Cancer Research Consortium of West Michigan
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FAST FACTS

EA1181 - (CompassHER2-pCR): Preoperative THP and postoperative HP in patients who achieve a pathologic complete response Part 1 Component of: The CompassHER2 Trials (COMprehensive Use of Pathologic Response ASSessment to Optimize Therapy in HER2-Positive Breast Cancer)

Eligibility Criteria

1. Patient must be ≥ 18 years of age.

2. Patients must have an ECOG performance status of 0 or 1.

3. Patient must have histologically confirmed HER2-positive primary invasive breast carcinoma, determined by local testing. **The tumor must have either HER2 IHC result of 3+ or HER2/CEP17 ratio ≥ 2 with ≥ 4.0 HER2 signals per cell by ISH.** Tumors with HER2/CEP17 ISH ratio < 2 are ineligible, even if HER2 copy number is ≥ 6, unless HER2 IHC result is 3+.

4. Patients hormone receptor (ER and PR) status must be known and will be determined by local testing. Patients with either hormone receptor –positive or hormone receptor- negative HER2-positive breast cancer are eligible.

5. Patients must have AJCC 8th edition stage II or IIIa according to anatomic staging table at diagnosis.
   - Patients without nodal involvement (cN0) are eligible if T size ≥ 2.0 cm (T2-3)
   - Patients with nodal involvement (cN1-2) are eligible if T1-3Patients with clinical T4 or N3 disease are not eligible

     NOTE: Cohort for patients with 2-3 cm, ER+ and node negative HER2-positive/ER-positive disease closed onJuly 27, 2022.
   - Patients with HER2-positive/ER-negative disease without nodalinvolvement (cN0) are eligible if T size > 2.0 cm (T2-3)
   - Patients with HER2-positive/ER-positive disease without nodalinvolvement (cN0) are eligible if T size > 3.0 cm
   - Patients with nodal involvement (cN1-2) are eligible if T1-3
   - Patients with clinical T4 or N3 disease are not eligible

6. Patient must be willing and able (i.e., have no contraindication) to receive standard adjuvant therapy, consisting of HER2-directed therapy, radiation (if indicated) and endocrine therapy (if ER+) if achieving pCR at surgery.

7. Patient with bilateral invasive breast cancers are eligible if both cancers are HER2-positive (as defined in 3.1.3) and at least one meets protocol eligibility and neither cancer renders the patient ineligible (i.e. per eligibility 3.1.5).

8. Patients with multiple ipsilateral invasive tumors are eligible as long as all tumors are HER2-positive, and at least one tumor focus meets eligibility criteria(per eligibility 3.1.5).

   Multiple lesions that appear part of the same index tumor do not require additional biopsy/HER2 testing. However, even if biopsy is not deemed necessary, consideration must be given to placing a

clip in any lesion that is 1 cm or further from the primary tumor to ensure that all tumor is removed at surgery AND that the pathologist can locate all primary sites of tumor to assess pathologic response at surgery.

9. Patients must not have impaired decision-making capacity.

10. Patient must not have a history of any prior (ipsilateral or contralateral) invasive breast cancer.
    One exception: a patient with a history of T1N0 triple negative breast cancer diagnosed more than 10 years earlier, who remains disease free is eligible.

11. Patient must not have prior ipsilateral DCIS. Patients with prior LCIS, atypical hyperplasia, other high risk benign lesions or contralateral DCIS (without evidence of microinvasion) are eligible.
    NOTE: Patients currently receiving endocrine therapy for prior contralateral DCIS are eligible. Current ipsilateral or contralateral DCIS (diagnosed at the time of the current invasive cancer) is permitted.

12. Patient must not have Stage IV (metastatic) breast cancer.
    Staging Studies (CT Chest/abdomen/pelvis and a bone scan or PET- CT scan) are required for Stage III disease (according to AJCC cancer staging manual anatomic staging table, 8th edition) or those with abnormal baseline LFTs, symptoms (e.g. new bone pain) or abnormal physical exam findings (NCCN guidelines V1.2019).

