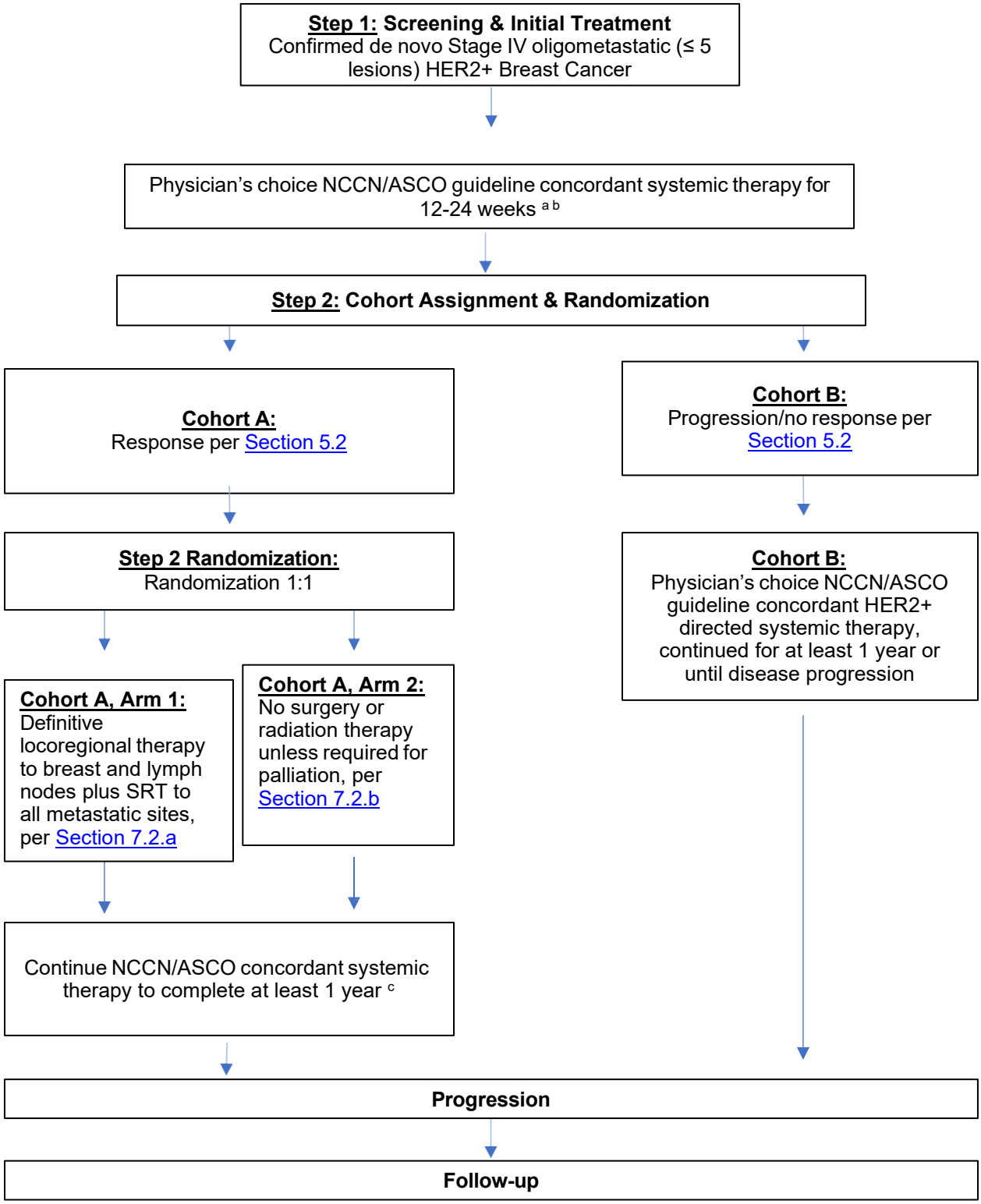
SCHEMA



[a] For the purposes of this protocol, one week is defined as seven (7) calendar days
[b] Preferred regimens are those used for stage III disease
[c] Preferred regimens are those used for residual disease after neoadjuvant chemotherapy

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 it 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 14 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1. Registration Step 1 – Screening & Initial Treatment

a. Disease Related Criteria

1. Participants must have histologically confirmed de novo metastatic (i.e. AJCC stage IV, no prior history of breast cancer) HER2+ breast cancer with 1 to 5 distant metastatic lesions (oligometastatic). Metastatic breast cancer must be histologically confirmed through biopsy of a distant metastatic lesion unless it is not feasible or safe to biopsy a metastatic lesion, then there must be unequivocal evidence of metastasis on imaging and laboratory studies. HER2+ status must be confirmed in the breast tumor and distant metastatic site as defined per NCCN guidelines version 4.2025.

