HER2CLIMB-02: A Randomized, Double-Blind, Phase 3 Study of Tucatinib or Placebo With T-DM1 for Unresectable Locally-Advanced or Metastatic HER2+ Breast Cancer (Trial in Progress)

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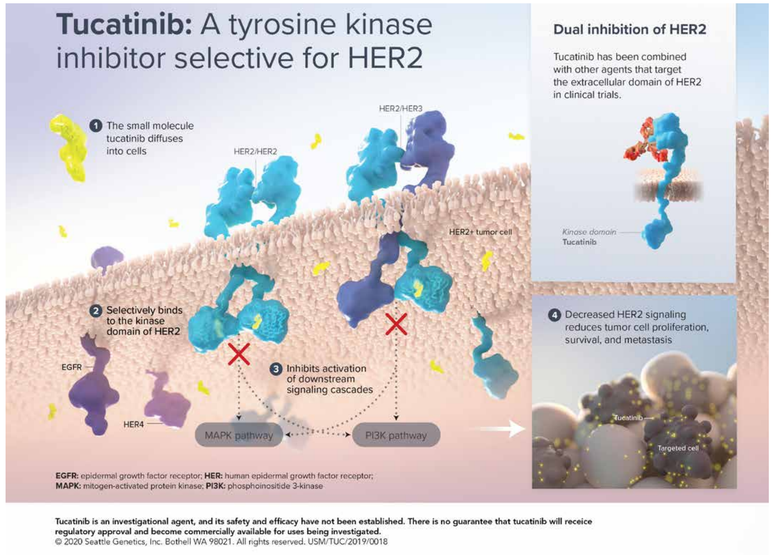
Background and Rationale

- Approximately 15–20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2)[1-4]
- HER2+ tumors are more aggressive and associated with poorer rates of overall survival (OS) vs HER2- tumors[5]
  - Approximately 50% of patients with HER2+ metastatic breast cancer (MBC) eventually develop brain metastases[6-8]
- Ado-trastuzumab emtansine (T-DM1), approved for treatment of patients with HER2+ MBC after trastuzumab and a taxane, has led to significant improvements in progression-free survival (PFS) and OS.
- While treatment with T-DM1 has led to significant improvements in PFS and OS, further improvements in therapy are needed, including for patients with HER2+ MBC and active or potential brain metastases[9]
- Tucatinib is an oral tyrosine kinase inhibitor (TKI) highly selective for HER2 with minimal inhibition of epidermal growth factor receptor (EGFR)[10]
- Tucatinib is approved in the United States (US), Australia, Switzerland, Canada, and Singapore for HER2+ MBC, including patients with brain metastases
- Tucatinib in combination with trastuzumab and capecitabine[11]:
  - Reduced the risk of death by approximately one third (HR=0.66, P=0.0048)
  - Reduced the risk of progression or death by approximately half in all patients (HR=0.54, P<0.00001), including those patients with brain metastases (HR=0.48, P<0.00001)
  - Nearly doubled the confirmed objective response rate (41% vs 23%, P=0.00008)

Proposed Mechanism of Action



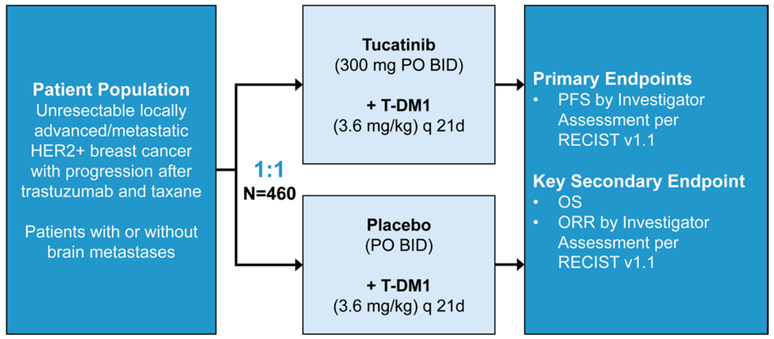
Tucatinib is an investigational agent, and its safety and efficacy have not been established. There is no guarantee that tucatinib will receive regulatory approval and become commercially available for uses being investigated.

Clinical Rationale

- A phase 1b trial (NCT01983501) evaluated tucatinib (300 mg PO BID) in combination with T-DM1 in 50 patients with HER2+ MBC who received prior treatment with trastuzumab and a taxane[12]
- Tucatinib in combination with T-DM1 showed encouraging clinical activity with median PFS of 8.2 months (95% CI: 4.8–10.3), and objective response rate (ORR) in patients with measurable disease (n=34) was 47%
- 60% of patients treated with tucatinib + T-DM1 had brain metastases at baseline and showed a brain specific response rate (per Response Evaluation Criteria Solid Tumors [RECIST] v1.1) of 36% in patients with measurable brain metastases (5/14)
- Tucatinib in combination with T-DM1 showed a tolerable safety profile
  - Common adverse events (AEs) included nausea (72%), diarrhea (60%), and fatigue (56%); mostly Grade 1/2