13. Patient must not have T4 and/or N3 disease, including inflammatory breast cancer.

14. Patient must not have any prior treatment for the current breast cancer, including surgery, chemotherapy, hormonal therapy, radiation or experimental therapy.

15. Patients with a history of other non-breast malignancies are eligible if they have been disease-free for at least 5 years, and are deemed by the investigator to be at low risk for recurrence of that malignancy.
    Patients with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer in situ, basal cell or squamous cell carcinoma of the skin, melanoma-in-situ and localized papillary or follicular thyroid cancer who have completed recommended treatment including surgery. Patients with any other cancers within the last 5 years are ineligible.

16. Patients must have a left ventricular ejection fraction (LVEF) within normal institutional parameters (or $\geq$ 50%).

17. Patients must not have > grade 1 peripheral neuropathy of any etiology.

18. Patients must have a bilateral mammogram and a diagnostic breast ultrasound [on the side of the cancer(s)] (with or without breast MRI) performed at screening. An axillary ultrasound on the side of the cancer(s) is also required. Comprehensive breast and axillary imaging must be performed within 60 days of registration (i.e. the patient's mammogram/ breast ultrasound /axillary ultrasound OR their breast MRI). Either mammogram/ultrasound (including imaging of the ipsilateral axilla) or breast MRI must be performed within 60 days of registration.

19. Baseline imaging of the ipsilateral axilla by ultrasound is mandatory.
    - For subjects with axillary lymph node(s) suspicious on clinical exam or imaging, patient must be willing to have a needle aspiration or core biopsy to determine the presence of metastatic disease

in the lymph nodes. A clip must be placed in the involved axillary lymph node. (if there are more than 1 suspicious axillary nodes, only one clipped node is required). Alternatives to a clip that reliably mark the involved node for removal at surgery are acceptable (e.g., carbon tattooing, Savi scout, RFID etc.)

20. Patient must not have a concurrent serious medical condition that would preclude completion of study therapy. For example, uncontrolled hypertension (systolic >180 mm Hg and/or diastolic >100 mm Hg) or clinically significant (i.e. active) cardiovascular disease: cerebrovascular accident/stroke or myocardial infarction within 6 months prior to registration, unstable angina, congestive heart failure (CHF) or serious cardiac arrhythmia requiring medication and other concurrent serious diseases that may interfere with planned treatment.

21. Patient must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used. Patients must also not expect to conceive from the time of registration, while on study treatment, and until at least 7 months after the last dose of study treatment.
    - All patients of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy. If the pregnancy test (e.g., HCG level) is abnormal but is felt to represent a false positive test for pregnancy (e.g., due to treatments being administered for egg harvesting, or because of recent miscarriage), anote by the treating gynecologist explaining why the team is confidentthe woman is not pregnant is required.
    - A patient of childbearing potential is anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

22. Patient of childbearing potential and sexually active patients must use accepted and effective method(s) of contraception or to abstain from sexual intercourse for the duration of their participation in the study and for 7 months after the last dose of study treatment.

