**Background and Rationale**

- Approximately 15-20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2).
- HER2+ tumors are more aggressive and associated with poorer rates of overall survival (OS) vs HER2- tumors.
- Approximately 50% of patients with HER2+ metastatic breast cancer (MBC) eventually develop brain metastases.
- Ado-trastuzumab emtansine (T-DM1), approved for treatment of patients with HER2+ MBC after anthracyclines 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.
- Tucatinib is an oral tyrosine kinase inhibitor (TKI) highly selective for HER2 with minimal inhibition of epidermal growth factor receptor (EGFR).
- 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 (T-DM1) has demonstrated clinical activity in patients with HER2+ MBC who have prior treatment with trastuzumab and capecitabine.
- 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).
- HER2CLIMB-02 (EudraCT no. 2019-005017-39) is a randomized, double-blind, phase III study to evaluate the safety and efficacy of tucatinib in combination with T-DM1 in patients with unresectable locally advanced or HER2+ MBC who have had prior treatment with trastuzumab and capecitabine.
- Tucatinib in combination with T-DM1 showed a tolerable safety profile, mostly Grade 1/2.
- The median PFS of 8.2 months (95% CI: 4.8–10.3) and objective response rate (ORR) of 36% in patients with measurable brain metastases (5/14) is consistent with previous studies of T-DM1 in patients with HER2+ MBC.
- Key exclusion criteria include known leptomeningeal disease, ongoing treatment with corticosteroids at a total daily dose of >2 mg dexamethasone, and previous treatment with T-DM1.
- The primary endpoint of HER2CLIMB-02 is confirmed objective response rate (CBR) per RECIST v1.1 by investigator assessment.
- Key secondary endpoints include OS, PFS per RECIST v1.1 by investigator assessment, ORR per RECIST v1.1 by investigator assessment and ORR per RECIST v1.1 by BICR and DOR per RECIST v1.1 by investigator assessment and by BICR.
- HER2CLIMB-02 is a randomized, double-blind, placebo-controlled phase III study to evaluate the safety and efficacy of tucatinib in combination with T-DM1 in patients with unresectable locally advanced or HER2+ MBC who have prior treatment with trastuzumab and capecitabine.

**Key Facts**

- Approximately 20% of advanced breast cancer patients present with brain metastases.
- Tucatinib is an oral TKI that is highly selective for HER2.
- HER2CLIMB-02 is a randomized, double-blind, placebo-controlled phase III study to evaluate the safety and efficacy of tucatinib in combination with T-DM1 in patients with HER2+ MBC.
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**Study Design**

- **Patient Population**
  - HER2+ locally advanced/metastatic breast cancer (MBC), including patients with brain metastases
  - Median number of prior therapies (not including study treatment) = 5
  - Her2 status confirmed by a sponsor-designated central lab

- **Randomization**
  - 1:1 allocation to tucatinib or placebo
  - Placebo-controlled phase III study

- **Study Duration**
  - 12 months of study treatment
  - Median follow-up of 17.4 months
  - OS = 20.9 months (95% CI: 18.7–23.0)
  - PFS = 8.2 months (95% CI: 4.8–10.3)
  - ORR = 36% (95% CI: 28–44)
  - CBR = 35% (95% CI: 27–43)

- **Study Sites**
  - 144 study sites worldwide

- **Study Assessments**
  - Efficacy
    - Radiographic disease evaluations (contrast computed tomography [CT], position 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 thereafter
    - Brain MRI for patients with known brain metastases (including history of brain metastases) every 4 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)**
  - Pharmacokinetic (PK) data to be collected in Cycle 1 and Cycle 6
  - PK parameters for tucatinib and T-DM1

**Proposed Mechanism of Action**

- Tucatinib targets HER2, preventing HER2 activation.
- HER2 activation is critical for cancer cell proliferation and survival.
- Tucatinib inhibits HER2-mediated signaling pathways, leading to cell cycle arrest and apoptosis.
- Tucatinib is selectively cytotoxic to HER2-overexpressing breast cancer cells.

**Study Endpoints**

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

- **Secondary Endpoint**
  - PFS per RECIST v1.1 by BICR
  - 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-PR/SD-PD for at least 36 months, CR or PR by investigator assessment and by BICR)
  - Incidence of AEs

**Eligibility Criteria**

- **HER2** status confirmed by a sponsor-designated central lab
- Prior treatment with trastuzumab and capecitabine (T-DM1)
- Prior treatment with trastuzumab, atezolizumab, 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 (exception in cases where lapatinib was given for ≥6 months and discontinued for reasons other than disease progression or severe toxicity)
- Prior treatment with T-DM1

**References**