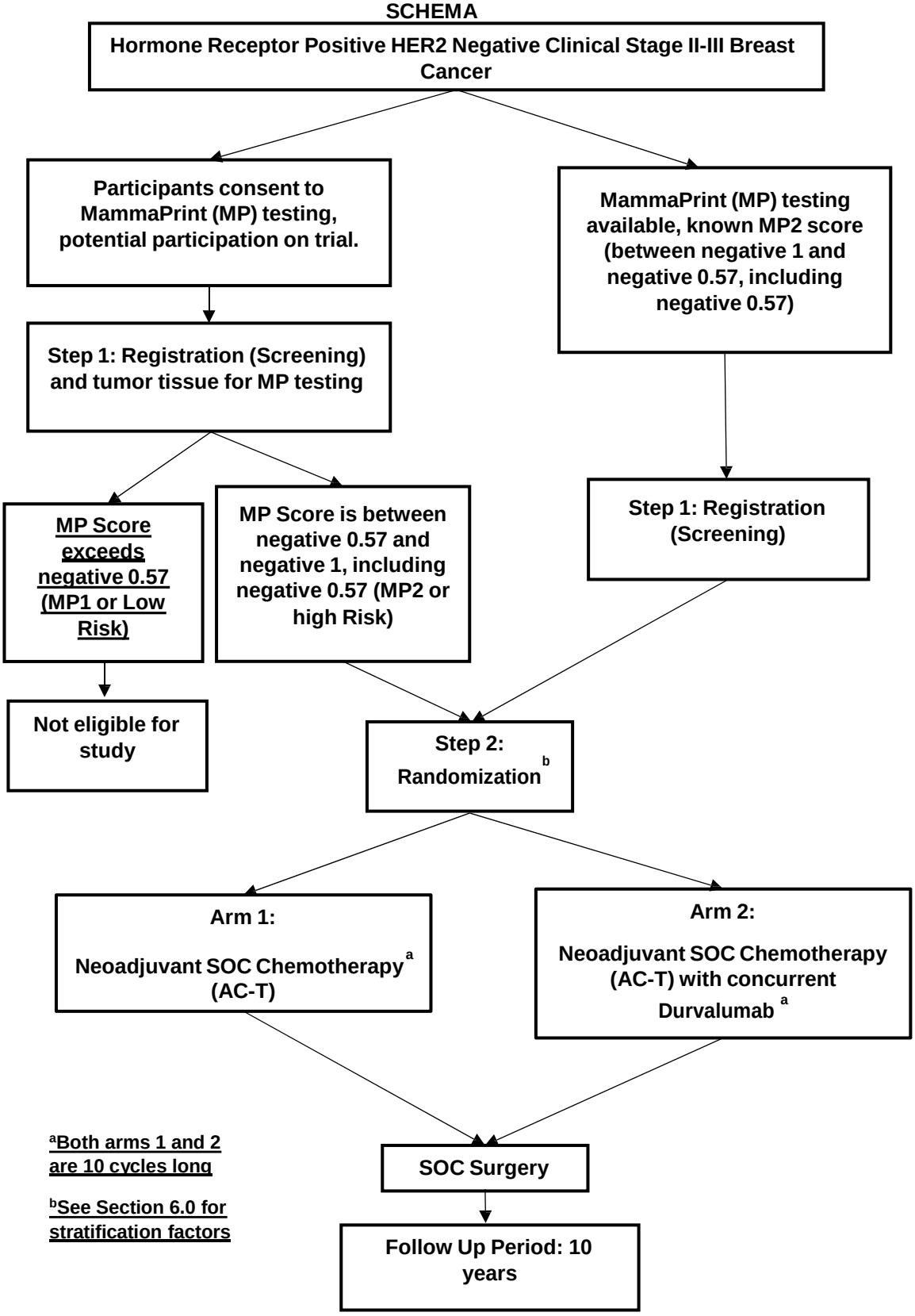
SCHEMA



[a]Both arms 1 and 2 are 10 cycles long

[b]See Section 6.0 for stratification factors

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 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 14.3). 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 28 or 120 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Step 1: Registration (Screening)

a. Disease Related Criteria

1. Participants must have histologically confirmed ER positive and/or PR positive (hormone receptor positive) and HER2 negative breast cancer, as per ASCO CAP guidelines.

   NOTE: Participants with HER2 positive disease by ASCO CAP guidelines are ineligible. HER2 negative and HER2 low or equivocal cases as per ASCO CAP guidelines that do not receive HER2 targeted therapy are eligible.

2. Participants must have clinical stage II or III breast cancer.

NOTE: Participants with inflammatory breast cancer are eligible.

3. Participants must not have metastatic disease (i.e., must be clinically M0 or Mx) Systemic staging studies with imaging should follow routine practice as per NCCN and ASCO guidelines.

4. Participants must not have locally recurrent breast cancer

5. Participants with multifocal disease or synchronous primary tumors are eligible, however, all tumors must be hormone receptor positive and HER2 negative per ASCO CAP guidelines. It is sufficient to have MP2 status on at least one of the lesions.

b. Additional Criteria

Participants must have either adequate tissue available to submit on-study or a prior known MammaPrint Index Score that is MP2 status.

1. Submitting tissue for on-study MammaPrint testing:

   Participants must have a minimum of ten, unstained formalin-fixed paraffin-embedded (FFPE) slides (4-5 micron thickness) available from initial tumor biopsy for MammaPrint assessment as outlined in Section 15.1.

   NOTE: Participants must agree to have this tissue submitted to Agendia for MammaPrint Index Scoring and to have subsequent results disclosed to SWOG Cancer Research Network.

