EA1181/CompassHER2 pCR

Preoperative THP and Postoperative HP in Patients Who Achieve a Pathologic Complete Response

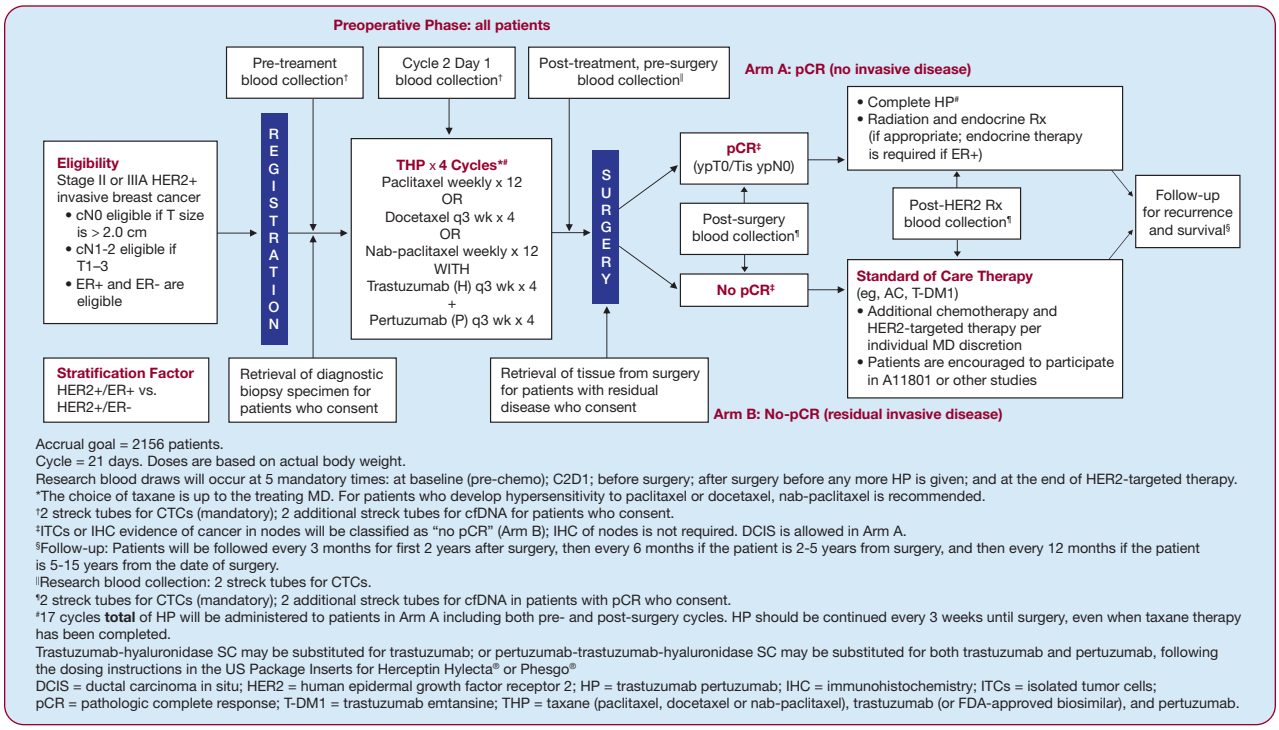
Part 1 Component of: The CompassHER2 Trials (COMprehensive use of Pathologic response ASSessment to optimize therapy in HER2-positive breast cancer)

Overall EA1181 Study Objective

EA1181 is a single arm de-escalation trial and the first study in the CompassHER2 research program, which aims to optimize treatment for patients with HER2-positive (HER2+) breast cancer.

This trial will determine whether the neoadjuvant combination of a taxane (paclitaxel, docetaxel, or nab-paclitaxel), trastuzumab, and pertuzumab (THP) in patients with stage II and IIIa HER2+ disease allows for omission of additional postoperative chemotherapy in patients who achieve a pathologic complete response (pCR), without compromising long-term survival.

