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 (see Section 3.2)

- HER2-positive breast cancer per Section 3.2.1
- 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). See Section 3.2.3.
- Prior receipt of T-DM1 in the neoadjuvant setting is not allowed.
- Prior treatment must have consisted ≥ 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 chemotherapy prior to enrollment. See Section 3.2.3.

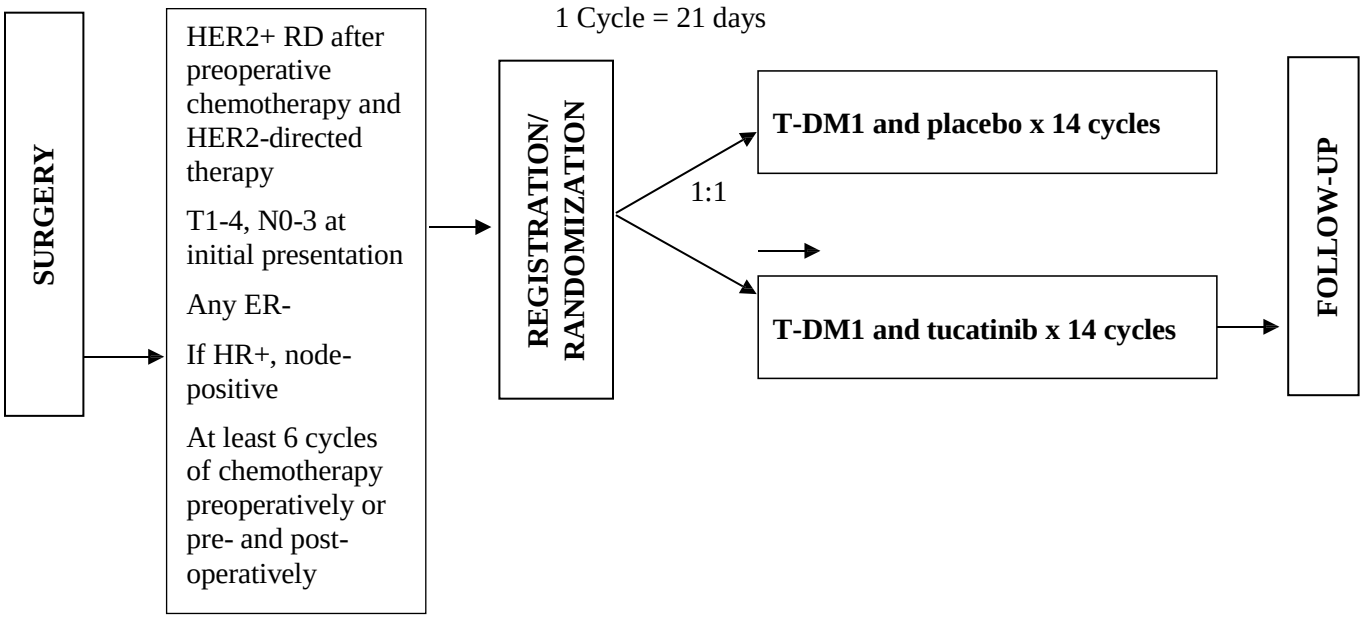
Required Initial Laboratory Values

Absolute neutrophil count (ANC): ≥ 1000/mm^3
Hemoglobin: ≥ 8 g/dL
Platelet count: ≥ 100,000/mm3
Total bilirubin: ≤ 1.5 x ULN (or direct bilirubin within the institutional normal range for patients with Gilbert's syndrome)
AST and ALT: ≤ 2.5 x ULN
Creatinine: ≤ 1.5 x upper limit of normal (ULN)

- Patients who received neoadjuvant systemic therapy which included experimental HER2-directed therapy are potentially eligible, as long as the investigational agent was not a HER2-targeted antibody-drug conjugate (e.g. T-DM1 or DS-8201a [trastuzumab deruxtecan]) or a HER2 targeted tyrosine kinase inhibitor (TKI) (e.g. tucatinib, lapatinib, neratinib).
- No adjuvant treatment with any anti-cancer investigational drug within 28 days prior to registration
- Patients may have received ≤ 1 cycle of T-DM1 in the adjuvant setting. See Section 3.2.3.
- Both of the following points must be true:
  -An interval of no more than 12 weeks between the completion date of the last definitive treatment and the date of registration AND
  -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 pCR) or the BIG DECRESCENDO Trial (which is very similar to EA1181 in terms of the study design, drugs, and eligibility criteria).
- 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).
- Toxicities related to prior systemic treatment should have resolved or be at baseline, apart from alopecia and peripheral neuropathy ≤ grade 1.
- Adequate excision: surgical removal of all clinically evident disease in the breast and lymph nodes (see Section 3.2.3)
- Not pregnant and not nursing
- Age ≥ 18 years (male or female)
- ECOG Performance Status 0-1
- 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.
- No stage IV (metastatic) breast cancer
- No history of any prior (ipsi- or contralateral) invasive breast cancer within 3 years of registration
- No patients with ER+ HER2+ residual invasive disease that is lymph node-negative per the surgical pathology report
- No evidence of recurrent disease following preoperative therapy and surgery
- No 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).
- No 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.

