Background and Rationale

- Approximately 15–20% of breast cancers express the human epidermal growth factor receptor 2 (HER2).\(^1\)
- HER2+ tumors are more aggressive and associated with poorer rates of overall survival (OS) vs HER2- tumors.\(^2\)

- Approximately 50% of patients with HER2+ metastatic breast cancer (MBC) eventually develop brain metastases.\(^3\)
- 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 compared with lapatinib/capecitabine.\(^4\)

- While treatment with T-D1M 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.\(^5\)

- Tucatinib is an oral tyrosine kinase inhibitor (TKI) highly selective for HER2 with minimal inhibition of epidermal growth factor receptor (EGFR).\(^6\)

- Tucatinib is approved in the United States (US), Australia, Switzerland, Canada, and Singapore for HER2+ MBC, including patients with brain metastases.\(^7\)

- In the randomized pivotal HER2CLIMB study, tucatinib in combination with trastuzumab and capecitabine, in patients with HER2+ MBC, with and without brain metastases, previously treated with trastuzumab, pertuzumab, and T-D1M.\(^8\)

  - 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).

- Doubled the confirmed intracranial response rate (ORR-IC) in patients with active brain metastases and measurable intracranial lesions at baseline (47% vs. 20%, P=0.03).

- Proposed Mechanism of Action

  - Treatment with tucatinib in combination with trastuzumab and capecitabine was well tolerated and had a manageable safety profile.

- Study Design

  - **Patient Population**
    - Unresectable locally-advanced/metastatic HER2+ breast cancer with progression after trastuzumab and taxane

  - **Placebo**
    - Patients with or without brain metastases

  - **Tucatinib (300 mg PO BID)**
    - Patients with or without brain metastases

  - **Tucatinib (300 mg PO BID) + T-D1M (3.6 mg/kg q 21d)**
    - Patients with or without brain metastases

  - **Primary Endpoints**
    - PFS by Investigator Assessment per RECIST v1.1

  - **Key Secondary Endpoints**
    - OS
    - QoL by Investigator Assessment per RECIST v1.1

- 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)

  - **Key Exclusion Criteria**
    - Prior treatment with tucatinib, neratinib, afatinib, trastuzumab deruxtecan, 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 ≥51 days and discontinued for reasons other than disease progression or severe toxicity)

  - **Key Brain Metastases Inclusion Criteria**
    - No evidence of brain metastases

  - **Key Brain Metastases Exclusion Criteria**
    - Untreated brain metastases not requiring immediate local therapy

- Key Brain Metastases Inclusion Criteria

- Key Brain Metastases Exclusion Criteria

- 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

  - **Quality of life assessments collected in all cycles and at end of treatment and follow-up visits while undergoing treatment**

  - **Pharmacokinetics (PK)**

  - **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 (CTCAE v4.03)

- Study Endpoints

  - **Primary**
    - PFS per RECIST v1.1 by investigator assessment

  - **Key secondary**
    - OS
    - QoL 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

  - QoL per RECIST v1.1 by BICR
  - ORR per RECIST v1.1 by investigator assessment and by BICR

  - CBR per RECIST v1.1 (proportion of patients with SD or non-CR/PD for 36 months, CR or PR by investigator assessment and by BICR and incidence of AEs

- Exploratory Endpoints

  - PK parameters for tucatinib and T-D1M
  - Relationship between biomarkers in blood and response following tucatinib
  - HRU based on the number of medical care encounters and other procedures
  - Health-related QoL assessed by patient-reported outcomes

- References