

FAST FACTS

A011801 - THE COMPASSHER2 TRIALS (COMPREHENSIVE USE OF PATHOLOGIC RESPONSE ASSESSMENT TO OPTIMIZE THERAPY IN HER2-POSITIVE BREAST CANCER): COMPASSHER2 RESIDUAL DISEASE (RD), A DOUBLE-BLINDED, PHASE III RANDOMIZED TRIAL OF T-DM1 AND PLACEBO COMPARED WITH T-DM1 AND TUCATINIB

Eligibility Criteria

1. HER2-positive breast cancer

- a. HER2-positive status will be based on pretreatment biopsy material and defined as an immunohistochemistry (IHC) score of 3+ and/or positive by in situ hybridization (ISH) according to current ASCO/CAP guidelines. Central testing is not required.
 - i. Known hormone receptor (HR) status as defined by ASCO/CAP guidelines (based on pretreatment biopsy material). Hormone receptor positive status can be determined by either known positive ER or known positive PR status; hormone receptor negative status must be determined by both known negative ER and known negative PR.
- b. Patients with clinical stage T1-4, N0-3 disease at presentation and residual invasive disease postoperatively as defined above are eligible. Patients with clinical stage TX disease at presentation are also eligible if their pathologic staging meets eligibility criteria. (Note: Patients with T1a/bN0 tumors at initial breast cancer diagnosis are not eligible).
- c. Patients with residual HR-negative, HER2+ disease in the breast and/or lymph nodes per the surgical pathology report are eligible. Patients with HR-positive, HER2+ disease must have disease in their lymph node(s) per the surgical pathology report in order to qualify for the study. The presence of residual invasive disease in the breast is not mandatory for node-positive patients.
- d. Patients with weakly ER-positive and/or PR-positive (1-10%) breast cancer (based on the pretreatment core biopsy) are eligible even if they have node-negative disease per the surgical pathology report.
- e. The residual disease tissue (breast and/or lymph nodes) is not required to be HER2-positive, as eligibility for A011801 is based on a positive HER2 status at the time of the initial breast cancer diagnosis.

Note: The presence of micrometastases in lymph nodes after preoperative therapy counts as residual disease, whereas the presence of isolated tumor cells does not.
- f. Patients with synchronous bilateral invasive disease are eligible provided both lesions were confirmed to be HER2-positive, and at least one of the lesions meets the criteria outlined above. Multifocal disease is allowed, as long as the largest biopsied breast tumor was HER2-positive.

2. Prior Treatment

- a. Patients must have received neoadjuvant chemotherapy with one of the following regimens: THP, TMP, AC-TH(P); TCH(P); FAC-TH(P), or FEC-TH(P).

Note: apart from TCHP, where T is docetaxel, treatment with docetaxel or paclitaxel is acceptable.
- b. Prior receipt of T-DM1 in the neoadjuvant setting is not allowed.

- i. Prior treatment must have consisted of ≥ 6 cycles of chemotherapy and HER2-directed therapy, with a total duration of ≥ 12 weeks, including at least 9 weeks of preoperative taxane and trastuzumab with or without pertuzumab (or FDA-approved biosimilars). Patients who have received at least 9 weeks of preoperative taxane, pertuzumab and margetuximab are also eligible if they received ≥ 6 cycles of systemic therapy prior to registration.
 Note: Patients who complete at least nine of a planned twelve doses of weekly paclitaxel, or three of a planned four doses of docetaxel, or four of a planned six cycles of docetaxel, but discontinue prematurely due to toxicity are eligible. This also applies to patients receiving TCHP who did not receive planned carboplatin doses due to the nationwide carboplatin shortage. Patients receiving dose-dense chemotherapy regimens are also eligible. Prior use of nab-paclitaxel (Abraxane) instead of paclitaxel or docetaxel is permitted. Prior use of subcutaneous trastuzumab (Hylecta) and subcutaneous trastuzumab and pertuzumab (Phesgo) is also allowed.
- ii. Patients who received neoadjuvant systemic therapy which included experimental HER2-targeted therapy/therapies are potentially eligible, as long as the investigational agent was not a HER2-targeted antibody-drug conjugate (e.g. T-DM1 or trastuzumab deruxtecan) or a HER2 targeted tyrosine kinase inhibitor (TKI) (e.g. tucatinib, lapatinib, neratinib).
- c. No adjuvant treatment with any anti-cancer investigational drug within 28 days prior to registration.
- d. Patients may have received ≤ 1 cycle of T-DM1 in the adjuvant setting. Note: These patients will be randomized to receive a further 14 cycles of T-DM1 and tucatinib/placebo as tolerated. The most recent cycle of T-DM1 should have been administered ≤ 5 weeks prior to registration.
 - i. Note: Both of the following two criteria need to be met for the patient to be eligible for this study:
 1. An interval of no more than 12 weeks between the completion date of the last definitive treatment (e.g. postoperative chemotherapy or radiation, or if neither given, breast surgical date) and the date of registration. Concurrent radiation therapy is permitted while receiving study treatment.
 2. Patients must be registered on study within ≤ 180 days of the date of the most recent definitive breast cancer surgery (not including reconstructive surgery).
- e. All systemic chemotherapy should have been completed preoperatively unless participating in EA1181 (CompassHER2 pCR) or the BIG DECRESCENDO Trial (which is very similar to CompassHER2 pCR in terms of study design, drugs, and eligibility). However, patients who received 4 cycles of neoadjuvant THP off study can receive a further 2-4 cycles of chemotherapy postoperatively to meet eligibility for A011801. Patients who participated in EA1181 or MA41 and proceeded to surgery immediately after the de-escalated trial regimen must receive postoperative chemotherapy to complete a total of ≥ 6 cycles of systemic treatment prior to registration on A011801, as outlined above (e.g. 4 cycles pre-operatively, and 2 cycles post-operatively). The postoperative chemotherapy regimen prescribed is at the discretion of the treating oncologist (i.e. 2-4 cycles AC or THP, other). Continuation of trastuzumab + pertuzumab (HP) pre- or post-operatively as