- No cardiopulmonary dysfunction as defined in Section 3.2.9
- No current severe uncontrolled systemic disease
- No 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.
- No history of intolerance, including Grade 3 to 4 infusion reaction or hypersensitivity to trastuzumab or murine proteins or any components of the product
- No peripheral neuropathy of any etiology that exceeds grade 1
- No assessment by the investigator as being unable or unwilling to comply with the requirements of the protocol.
- See Section 3.2.10 for concomitant medication restrictions.
- Screening left ventricular ejection fraction (LVEF) ≥ 50% on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) after receiving neoadjuvant chemotherapy and no decrease in LVEF by more than 15% absolute points from the pre-chemotherapy LVEF. Or, if pre-chemotherapy LVEF was not assessed, the screening LVEF must be ≥ 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.

Schema



Note: HR stands for "hormone-receptor."

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.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Chemotherapy will be conducted at the registering institution. Radiation and surgery may be conducted at a non-registering institution. The non-registering institution does not need to be an NCTN site.
If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

3.1 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.2 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and 7 months after last dose of study drug due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.3 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 HER2-positive breast cancer**

___**3.2.1.1** 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.

- Known hormone receptor (HR) status as defined by ASCO/CAP guidelines. 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.

___**3.2.1.2** 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).

___**3.2.1.3** Patients with residual HR-negative, HER2+ 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. Note: The presence of micrometastases in lymph nodes after preoperative therapy counts as residual disease, whereas the presence of isolated tumor cells does not.

___**3.2.1.4** 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.

___ **3.2.3 Prior Treatment**

___**3.2.3.1** 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.

___**3.2.3.2** 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 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 (i.e. peripheral neuropathy ≤ grade 1) 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).

___**3.2.3.3** No adjuvant treatment with any anti-cancer investigational drug within 28 days prior to registration.

___**3.2.3.4** 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.

- **N.B: 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.

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

___**3.2.3.5** 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). 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).

___**3.2.3.6** Toxicities related to prior systemic treatment should have resolved or be at baseline, apart from alopecia and peripheral neuropathy ≤ grade 1.

___**3.2.3.7** 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: ALND or planned nodal irradiation. If patients have micro- or macro-metastatic nodal disease, an ALND is required.

___ **3.2.4 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.

___ **3.2.5 Age ≥ 18 years (male or female)**

___ **3.2.6 ECOG Performance Status 0-1**

___ **3.2.7 Adequate hepatic, renal, and bone marrow function.**

Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC) ≥ 1,000/mm3

Hemoglobin ≥ 8 g/dL (Note: PRBC transfusion is **not** permitted to achieve eligibility)

Platelet Count ≥ 100,000/mm3

Creatinine ≤ 1.5 x upper limit of normal (ULN)

Total Bilirubin ≤ 1.5 x upper limit of normal (ULN) or direct bilirubin within the institutional normal range for patients with Gilbert's syndrome

AST / ALT ≤ 2.5 x upper limit of normal (ULN)

___ **3.2.8** 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.

___ **3.2.9 Comorbid conditions**

The following are excluded:

___**3.2.9.1** Stage IV (metastatic) breast cancer

___**3.2.9.2** History of any prior (ipsi- or contralateral) invasive breast cancer within 3 years of registration

___**3.2.9.3** Patients with ER+HER2+ residual invasive disease that is lymph node-negative per the surgical pathology report

___**3.2.9.4** Evidence of recurrent disease following preoperative therapy and surgery.

___**3.2.9.5** 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).

___**3.2.9.6** History of exposure to the following cumulative doses of anthracyclines: Doxorubicin > 240 mg/m^2; Epirubicin or Liposomal Doxorubicin-Hydrochloride (Myocet®) > 480 mg/m^2. For other anthracyclines, exposure equivalent to doxorubicin > 240 mg/m^2.

___**3.2.9.7** Cardiopulmonary dysfunction as defined by any of the following:

- History of NCI CTCAE v 5.0 Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) criteria Class ≥ 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 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 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)

___**3.2.9.8** Current severe, uncontrolled systemic disease

___**3.2.9.9** 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.

___**3.2.9.10** History of intolerance, including Grade 3 to 4 infusion reaction or hypersensitivity to trastuzumab or murine proteins or any components of the product

___**3.2.9.11** Peripheral neuropathy of any etiology that exceeds grade 1

___**3.2.9.12** Assessment by the investigator as being unable or unwilling to comply with the requirements of the protocol.

___ **3.2.10 Concomitant medications**

- 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.

___ **3.2.11 Other**

Screening left ventricular ejection fraction (LVEF) ≥ 50% on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) after receiving neoadjuvant chemotherapy and no decrease in LVEF by more than 15% absolute points from the pre-chemotherapy LVEF. Or, if pre-chemotherapy LVEF was not assessed, the screening LVEF must be ≥ 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.