   OR

2. Submitting prior known MammaPrint Index Score:

   If a MammaPrint Index Score report from within the last 12 weeks is already known and is MP2 status, the participant must be registered to Step 2 immediately following Step 1 registration provided they meet all other criteria. MP2 status is defined as a MammaPrint Index score between negative 1.0 and negative 0.57 (-1.0 to -0.57, including negative 0.57) tested from initial tumor biopsy.

   NOTE: Participants must agree to have their commercial MammaPrint Index Score disclosed to SWOG Cancer Research Network.

   NOTE: Participants with prior known MammaPrint result that is not MP2 status should not be enrolled to either step of this study.

c. Prior/Concurrent Therapy Criteria

Participants must not have received any prior treatment for their current breast cancer, including chemotherapy, immunotherapy, biologic or hormonal therapy, and must be candidates for doxorubicin, paclitaxel, and durvalumab therapy.

d. Clinical/Laboratory Criteria

1. Participants must be ≥ 18 years old at the time of registration.

2. Participants must have a complete medical history and physical exam within 28 days prior to Step 1 Registration.

3. Participants must have body weight > 30 kg.

4. Participants must have Zubrod Performance Status of 0-2 (see Section 10.9).

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

6. Participant must not have medical contraindications to receiving immunotherapy, including history of non-infectious pneumonitis that required steroids or active autoimmune disease that has required systemic treatment with disease modifying agents, corticosteroids or immunosuppressive drugs in the past two years. Replacement therapy (e.g. thyroxine for pre-existing hypothyroidism, insulin for type I diabetes mellitus, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Intra-articular steroid injections are allowed.

e. 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.

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.

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.

5.2 Step 2: Randomization

a. Disease Related Criteria

5. Participants must have met all eligibility criteria for Step 1 Registration

6. Participants must have MP2 MammaPrint result.

For participants submitting tissue for on-study MammaPrint testing:

Participants must be registered to Step 2: Randomization within 84 calendar days (12 weeks) after receiving an MP2 status from the MammaPrint Index score. MP2 status is defined as a MammaPrint Index score between negative 1.0 and negative 0.57 (-1.0 to -0.57, including negative 0.57) from initial tumor biopsy.

OR

Submitting commercial MammaPrint Index Score:

If a MammaPrint Index Score report from within the last 12 weeks is already known and is MP2 status, the participant must be registered to Step 2 immediately following Step 1 registration provided they meet all other criteria. MP2 status is defined as a MammaPrint Index score between negative 1.0 and negative 0.57 (-1.0 to -0.57, including negative 0.57) tested from initial tumor biopsy.

b. Prior/Concurrent Therapy Criteria

1. Participants must not have received live vaccines within 28 days prior to study Step 2: Randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines and COVID-19 vaccines are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist) are live attenuated vaccines, and are not allowed.

2. Participants must not be planning to receive any concurrent non-protocol directed chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment while receiving treatment on this study.

c. Clinical/Laboratory Criteria

1. Participant must have Zubrod Performance Status of 0-2 (see Section 10.9).

2. Participants must not have a history of (non-infectious) pneumonitis that required steroids or evidence of active pneumonitis within two years prior to Step 2: Randomization.

3. Participants must not have active autoimmune disease that has required systemic treatment in the past two years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs) prior to Step 2: Randomization. Replacement therapy (e.g. thyroxine for pre-existing hypothyroidism, insulin for type I diabetes mellitus, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Intra-articular steroid injections are allowed.

4. Participant must have a complete medical history and physical exam within 28 days prior to Step 2: Randomization.

5. Participants must have adequate organ and marrow function as defined below within 28 days prior to Step 2: Randomization:

• leukocytes	≥3 x 10^3/uL
• absolute neutrophil count	≥1.5 x 10^3/uL
• platelets	≥100 x 10^3/uL
• total bilirubin	≤ institutional upper limit of normal (ULN) unless history of Gilbert's disease. Participants with history of Gilbert's disease must have total bilirubin ≤ 5 x institutional ULN.
• AST/ALT	≤ 3 × institutional ULN

6. Participants must have a calculated creatinine clearance ≥ 50 mL/min using the following Cockcroft- Gault Formula. This specimen must have been drawn and processed within 28 days prior to Step 2: Randomization:

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

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.

7. Participants must have adequate cardiac function. 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 18.6). To be eligible for this trial, participants must be class 2B or better.

8. Participants must not have uncontrolled diabetes, defined as hemoglobin A1c of 9.0% or greater, within 28 days prior to Step 2: Randomization.

9. Participants with history of human immunodeficiency virus (HIV)-infection must be on effective anti-retroviral therapy at registration and have an undetectable viral load on the most recent test results obtained within 6 months prior to Step 2: Randomization.

10. Participants with history of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load on the most recent test results obtained while on suppressive therapy within 6 months prior to Step 2: Randomization, if indicated.

11. 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 on the most recent test results obtained within 6 months prior to Step 2: Randomization, if indicated.

12. Participants must not be pregnant or nursing. Individuals who are of reproductive potential must have agreed to use an effective contraceptive method during protocol therapy and for 6 months following completion of protocol therapy with details provided as a part of the consent process and must have a negative pregnancy test at screening. 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. Participants should not breastfeed during protocol therapy and for 6 months following completion of protocol therapy.

d. Additional Criteria

1. Participants must be offered the opportunity to participate in specimen banking as outlined in Section 15.2. With participant consent, specimens must be collected and submitted via the SWOG Specimen Tracking System as outlined in Section 15.4.

2. Participants who can complete questionnaires in English, or Spanish must be offered the opportunity to participate in the Quality of Life study as outlined in Section 15.5. For further information, please also refer to Section 18.2.

e. 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.

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.