maintenance therapy (while awaiting a surgical date or an official pathology report) is allowed for all study participants.

Note: Treatment received as part of EA1181 (i.e., the number of cycles of pre-operative chemotherapy and HER2-directed therapy) counts towards A011801 eligibility only, and does not count toward the total number of treatment cycles to be administered on A011801.

- f. Toxicities related to prior systemic treatment should have resolved or be at baseline, apart from alopecia, peripheral neuropathy \leq grade 1, and other AEs not felt to be of clinical significance by the treating physician (e.g. nail changes from prior taxane-based chemotherapy).
- g. Adequate excision: surgical removal of all clinically evident disease in the breast and lymph nodes as follows:
 - i. Breast surgery: total mastectomy with no gross residual disease at the margin of resection, or breast-conserving surgery with histologically negative margins of excision with the following exception: if the margins of resection include the pectoralis fascia or subcutaneous tissue, and no further surgery can be done to clear that margin, the patient may be enrolled.
 - ii. For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. Patients with margins positive for classic lobular carcinoma in situ (LCIS) are eligible without additional resection.

Lymph node surgery:

- iii. The axilla needs to be evaluated with either sentinel node biopsy or axillary lymph node dissection. If patients have a sentinel lymph node biopsy and sentinel nodes are negative for residual disease, no further axillary treatment is necessary. If patients have a sentinel lymph node biopsy and sentinel nodes are positive for residual nodal disease, then ALND is strongly encouraged. If ALND is not performed, then nodal irradiation to the level I/II axilla is required. If patients have micro- or macro-metastatic nodal disease, regional nodal irradiation is required.
3. Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.
Therefore, for women of childbearing potential only, a negative serum pregnancy test done \leq 7 days prior to registration is required.
 4. **Age \geq 18 years (male or female)**
 5. ECOG Performance Status 0-1
 6. Adequate hepatic, renal, and bone marrow function.

Required Initial Laboratory Values:

- Absolute Neutrophil Count (ANC) \geq 1,000/mm³
- Hemoglobin \geq 8 g/dL (Note: PRBC transfusion is **not** permitted to achieve eligibility)
- Platelet Count \geq 100,000/mm³
- Creatinine \leq 1.5 x upper limit of normal (ULN)

Total Bilirubin $\leq 1.0 \times$ upper limit of normal (ULN) or direct bilirubin within the institutional normal range for patients with Gilbert's syndrome
 AST / ALT $\leq 2.5 \times$ upper limit of normal (ULN)

7. Patients with known active and/or untreated Hepatitis B or Hepatitis C or chronic liver disease are ineligible. Patients with a diagnosis of Hepatitis B or C that has been treated and cleared and normal liver function are eligible to participate in the study if the other eligibility parameters are met.
8. Comorbid conditions
 - a. The following are excluded:
 - i. Stage IV (metastatic) breast cancer
 - ii. History of any prior (ipsi- or contralateral) invasive breast cancer within 3 years of registration
 - iii. Patients with ER+HER2+ residual invasive disease that is lymph node-negative per the surgical pathology report
 - iv. Evidence of recurrent disease following preoperative therapy and surgery
 - v. Patients for whom radiotherapy would be recommended for breast cancer treatment but for whom it is contraindicated because of medical reasons (e.g., connective tissue disorder or prior ipsilateral breast radiation). Patients who refuse a recommended course of radiotherapy are also excluded.
 - vi. History of exposure to the following cumulative doses of anthracyclines: Doxorubicin $> 240 \text{ mg/m}^2$; Epirubicin or Liposomal Doxorubicin-Hydrochloride (Myocet®) $> 480 \text{ mg/m}^2$. For other anthracyclines, exposure equivalent to doxorubicin $> 240 \text{ mg/m}^2$.
 - vii. Cardiopulmonary dysfunction as defined by any of the following:
 1. History of NCI CTCAE v 5.0 Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) criteria Class \geq II
 2. Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
 3. High-risk uncontrolled arrhythmias: i.e., atrial tachycardia with a heart rate $> 100/\text{min}$ at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block)
 4. Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia while on or since receiving preoperative therapy.
 5. History of a decrease in LVEF to $< 40\%$ with prior trastuzumab treatment (e.g., during preoperative therapy)
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 - viii. Current severe, uncontrolled systemic disease
 - ix. Major surgical procedure unrelated to breast cancer or significant traumatic injury within 28 days prior to registration or anticipation of the need for major surgery during the course of study treatment. Laparoscopic or vaginal hysterectomies and reconstructive surgery are not considered major surgeries for the purposes of study eligibility.

