

PHASE 3 STUDY OF TUCATINIB OR PLACEBO IN COMBINATION WITH TRASTUZUMAB AND PERTUZUMAB AS MAINTENANCE THERAPY FOR HER2+ METASTATIC BREAST CANCER (HER2CLIMB-05, TRIAL IN PROGRESS)

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BACKGROUND

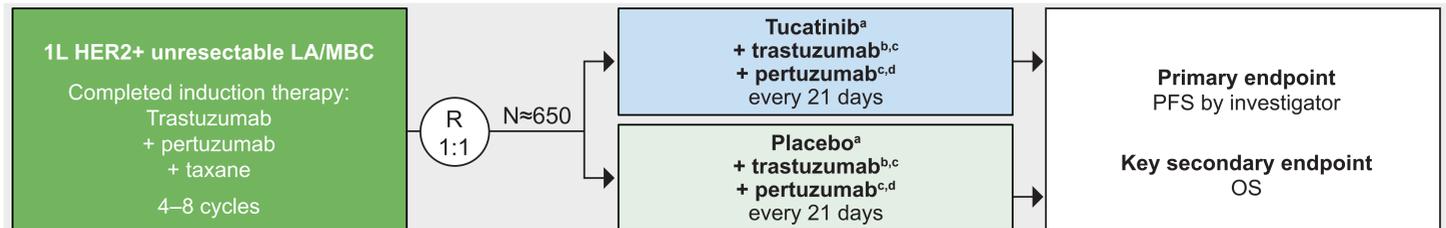
- The current 1L SOC for HER2+ MBC is trastuzumab plus pertuzumab and a taxane^{1,2}
 - This regimen improved overall survival outcomes by 16 months compared with the prior SOC, trastuzumab and a taxane³
 - Despite advances in 1L SOC therapy, most patients progress on maintenance therapy with trastuzumab and pertuzumab¹
- Tucatinib is an oral TKI approved in multiple countries in combination with trastuzumab and capecitabine for adult patients with HER2+ MBC who have received at least 2 prior anti-HER2 treatment regimens, with or without BMs⁴⁻⁷
 - Tucatinib in combination with trastuzumab and capecitabine has been proven to demonstrate a statistically significant and clinically meaningful improvement in PFS and OS with a tolerable safety profile in patients with HER2+ MBC^{4,7,8}
- As up to 50% of patients with HER2+ MBC will develop BMs, prevention and treatment of BMs is an urgent unmet clinical need⁹
 - Adding tucatinib to trastuzumab plus capecitabine also reduced the risk of disease progression or death in patients with active or stable BMs^{4,7,8}
- The addition of tucatinib to 1L SOC maintenance therapy with trastuzumab and pertuzumab may extend PFS while maintaining QOL¹⁰
 - In patients with BMs, tucatinib has demonstrated the ability to improve PFS and OS and/or delay the emergence of BMs; therefore, it is thought that patients in the 1L setting may also benefit from receiving tucatinib⁸

Key Exclusion Criteria

- Prior treatment with any anti-HER2 and/or anti-EGFR TKI including pyrotinib, lapatinib, tucatinib, neratinib, and afatinib (except neratinib if given in the extended adjuvant setting and ≥ 12 months have elapsed since the last neratinib dose prior to the start of study drug)
- Unable to undergo contrast MRI of the brain
- CNS exclusion criteria:** Based on screening brain MRI and clinical assessment
 - Symptomatic BMs
 - Progression of BMs since starting 1L trastuzumab, pertuzumab, and taxane
 - Ongoing use of systemic corticosteroids at a total daily dose of >2 mg of dexamethasone (or equivalent)
 - Any untreated brain lesion in an anatomic site which may pose a risk to subject
 - Known or suspected LMD
 - Poorly controlled (>1 /week) seizures or other persistent neurologic symptoms

STUDY SCHEMA

- HER2CLIMB-05 (NCT05132582) is a phase 3, randomized, double-blind study evaluating tucatinib or placebo in combination with trastuzumab plus pertuzumab as maintenance therapy in the 1L setting for patients with unresectable LA or metastatic HER2+ breast cancer following SOC induction therapy



