FAST FACTS

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

ELIGIBILITY CRITERIA

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 either

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

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.

c. Participants must have breast and axillary imaging (on 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).

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.

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

f. Participants must have a serum creatinine ≤ the IULN OR calculated creatinine clearance ≥ 50 mL/min/1.73m2 using the following Cockcroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to registration:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})\ \dagger}{72 \times \text{serum creatinine}\ *}$$

Multiply this number by 0.85 if the participant is a female.

† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.

* Actual lab serum creatinine value with a minimum of 0.7 mg/dL.

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.

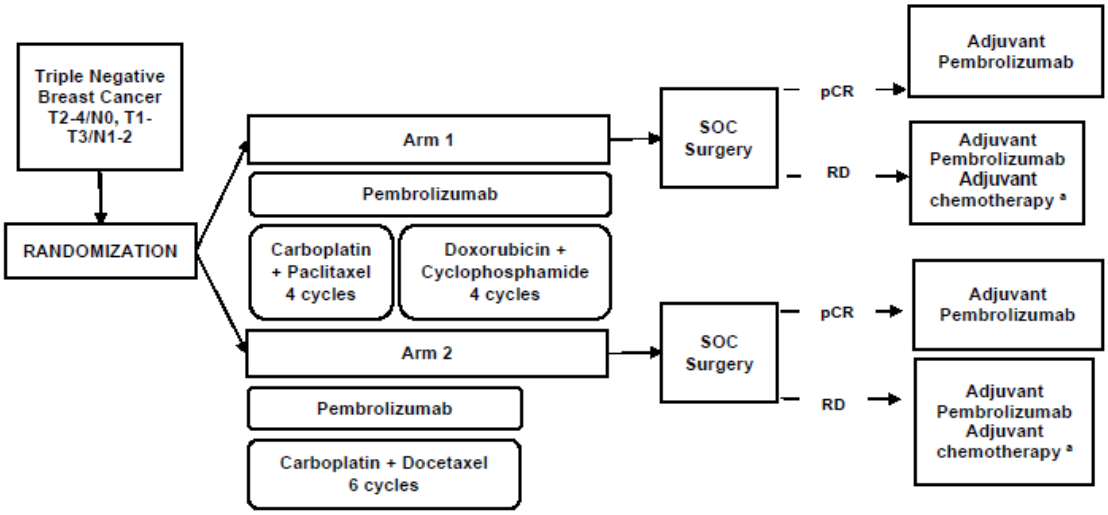
4. Additional Criteria

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 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 questionnaires in English, Spanish, or French must be offered the opportunity to participate in the Quality of Life studies as outlined in Section 15.6.

SCHEMA



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