- x. History of intolerance, including Grade 3 to 4 infusion reaction or hypersensitivity to trastuzumab or murine proteins or any components of the product
- xi. Peripheral neuropathy of any etiology that exceeds grade 1 (mild symptoms)
- xii. Assessment by the investigator as being unable or unwilling to comply with the requirements of the protocol.

9. Concomitant medications

- a. Use of a strong CYP3A4 or CYP2C8 inhibitor within 2 weeks, or use of a strong CYP3A4 or CYP2C8 inducer within 5 days prior to registration (see [Appendix IV](#) and [V](#)) is prohibited.

Please note that use of sensitive CYP3A substrates ([Appendix VI](#)) should be avoided two weeks before registration and during study treatment. Additionally, CYP3A4 or CYP2C8 inducers are prohibited as concomitant medications within 5 days following discontinuation of tucatinib treatment. Patients who require medications that are known to be sensitive substrates of CYP3A4 with a narrow therapeutic window should be excluded. See [Section 8.1](#) for more information regarding the use of CYP3A4 or CYP2C8 inhibitors, inducers, and substrates during protocol treatment.

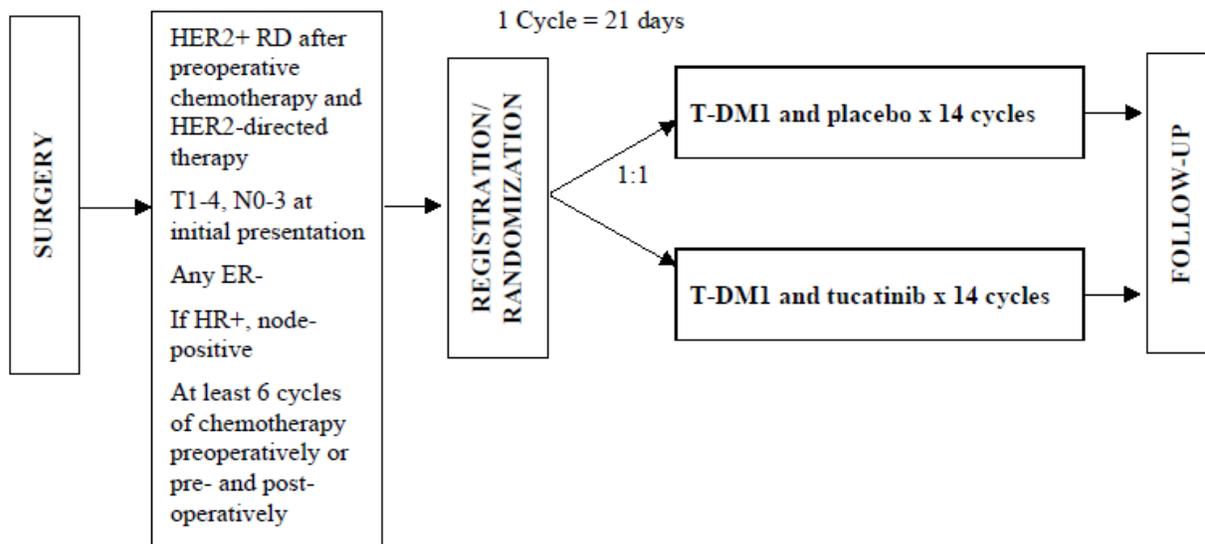
10. Other

- a. Screening* left ventricular ejection fraction (LVEF) $\geq 50\%$ on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) after receiving neoadjuvant chemotherapy and no decrease in LVEF by more than 15 absolute percentage points from the pre- chemotherapy** LVEF. Or, if pre-chemotherapy LVEF was not assessed, the screening LVEF must be $\geq 55\%$ after completion of neoadjuvant chemotherapy. Note: LVEF assessment may be repeated once up to 3 weeks following the initial screening assessment to assess eligibility.

*Screening assessment refers to the assessment done after the completion of neoadjuvant treatment but before the date of A011801 registration

**Pre-chemotherapy assessment refers to the assessment done before the start of neoadjuvant treatment

Schema



Note: HR stands for “hormone-receptor.” Patients with weakly ER-positive (1-10%) and/or PR-positive (1-10%) and node-negative disease per the surgical pathology report are eligible.

Treatment is to continue until breast cancer recurrence, completion of 14 cycles, or unacceptable adverse event. Patients will be followed for 10 years after registration or until death, whichever comes first.