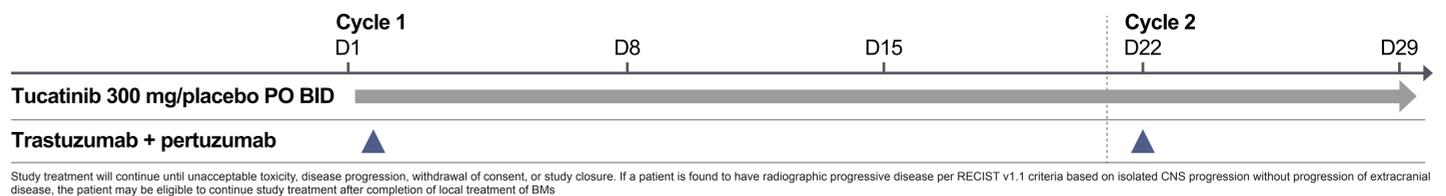
Randomization will be stratified by diagnosis (de novo vs recurrent MBC), hormone receptor status (positive vs negative), and presence or history of BM (yes vs no)
^aTucatinib/placebo 300 mg will be administered PO from Cycle 1 Day 1 onward, BID on each day of study treatment. ^bIV trastuzumab will be given at a dose of 6 mg/kg once every 21 days. Alternatively, trastuzumab may be administered as an SC dose, at a fixed dose of 600 mg once every 21 days. SC trastuzumab does not require a loading dose. ^cA fixed dose of trastuzumab + pertuzumab (600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase) can be administered every 21 days by SC administration, in lieu of trastuzumab and pertuzumab administered IV individually. ^dPertuzumab 420 mg will be administered every 21 days intravenously over 30–60 minutes.

STUDY TREATMENT

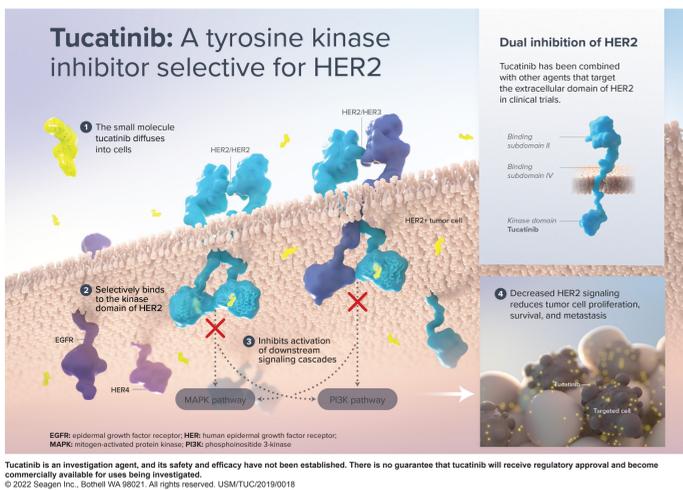
- Patients will receive tucatinib 300 mg or placebo PO BID, trastuzumab 6 mg/kg IV or 600 mg SC, and pertuzumab 420 mg IV every 21-day cycle
- Alternatively, patients will receive pertuzumab 600 mg, trastuzumab 600 mg, and 20,000 units hyaluronidase SC

every 21-day cycle in place of trastuzumab and pertuzumab individually

- Patients with HR+ tumors may receive endocrine therapy per institutional SOC



TUCATINIB PROPOSED MECHANISM OF ACTION



ELIGIBILITY

Key Inclusion Criteria

- Centrally confirmed HER2+ breast carcinoma per 2018 ASCO CAP guidelines
- Unresectable locally advanced or metastatic disease
 - If recurrent (after [neo]adjuvant therapy), must be ≥ 6 months treatment free from any trastuzumab or pertuzumab received for advanced HER2+ disease
- Received 4–8 cycles (21-day cycles) of previous treatment with trastuzumab, pertuzumab, and taxane as 1L therapy for advanced HER2+ breast cancer with no evidence of disease progression
- Known hormone receptor status (per local guidelines; may be HR+ or HR–)
- ECOG performance status score of 0 or 1
- CNS inclusion criteria:** Based on screening contrast brain MRI at baseline or at screening, patients may have any of the following:
 - No evidence of BMs
 - Untreated BMs which are asymptomatic, and if identified on prior brain imaging, without evidence of progression since starting 1L induction therapy with trastuzumab, pertuzumab, and taxane
 - Previously treated BMs which are asymptomatic or must not have progressed since treatment

Abbreviations

1L, first-line; AE, adverse event; APAC, Asia-Pacific; ASCO CAP, American Society of Clinical Oncology College of American Pathologists; BICR, blinded independent central review; BID, twice a day; BM, brain metastasis; CNS, central nervous system; CNS-PFS, time from randomization to investigator-assessed disease progression in brain; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, EORTC Core Quality of Life Questionnaire; EOT, end of treatment; EQ-5D-5L, 5-level EQ-5D; ET, endocrine therapy; EU, European Union; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR+, hormone receptor positive; HR-, hormone receptor negative; HR-QOL, health-related quality of life; IV, intravenous; LA, locally advanced; LMD, leptomeningeal disease; MBC, metastatic breast cancer; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PO, by mouth; PK, pharmacokinetic; QOL, quality of life; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SOC, standard of care; SC, subcutaneous; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor; US, United States.

Disclosures:

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