Study Schema



Accrual goal = 2156 patients.
Cycle = 21 days. Doses are based on actual body weight.
Research blood draws will occur at 5 mandatory times: at baseline (pre-chemo); C2D1; before surgery; after surgery before any more HP is given; and at the end of HER2-targeted therapy.
*The choice of taxane is up to the treating MD. For patients who develop hypersensitivity to paclitaxel or docetaxel, nab-paclitaxel is recommended.
†2 streck tubes for CTCs (mandatory); 2 additional streck tubes for cfDNA for patients who consent.
‡ITCs or 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.
§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 the date of surgery, and then every 12 months if the patient is 5-15 years from the date of surgery.
‖Research blood collection: 2 streck tubes for CTCs.
¶2 streck tubes for CTCs (mandatory); 2 additional streck tubes for cfDNA in patients with pCR who consent.
#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.
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®
DCIS = ductal carcinoma in situ; HER2 = human epidermal growth factor receptor 2; HP = trastuzumab pertuzumab; IHC = immunohistochemistry; ITCs = isolated tumor cells; pCR = pathologic complete response; T-DM1 = trastuzumab emtansine; THP = taxane (paclitaxel, docetaxel or nab-paclitaxel), trastuzumab (or FDA-approved biosimilar), and pertuzumab.

Study Objectives

Independent Primary Objective

- Determine if 3-year recurrence-free survival (RFS) is greater than 92% among clinical stages II or IIIa (AJCC, 8th ed.) with HER2+/ER+, or HER2+/ER- breast cancer who achieve pCR (ypT0/is ypN0) after preoperative therapy with 12 weeks of THP

Secondary Objectives

Secondary Clinical Objectives

- Determine 3-year invasive disease-free survival (IDFS), distant disease-free survival (DDFS), distant relapse-free survival (DRFS), recurrence-free interval (RFI), overall survival (OS), and Breast Cancer-Specific Survival in patients who achieve pCR (and by pre-treatment clinical stage)
- Determine 3-year event-free survival (EFS) in all patients from time of study registration
- Evaluate safety and tolerability for all patients during the preoperative phase and for patients who attain pCR and de-escalate therapy (Arm A) until the completion of post-surgery therapy

Secondary Correlative Objectives

- Evaluate the association of estrogen receptor (ER) status in the untreated primary tumor with pathologic response and with long-term survival outcomes
- Evaluate the association of detection of circulating tumor cells (CTCs) in the blood at baseline with pCR
- Evaluate the association of detection of CTCs in the blood at baseline, after 3 weeks of THP, after 12 weeks of THP (before surgery), after surgery before any additional therapy, and after completion of HER2-targeted therapy with RFS in patients who achieve pCR or not

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Treatment Plan

- Surgical assessments will occur at baseline and preoperative visit. Baseline bilateral mammogram, diagnostic breast ultrasound, as well as imaging of the ipsilateral axilla (by ultrasound or breast MRI) are required.
- Any suspicious breast lesions must be biopsied. Either mammogram/ultrasound (including imaging of the ipsilateral axilla) or breast MRI must be performed within 60 days of registration.
- Breast MRI is optional but is strongly recommended at baseline and pre-surgery for those desiring breast conservation
- Preoperative or neoadjuvant therapy consists of a taxane, trastuzumab (or FDA-approved biosimilar) and pertuzumab, termed THP.* Three taxane options are available per treating oncologist and patient sensitivity:
  - Option 1: *paclitaxel* (weekly), trastuzumab, pertuzumab
  - Option 2: *docetaxel* (every 3 weeks), trastuzumab, pertuzumab
  - Option 3: *nab-paclitaxel* (weekly), trastuzumab, pertuzumab
- Doses are based on actual body weight at baseline (and altered if > 10% weight change). Treatment must be administered within -/+ 3-day window of each cycle (cycle length 21 days) for 4 cycles.
- Definitive tumor surgery (lumpectomy or mastectomy) will be performed no later than 126 days from administration of the first dose of neoadjuvant taxane therapy
- For postoperative, adjuvant therapy, patients will be grouped into 2 arms with criteria based on whether patients exhibit a pCR or residual invasive disease after THP and surgery
  - Arm A: pCR (no invasive disease in breast or nodes; ypT0/Tis ypN0)
    - Systemic therapy: trastuzumab, pertuzumab (HP)
    - Radiation and endocrine therapy, if appropriate (endocrine therapy is required if ER+)
  - Arm B: standard of care for patients who do NOT achieve pCR with THP
- For patients in Arm A, a total of 17 doses of HP will be administered every 3 weeks, including preoperative treatment
- Patients will be followed for recurrence or progression and survival for 15 years from the date of surgery