   NOTE: If HER2 positivity at metastatic site is equivocal due to limitations in HER2 analysis in bone, or it is not feasible or safe to biopsy the metastatic lesion, then HER2 positivity based on breast tumor only is acceptable. If there is no breast lesion, HER2+ must be confirmed in at least one metastatic site.

2. Participants with brain metastases are eligible if they meet all of the following criteria at baseline:

   a) There are 5 or fewer intracranial lesions.

   b) Each intracranial lesions is no larger than 2cm in longest dimension.

   NOTE: The brain is counted as 1 distant site towards the oligometastatic definition. Brain imaging is not required for participants who have no neurological signs or symptoms suggestive of CNS involvement; however, assessment of neurological symptoms and brain MRI is strongly encouraged to rule out CNS disease.

3. Participants must have no known leptomeningeal disease.

b. Prior/Concurrent Therapy Criteria

1. Participants must meet **one** of the following criteria prior to **Step 1 registration**:

- Treatment naïve and planning to initiate standard of care systemic HER2+ targeted treatment.
  OR
- Have already initiated standard of care systemic HER2+ targeted treatment and have completed at least one (≥1) but no more than three (≤3) cycles prior to enrollment, without progression.
  NOTE: Standard of care scans for baseline disease assessment must have been performed within **28 days** prior to initiation of treatment.

2. Participants must not be receiving or planning to receive any investigational systemic therapy during study before disease progression.

3. Participants must not have received whole brain irradiation.

   NOTE: Participants with up to five brain metastases may have received SRS/SRT either before or after initiation of systemic therapy. If lesions are small and asymptomatic and the participant is receiving CNS penetration they may be managed with observation.

c. Clinical/Laboratory Criteria

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

2. Participants must have Zubrod Performance Status of 0-2 (see Section 10.4).

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

4. Participants must be able to safely receive the physician's choice of standard of care systemic HER2+ targeted treatment per the current FDA-approved package insert(s), treating physician's discretion, and institutional guidelines.

5. Participants must be candidates for definitive surgical and radiotherapeutic management of locoregional disease in the opinion of the treating physician.

6. Participants must be able to receive ablative dose stereotactic radiation therapy (SRT) to all metastatic lesions identified at baseline, in the opinion of the treating physician.

d. Additional Criteria

Participants must be offered the opportunity to participate in specimen banking as outlined in Section 15.

NOTE: Non-US sites are exempt from optional specimen collection per SWOG Policy 40.

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.

1. 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. Registration Step 2 – Cohort Assignment & Randomization

a. Criteria for Cohort A assignment and randomization:

1. Participants must be registered to **Step 2** within **14 days** of staging scans performed after completing Step 1 systemic therapy.

2. Participants must have standard of care (SOC) staging scans and breast imaging performed following **12-24 weeks (minimum of 4 cycles)** of initial systemic therapy and within **14 days** prior to **Step 2** Registration.

3. Participants must have experienced partial or complete response in the breast (in the opinion of the treating physician) following **12-24 weeks** of initial systemic therapy based on staging scans performed within **14 days** prior to **Step 2** Registration.

- Participants with breast lesion(s) at diagnosis must have a clinical response on breast imaging per the treating physician (see Section 10.3).
- Metastatic lesions, as assessed by RECIST and bone response criteria (per Section 10.3), must have at least stable disease.
- Brain metastases treated with SRS/SRT must have at least stable disease as per RANO BM and must not require steroid treatment.
- Participants with no known breast lesions at diagnosis must have at least partial response in the metastatic sites as assessed by RECIST and bone response criteria.

NOTE: The same imaging modality must be used as in **Step 1**.

4. Participants must be eligible for definitive surgical and radiotherapeutic management of locoregional disease per the discretion of the treating physician.

5. Participants must not have metastatic lesions that are not amenable to ablative dose stereotactic radiation therapy (SRT).

- Lung lesions that completely resolve after systemic therapy will not be targeted with SRT, as it is not possible to achieve dose build-up.

- The development of new sclerotic bone lesions after systemic therapy is not to be interpreted as disease progression, and all such lesions should be targeted with SRT.

b. Criteria for Cohort B assignment:

1. Participants must be registered to **Step 2** within **14 days** of staging scans performed after completing Step 1 systemic therapy.

2. Participants must have standard of care (SOC) staging and breast imaging performed following **12-24 weeks (minimum of 4 cycles)** of initial systemic therapy and within **14 days** prior to **Step 2** Registration.

3. Participants must experience clinically stable disease or progression following **12-24 weeks (minimum of 4 cycles)** of initial systemic therapy and within **14 days** prior to **Step 2** Registration.

   - Participants must have progression in metastatic lesions as assessed by RECIST and bone response criteria or may have stable disease in metastatic lesions by RECIST and bone response criteria if there is progression or no clinical response in the breast.

   - Participants with known breast lesion must have progression or no clinical response on breast imaging as per the treating physician.

   NOTE: The same modality must be used as in **Step 1**.