

- PRO-CTCAE Website: https://healthcaredelivery.cancer.gov/pro-ctcae/
- PRO-CTCAE Items Library
- PRO-CTCAE NCI Scientific Leadership Team
- PRO-CTCAE Development Team
- Publications

18.5 Guidance for Decentralized Clinical Trial Activities and Streamlining Data Collection

NOTE: These standard practices for submission of data to Medidata Rave do not override or otherwise affect clinical practice standards for data collected in the local medical record. Participating investigators and clinical staff at trial sites should adhere to all applicable standards for recording clinical information in the local medical record.

Some of the following clinical trial activities refer to care provided by Local Health Care Professionals (HCPs) (Non-Research Staff). Local HCPs are defined as HCPs who are not registered as an investigator for this clinical trial. Local HCPs must perform trial activities under the oversight of the Responsible Investigator (RI), who is the investigator responsible for the participant's care at the clinical trial site.

The RI must ensure that the data is entered into Medidata Rave and is responsible for making any decisions regarding study objectives.

a. Remote Consent

Remote consent, eSignature, and eConsent are permitted for this study in accordance with local policies and procedures. Participating sites within the United States must also adhere to the NCI Central Institutional Review Board (CIRB) Standard Operating Procedures (SOP) for remote consent, eSignature, and eConsent (https://www.ncicirb.org/about-cirb/sops).

b. Telehealth Visits with Study Team

Following cycle 8 (Arm 1) and cycle 6 (Arm 2) study visits that do not require a disease assessment may be conducted by phone or videoconferencing technology (i.e., "virtual visits"), including adverse event assessments, in accordance with local laws and regulations.

c. Local Performance of Laboratory Tests

Laboratory tests outlined in Section 9.0 Study Calendar may be performed by a local laboratory. The RI should submit laboratory test results to Medidata Rave.

d. Local Performance of Imaging Tests

Scans outlined in Section 9.0 Study Calendar may be performed by a local laboratory. The RI should submit laboratory test results to Medidata Rave.

e. Administration of Commercial Agents by a Local HCP

The standard of care protocol-specified therapy may be administered by a local healthcare professional (HCP) with appropriate reporting of therapy administration data and adverse event information to the Responsible Investigator (RI).

All decisions on care within the clinical trial are made by the RI.

The RI is still required to report any protocol deviations and unanticipated problems that occur (e.g., non-compliance with protocol therapy) per standard procedures. All requirements necessary to document agreement for provision of data from a local HCP to the RI are left to the discretion of the registered clinical trial site.