*Trastuzumab-hyaluronidase SC (Herceptin Hylecta®) may be substituted for IV trastuzumab following the same schedule. Pertuzumab-trastuzumab-hyaluronidase SC (Phesgo®) may be substituted for both IV trastuzumab and IV pertuzumab, following the same schedule. Patients receiving IV therapy may switch to the subcutaneous product. The switch should take place on Day 1 of the next cycle.

Eligibility Criteria*

Main Inclusion Criteria

- ≥ 18 years of age with histologically confirmed HER2+ primary invasive breast carcinoma, as determined by local testing. 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+.
- Hormone receptor (ER or PR) status must be known and will be determined by local testing. Either hormone receptor-positive or hormone receptor-negative HER2+ breast cancer are eligible
- AJCC 8th ed. stage II or IIIa at diagnosis
  - Without nodal involvement (cN0) are eligible if T size > 2.0 cm (T2–3)
  - With nodal involvement (cN1–2) are eligible if T1–3
- Willing and able (ie, 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
- Two separate invasive breast cancers are eligible if both cancers are HER2+, at least one tumor meets eligibility criteria, and neither tumor renders the patient ineligible (e.g., T4)
- Multiple ipsilateral invasive tumors are eligible as long as all tumors are HER2+, and at least one tumor focus meets eligibility criteria
- History of other non-breast malignancies are eligible if disease-free for at least 5 years, and deemed by the investigator to be at low risk for recurrence of that malignancy
- Left ventricular ejection fraction within normal institutional parameters (or ≥ 50%)
- Bilateral mammogram and diagnostic ipsilateral ultrasound of breast and axilla are required at screening. An axillary ultrasound on the side of the cancer(s) is also required, unless patient has has a prior negative axillary physical exam and a baseline MRI without suspicious lymph nodes.
- ECOG performance status 0 or 1
- Adequate organ and marrow function obtained ≤ 28 days prior to protocol registration
- HIV positivity and on an effective anti-retroviral therapy with undetectable viral load within 6 months are eligible
- If evidence of chronic HBV infection, then viral load must be undetectable and on suppressive therapy
- History of HCV infection that is treated and cured; currently on treatment for HCV infection with an undetectable viral load are eligible
- Use of effective contraception or abstinence

Main Exclusion Criteria

- History of any prior (ipsilateral or contralateral) invasive breast cancer, except for a history of T1N0 triple-negative breast cancer diagnosed more than 10 years earlier, and disease-free
- Prior ipsilateral DCIS; **however**, prior LCIS, atypical hyperplasia, other high-risk benign lesions or contralateral DCIS (without evidence of microinvasion) are eligible, as is current ipsilateral/contralateral DCIS
- Stage IV (metastatic) breast cancer
- T4 and/or N3 disease, including inflammatory breast cancer
- Prior treatment for the current breast cancer, including surgery, chemotherapy, hormonal therapy, radiation, or experimental therapy
- Peripheral neuropathy of any etiology > grade 1
- Pregnancy or breast-feeding

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.

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