Open-label, multinational, multicenter, phase 3b/4 study of trastuzumab deruxtecan (T-DXd) in patients with or without baseline brain metastasis with previously treated advanced/metastatic human epidermal growth factor receptor 2–positive breast cancer: DESTINY-Breast12

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Study Design and Population

- **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

Enrollment Start: 22 June 2021 | Currently Recruiting Patients

Key Study Endpoints

- **ORR in cohort 1**: patients with CNS progression
- **ORR × CNS PFS**: time to new CNS lesions, CNS ORR, and CNS PFS in cohort 2
- **OS, DOR, and TTF2** on subsequent lines of therapy, and PFS2 in both cohorts
- **Incidence of new symptomatic CNS metastasis during treatment in cohort 1**: Time to next progression (CNS or extracranial) or death after first-line T-DXd
- **Site (CNS, extracranial, or both) of progression in cohort 2**: CNS ORR, CNS PFS, CNS DOR, and time to progression per RANO-BM by ICR in cohort 2

Key Study Inclusion Criteria

- **AEs**: any AE of ≤1/1, ≤1/10, ≤1/100, ≤1/1000, or ≤1/\(10^4\) in the larger diameter of >1 cm or >1 cm in the baseline diameter ≥1 cm, as clinically relevant
- **Cohort 2 (n≈250):** patients with untreated BM at baseline
- **Cohort 1a (n≈50):** patients with baseline BM ≤2 prior lines of therapy in the HER2-positive mBC
- **Cohort 1b (n≈150):** patients with or without baseline BM ≤2 prior lines of therapy in the HER2-positive mBC

Key Exclusion Criteria

- **Prior CNS metastases**: patients with history of symptomatic CNS metastases
- **Prior brain radiotherapy**: received prior brain radiotherapy
- **Known active HBV or HCV infection**: patients with HBV or HCV infection
- **Known active hepatic disease**: patients with significant liver dysfunction

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 metastasis (BM)
- 85% of patients with HER2-positive mBC develop BM, which is associated with increased mortality and morbidity
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of an anti-HER2 antibody, a telisotuzumab medezim antibody-drug complex, and a topoisomerase I inhibitor payload

Structure of T-DXd

- Humanized anti-HER2 (549 kDa)
- Topoisomerase I Inhibitor Payload
- Cleavable Tandemly-Based Linker

T-DXd in HER2-Positive mBC

- Global approvals of T-DXd for the treatment of metastatic breast cancer (mBC), HER2-Positive mBC
- 5.3% (95% CI, 1.9-7.6%) median progression-free survival (PFS) of 18.1 months (95% CI, 18.1-18.1 months) were observed with T-DXd treatment
- Duration of response (DOR) of 16.9 months (95% CI, 16.9-16.9 months), and median overall survival (OS) of 35.4 months (95% CI, 34.3-36.6 months)

In a subgroup analysis of 24 patients with HER2-positive mBC and asymptomatic BM at baseline, OS, DOR, and median PFS of 18.1 months (95% CI, 6.7-18.1 months) were observed with T-DXd treatment

This study seeks to provide a more robust understanding of T-DXd that will complement ongoing and completed studies; this study will provide additional data regarding T-DXd as a treatment option for patients with HER2-positive mBC

Here, we describe the DESTINY-Breast12 open-label, phase 3b/4 trial evaluating the efficacy and safety of T-DXd in patients with previously treated advanced or metastatic HER2-positive breast cancer with or without BM at baseline

This study is sponsored by AstraZeneca. In March 2019, AstraZeneca entered license agreements with Seattle Genetics, Inc. (SGEN) and Daiichi Sankyo, Co., Ltd. (DY001) for the development and commercialization of T-DXd. Financial support was provided by Gilead Sciences, Inc. (GILD), and AstaZeneca

Key Study Endpoints

- **ORR in cohort 1**: patients with CNS progression
- **ORR × CNS PFS**: time to new CNS lesions, CNS ORR, and CNS PFS in cohort 2
- **Change in symptoms, functioning, and HRQOL**: patients with CNS progression
- **Safety and tolerability**: including AEs, investigator-assessed ILD/neuromytois, and AEs in patients with BM at baseline and concurrent high-dose steroid treatment

Exploratory Endpoints

- **Cohort 1**: 11% of patients with HER2-positive mBC with asymptomatic BM at baseline
- **Cohort 2**: 40% of patients with HER2-positive mBC at baseline

References