23. Patient must be willing and able to sign informed consent.

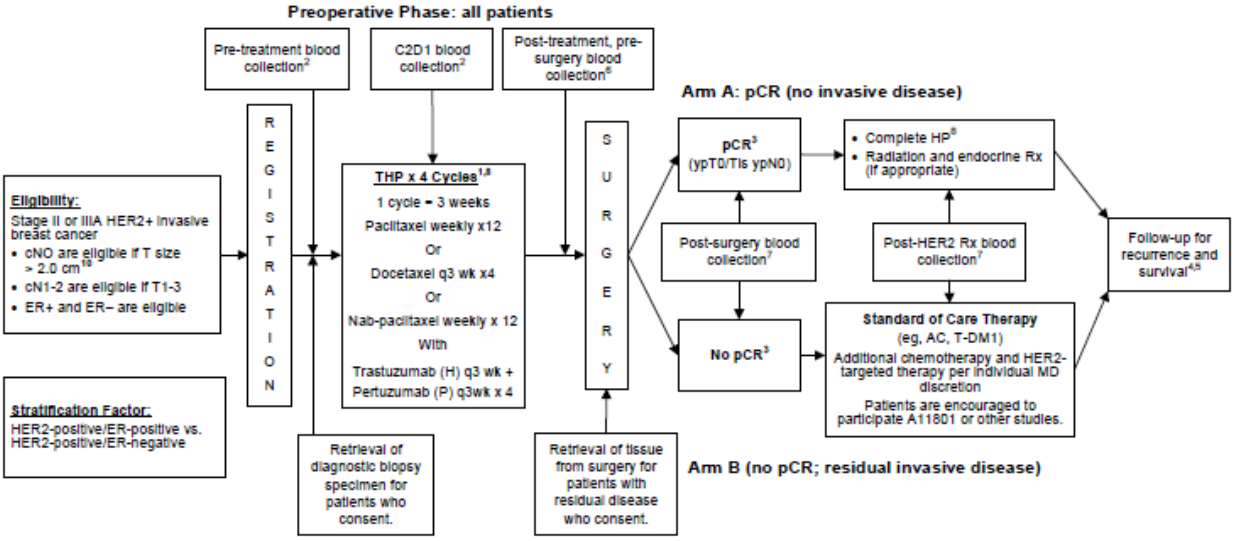
24. Patients must have adequate organ and marrow function as defined below (these must be obtained ≤ 28 days prior to protocol registration).
    - Leukocytes ≥ 3,000/mcL
    - Absolute neutrophil count ≥ 1,500/mcL
    - Platelets ≥ 100,000/mcL
    - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
    - AST(SGOT)/ALT(SGPT) ≤ 2.5 x institutional ULN
    - Creatinine ≤ 1.5 x institutional ULN

25. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

26. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

27. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

Schema (CompassHER2 pCR; EA1181; Compass Part 1)



1. The choice of taxane is up to the treating MD. For patients who develop hypersensitivity to paclitaxel or docetaxel, nab-paclitaxel is recommended.
2. 2 streck tubes for CTCs (mandatory); 2 additional streck tubes for cfDNA for patients who consent.
3. Isolated tumor cells (ITCs) or immunohistochemistry (IHC) evidence of cancer in nodes will be classified as "no pCR" (Arm B); IHC of nodes is not required. DCIS is allowed in Arm A.
4. Follow-up: Patients will be followed every 3 months for first 2 years after surgery, then every 6 months if the patient is 2-5 years from surgery, and then every 12 months if the patient is 5-15 years from date of surgery.
5. Primary objective is 3y RFS for patients who achieve pCR. Secondary objectives include 3 yr RFS for those without pCR and (for all patients): EFS, IDFS, DDFS, RFI, OS.
6. Research blood collection: 2 streck tubes for CTCs.
7. 2 streck tubes for CTCs (mandatory); 2 additional streck tubes for cfDNA in patients with pCR who consent.
8. 17 cycles total of HP will be administered to patients in Arm A including both pre- and post-surgery cycles. HP should be continued every 3 weeks until surgery, even when taxane therapy has been completed.
9. Trastuzumab-hyaluronidase SC may be substituted for trastuzumab; or pertuzumab-trastuzumab-hyaluronidase SC may be substituted for both trastuzumab and pertuzumab, following the dosing instructions in the US Package Inserts for Herceptin Hylecta® or Phesgo®.
10. As of July 28, 2022, for patients with HER2-positive/ER-positive disease with clinically negative nodes (cN0), tumor size(T) must be > 3.0 cm. Cohort for patients with 2-3 cm, ER+ and node negative HER2-positive/ER-positive disease closed on July 27, 2022.