Abstract No. 283
European Society for Medical Oncology - Asia Virtual Congress 2020; November 20–22, 2020

Study Design



- HER2CLIMB-02 (EudraCT no. 2019-005017-39) is a randomized, double-blind, placebo-controlled phase 3 study to evaluate efficacy and safety of tucatinib in combination with T-DM1 in patients with unresectable locally advanced or HER2+ MBC who have had prior treatment with trastuzumab and taxane
- Approximately 460 patients will be randomized 1:1 to receive 21-day cycles of tucatinib (300 mg PO BID) or placebo in combination with T-DM1 (3.6 mg/kg IV)
- Randomization is stratified by line of treatment for metastatic disease, hormone receptor (HR) status, presence or history of brain metastases, and Eastern Cooperative Oncology Group (ECOG) performance status

Eligibility Criteria

Key Inclusion Criteria

- Histologically confirmed HER2+ MBC as determined by a sponsor-designated central lab
- Prior treatment with trastuzumab and a taxane in any setting (adjuvant, neoadjuvant, or metastatic)
  - Prior pertuzumab is allowed but not required
- ≥18 years (Age of majority at time of consent in Japan)
- Measurable or non-measurable disease assessable by RECIST v1.1
- ECOG ≤1
- Adequate hepatic, hematologic, renal, and cardiac function

Key Exclusion Criteria

- Prior treatment with tucatinib, neratinib, afatinib, DS-8201a, or any investigational anti-HER2 or anti-EGFR agent or HER2 TKI agent
- Prior lapatinib within 12 months of starting study treatment (except in cases where lapatinib was given for ≤21 days and discontinued for reasons other than disease progression or severe toxicity)
- Prior treatment with T-DM1

Key Brain Metastases Inclusion Criteria

- No evidence of brain metastases, OR
- Untreated brain metastases not requiring immediate local therapy, OR
- Previously treated brain metastases that are stable or have progressed but do not require immediate local therapy

Key Brain Metastases Exclusion Criteria

- Ongoing treatment with corticosteroids at a total daily dose of >2 mg dexamethasone or equivalent
- Known leptomeningeal disease

Study Sites

- Enrollment is ongoing in the US and Canada, planned for the EU and the Asia/Pacific region
- Total number of planned sites (global): approximately 200
- Study start: Oct 2019
- Estimated study completion: Apr 2024

Study Assessments

- Efficacy
  - Radiographic disease evaluations (contrast computed tomography [CT], positron emission tomography [PET]/CT, or magnetic resonance imaging [MRI]) per RECIST v1.1 at baseline, followed by every 6 weeks for the first 24 weeks, and then every 9 weeks
  - Brain MRI for all patients at baseline and after completion of study treatment
  - Brain MRI for patients with known brain metastases (including history of brain metastases) every 6 weeks for the first 24 weeks, and then every 9 weeks
  - Additional contrast MRIs of the brain may also be performed in subjects without known brain metastases if there is clinical suspicion of new brain lesions
- Quality of life assessments collected in all cycles and at end of treatment and follow-up visits while undergoing treatment
- Pharmacokinetics (PK)
  - Performed from Cycle 3 to Cycle 6 in all subjects to assess the steady state PK of tucatinib and T-DM1
- Safety
  - Physical examination at baseline and every cycle
  - Laboratory measurements at baseline and every cycle
  - AEs will be recorded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 criteria
  - Assessment of cardiac ejection fraction performed by multi-gated acquisition (MUGA) scan or echocardiogram (ECHO) every 12 weeks while on treatment, and at the end of study treatment

Study Endpoints

Primary

- PFS per RECIST v1.1 by investigator assessment

Key secondary

- OS
- ORR per RECIST v1.1 by investigator assessment

Other secondary

- PFS per RECIST v1.1 by BICR
- PFS per RECIST v1.1 by investigator assessment and by BICR in patients with brain metastases at baseline
- ORR per RECIST v1.1 by BICR
- DOR per RECIST v1.1 by investigator assessment and by BICR
- CBR per RECIST v1.1 (proportion of patients with SD or non-CR/non-PD for ≥6 months, CR or PR) by investigator assessment and by BICR
- Incidence of AEs

Exploratory Endpoints

- PK parameters for tucatinib and T-DM1
- Relationship between biomarkers in blood and response following tucatinib treatment
- HCRU based on the number of medical care encounters and other procedures of interest
- Health-related QoL assessed by patient-reported outcomes

Abbreviations: BICR=blinded independent central review, CBR=clinical benefit rate, CR=complete response, DOR=duration of response, HCRU=healthcare resource utilization, PD=progressive disease, PR=partial response, QoL=quality of life, SD=stable disease

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Disclosures for Norikazu Masuda: Study sponsored by Seagen Inc. **Research grant/funding:** AstraZeneca, Chugai, Daiichi Sankyo, Eisai, Kyowa-Kirin, Lilly, Novartis, Pfizer. **Corporate board membership:** Japan Breast Cancer Research Group Association. **Honoraria:** AstraZeneca, Chugai, Eisai, Lilly, Pfizer, Takeda.

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