

T-DM1 and Tucatinib Compared with T-DM1 Alone in Preventing Relapses in People with High Risk HER2-Positive Breast Cancer, the CompassHER2 RD Trial

Status: RECRUITING

Eligibility Criteria

Age: 18 years and over

This study is NOT accepting healthy

Healthy Volunteers: volunteers

Inclusion Criteria:

* 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 American Society of Clinical Oncology (ASCO) College of American Pathologists (CAP) guidelines. Central testing is not required

* 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 estrogen receptor (ER) or known positive progesterone receptor (PR) status; hormone receptor negative status must be determined by both known negative ER and known negative PR

* Patients with clinical stage T1-4, N0-3 disease at presentation and residual invasive disease postoperatively as defined above are eligible. (Note: Patients with T1a/bN0 tumors are not eligible at initial breast cancer diagnosis are not eligible)

* Patients with residual HR-negative, HER2 positive (+) disease in the breast and/or lymph nodes per the surgical pathology report are eligible; however, patients with HR+ HER2+ cancers must have node-positive residual disease 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 these patients

* Patients with weakly ER-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

* The residual disease tissue (breast and/or lymph nodes) is not required to be HER2-positive, as eligibility for NCI-2020-03770 (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

* 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

* Patients must have received neoadjuvant chemotherapy with one of the following regimens: docetaxel/trastuzumab/pertuzumab (THP), paclitaxel/methotrexate/cisplatin (TMP), doxorubicin/cyclophosphamide/paclitaxel/trastuzumab/pertuzumab (AC-TH(P)); docetaxel/carboplatin/trastuzumab/pertuzumab (TCH(P)); fluorouracil/doxorubicin/cyclophosphamide-docetaxel/trastuzumab/pertuzumab (FAC-TH(P)), or fluorouracil/epirubicin/cyclophosphamide-docetaxel/trastuzumab/pertuzumab (FEC-TH(P)). Note: apart from TCHP, where T is docetaxel, treatment with docetaxel or paclitaxel is acceptable

* Prior receipt of T-DM1 in the neoadjuvant setting is not allowed.

* 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 Food and Drug Administration [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 enrollment. Note: Patients who complete at least nine of a planned twelve doses of weekly paclitaxel, or three of a planned four doses of docetaxel, but discontinue prematurely due to toxicity are eligible. 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.

* 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, DS-8201a [trastuzumab deruxtecan]) or a HER2 targeted tyrosine kinase inhibitor (TKI) (e.g. tucatinib, lapatinib, neratinib).

* Patients may have received ≤ 1 cycles 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

* Note: Both of the following two criteria need to be met for the patient to be eligible for this study

* 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

* Patients must be registered on study within ≤ 180 days of the date of the most recent definitive breast cancer surgery (not including reconstructive surgery)

* All systemic chemotherapy should have been completed preoperatively unless participating in EA1181 (CompassHER2 pathologic complete response [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 enrollment 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

* Toxicities related to prior systemic treatment should have resolved or be at baseline, apart from alopecia and peripheral neuropathy \leq grade 1

* Adequate excision: surgical removal of all clinically evident disease in the breast and lymph nodes as follows:

* Breast surgery: total mastectomy with no gross residual disease at the margin of resection, or breast-conserving surgery with histologically negative margins of excision

* 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

* 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, no further axillary treatment is necessary. If patients have isolated tumor cells (ITCs) in the setting of residual breast disease, at least one of the following is required: axillary lymph node dissection (ALND) or planned nodal irradiation. If patients have micro- or macro-metastatic nodal disease, ALND and planned nodal irradiation are required. Of note, co-enrollment on Alliance A011202 is not allowed

* Eastern Cooperative Oncology Group (ECOG) performance status 0-1

* Absolute neutrophil count (ANC) $\geq 1,000/\text{mm}^3$

* Hemoglobin ≥ 8 g/dL (Note: packed red blood cells [PRBC] transfusion is not permitted to achieve eligibility)

* Platelet count $\geq 100,000/\text{mm}^3$

* Creatinine $\leq 1.5 \times$ 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

* Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN)

* 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

Exclusion Criteria:

* No adjuvant treatment with any anti-cancer investigational drug within 28 days prior to registration

* 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 ≤ 7 days prior to registration is required

* 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

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Stage IV (metastatic) breast cancer * History of any prior (ipsi- or contralateral) invasive breast cancer within 3 years of registration * Patients with ER+ HER2+ residual invasive disease that is lymph node-negative per the surgical pathology report * Evidence of recurrent disease following preoperative therapy and surgery * 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) * History of exposure to the following cumulative doses of anthracyclines: doxorubicin ≥ 240 mg/m²; epirubicin or liposomal doxorubicin-hydrochloride (Myocet) ≥ 480 mg/m². For other anthracyclines, exposure equivalent to doxorubicin ≥ 240 mg/m² * Cardiopulmonary dysfunction as defined by any of the following: * History of National Cancer Institute (NCI) CTCAE version (v) 5.0 grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) criteria class \geq II * Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease * High-risk uncontrolled arrhythmias: i.e., atrial tachycardia with a heart rate ≥ 100 /min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade atrioventricular block (AV)-block (second degree AV-block type 2 [Mobitz 2] or third degree AV-block) * Significant symptoms (grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia while or since receiving preoperative therapy * History of a decrease in left ventricular ejection fraction (LVEF) to $< 40\%$ with prior trastuzumab treatment (e.g., during preoperative therapy) * Uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 100 mmHg) * Current severe, uncontrolled systemic disease * 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 * History of intolerance, including grade 3 to 4 infusion reaction or hypersensitivity to trastuzumab or murine proteins or any components of the product * Peripheral neuropathy of any etiology that exceeds grade 1 * Assessment by the investigator as being unable or unwilling to comply with the requirements of the protocol * 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 is prohibited. * Please note that use of sensitive CYP3A substrates 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.

Conditions & Interventions

Interventions:

BIOLOGICAL: Trastuzumab Emtansine, DRUG: Placebo Administration, DRUG: Tucatinib, OTHER: Questionnaire Administration, OTHER: Quality-of-Life Assessment

Conditions:

Anatomic Stage IA Breast Cancer AJCC v8, Anatomic Stage II Breast Cancer AJCC v8, Anatomic Stage IIA Breast Cancer AJCC v8, Anatomic Stage IIB Breast Cancer AJCC v8, Anatomic Stage III Breast Cancer AJCC v8, Anatomic Stage IIIA Breast Cancer AJCC v8, Anatomic Stage IIIB Breast Cancer AJCC v8, Anatomic Stage IIIC Breast Cancer AJCC v8, HER2 Positive Breast Carcinoma, Invasive Breast Carcinoma, Multifocal Breast Carcinoma, Prognostic Stage I Breast Cancer AJCC v8, Prognostic Stage IA Breast Cancer AJCC v8, Prognostic Stage IB Breast Cancer AJCC v8, Prognostic Stage II Breast Cancer AJCC v8, Prognostic Stage IIA Breast Cancer AJCC v8, Prognostic Stage IIB Breast Cancer AJCC v8, Prognostic Stage III Breast Cancer AJCC v8, Prognostic Stage IIIA Breast Cancer AJCC v8, Prognostic Stage IIIB Breast Cancer AJCC v8, Prognostic Stage IIIC Breast Cancer AJCC v8, Synchronous Bilateral Breast Carcinoma

More Information

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IRB

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