DESTINY-Breast12: A Phase 3b/4, Open-Label Trial of T-DXd for Previously Treated, Human Epidermal Growth Factor Receptor 2–Positive, Advanced/Metastatic Breast Cancer With or Without Brain Metastasis

Background

- Despite recent advances, better treatment options are needed for patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer (mBC) with brain metastases (BM).
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of an anti-HER2 antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload.

Structure of T-DXd

- HER2-positive mBC
- Absence or presence of BM at baseline
- 52 days prior to lines of therapy in the metastatic setting

Key Inclusion Criteria

- Age ≥18 years
- Pathologically documented unresectable/advanced or metastatic breast cancer with ≥1 lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter
- HER2-positive advanced or metastatic breast cancer with or without BM at baseline
- BM in the DESTINY-Breast01 phase 2 trial
- A confirmed objective response rate (ORR) in cohort 2 of 55% (95% CI, 47%-63.1%) within the first 6 months of treatment
- Change in symptoms, functioning, and HRQOL in cohort 2
- ORR, CNS PFS, CNS DOR, and time to new CNS lesions in cohort 2
- OS, DOR, a time to progression, b DOT on subsequent lines of therapy, and PFS2 in both cohorts
- Incidence of new symptomatic CNS metastases during treatment in cohort 1
- Change in symptoms, functioning, and HRQOL in cohort 2
- Safety and tolerability, including AEs, investigator-assessed SLD/neuromytoxicity, and AEs in patients with BM at baseline and concurrent high-dose steroidal treatment

Key Exclusion Criteria

- Known or suspected hypersensitivity to T-DXd or any of its components
- Prior exposure to immunosuppressive medication, except for intranasal and inhaled corticosteroids or systemic corticosteroids at doses ≤2 mg/day of dexamethasone or equivalent
- One or more concurrent serious or nonserious active infections
- Patients with active systemic neoplasms other than breast cancer
- Known or suspected leptomeningeal disease
- Known active HBV or HCV infection or positive for HCV antibody (unless PCR negative for HCV RNA); patients with past or resolved HBV infection must be negative for HBV DNA
- Presence of BM at baseline
- Refractory nausea and vomiting, chronic gastrointestinal disease, or previous or concurrent treatment for nausea and vomiting
- Prior exposure to tucatinib treatment
- Known or suspected insulinoma or insulin resistance
- History of brain injury caused by head trauma requiring hospitalization
- History of severe or persistent seizures
- Prior CNS radiotherapy within 12 months prior to enrolment in the study
- Known or suspected leptomeningeal disease
- Patients with past or resolved HBV infection must be negative for HBV DNA
- Known or suspected insulinoma or insulin resistance
- History of severe or persistent seizures
- Prior CNS radiotherapy within 12 months prior to enrolment in the study

Key Study Endpoints

- ORR in cohort 1
- OS, DOR, time to progression, DOT on subsequent lines of therapy, and PFS2 in both cohorts
- Incidence of new symptomatic CNS metastases during treatment in cohort 1
- Time to next progression (CNS or extracranial) or death after first progression per RANO-BM by ICR
- Site (CNS, extracranial, or both) of next progression in cohort 2
- ORR in cohort 2
- CNS ORR, CNS PFS, CNS DOR, and time to CNS progression per RANO-BM by ICR in cohort 2

Enrollment Start: 22 June 2021
Currently Recruiting Patients

Countries with participating study sites

- Australia, Belgium, Canada, Denmark, Finland, Germany, Italy, Japan, Netherlands, Norway, Poland, Portugal, Russia, Spain, Sweden, Switzerland, United Kingdom, United States

Key Findings

- ORR in cohort 1
- OS, DOR, time to progression, DOT on subsequent lines of therapy, and PFS2 in both cohorts
- Incidence of new symptomatic CNS metastases during treatment in cohort 1
- Time to next progression (CNS or extracranial) or death after first progression per RANO-BM by ICR
- Site (CNS, extracranial, or both) of next progression in cohort 2
- ORR in cohort 2
- CNS ORR, CNS PFS, CNS DOR, and time to CNS progression per RANO-BM by ICR in cohort 2

Explanatory Endpoints

- OS, DOR, time to progression, DOT on subsequent lines of therapy, and PFS2 in both cohorts
- Incidence of new symptomatic CNS metastases during treatment in cohort 1
- Time to next progression (CNS or extracranial) or death after first progression per RANO-BM by ICR
- Site (CNS, extracranial, or both) of next progression in cohort 2
- ORR in cohort 2
- CNS ORR, CNS PFS, CNS DOR, and time to CNS progression per RANO-BM by ICR in cohort 2

References