A phase 3, open-label trial of neoadjuvant trastuzumab deruxtecan (T-DXd) monotherapy or T-DXd followed by THP compared with ddAC-THP in patients with high-risk HER2-positive early-stage breast cancer (DESTINY-Breast11)

Nadia Harbeck,1 Jean-François Boileau,2 Shanu Modi,3 Catherine M. Kelly,4 Shinji Ohno,5 Jong Wu,6 Mark Brekenridge,7 Adam Konpa,7 Pia Herbolsheimer,7 Tinghui Yu,7 Lajos Pusztai8

Breadst Center, Department of Gynecology and Obstetrics and CCG Munich, LMU University Hospital, Munich, Germany; 2Jewish General Hospital Segal Cancer Centre, McGill University, Montreal, QC, Canada; 3Memorial Sloan Kettering Cancer Center/Wall Cornell Medical College, New York, NY; 4Mater Misericordiae University Hospital, Dublin, Ireland; 5Breast Oncology Center, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; 6Thudun University Shanghai Cancer Center, Shanghai, China; 7AstraZeneca Pharmaceuticals, Gaithersburg, MD; 8Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background
- The current standard of care (SOC) for neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early-stage breast cancer (EBC) consists of trastuzumab + pertuzumab and polychemotherapy.
- Many patients, particularly those with locally advanced or inflammatory disease, still experience relapse and/or death.
- These multilagging regimens expose patients to short- and long-term toxicities, and de-escalation approaches in the adjuvant setting, with regimens such as paclitaxel + trastuzumab + pertuzumab (THP), have been explored to reduce treatment burden. Therefore, better neoadjuvant therapies are needed to improve patient outcomes.
- 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
- T-DXd monotherapy demonstrated efficacy, with improved progression-free survival (hazard ratio, 0.28; P = 0.001) and an encouraging trend observed in the 12-month overall survival rate (94.1% vs 89.5%, respectively) vs trastuzumab emtansine (T-DM1) in patients with previously treated, HER2-positive, unresectable/metastatic breast cancer.
- Improvements were also observed with T-DXd in confirmed objective response rate (ORR; 79.7% [95% CI, 74.3%-84.4%] vs 34.2% [95% CI, 28.6%-40.3%]; complete response (16.1% vs 8.7%), and partial response (63.6% vs 25.5%) vs T-DM1, respectively.

Here we describe DESTINY-Breast11, a phase 3, global, open-label, multicenter trial assessing T-DXd monotherapy followed by T-DXd + THP as neoadjuvant treatment vs dose-dense doxorubicin + cyclophosphamide followed by THP (ddAC-THP) in patients with high-risk HER2-positive EBC

Key Inclusion Criteria
- Men or women aged ≥18 years
- Histologically documented HER2-positive EBC with:
  - Locally assessed HER2 positive (ICH 3+ or 3H+) per ASCO/CAP guidelines and centrally confirmed as HER2 positive
- Documented HR positive (ER and/or PgR positive ≥1%) and centrally confirmed as HR positive
- ECOG performance status 0 or 1
- History of invasive breast cancer
- Stage IV breast cancer by AJCC staging system
- History of another primary malignancy within 3 years except for adequately resected non-melanoma skin cancer or curatively treated in situ disease
- History of ductal carcinoma in situ except for patients treated with mastectomy only >5 years prior to current diagnosis
- Evidence of diseases (e.g., severe or uncontrolled systemic diseases) that in the investigator’s opinion may interfere with study participation and compliance
- History of (noninfectious) IBD/pneumonitis that required steroids, current IBD/pneumonitis, or suspected IBD/pneumonitis that cannot be ruled out by imaging at screening
- Prior systemic therapy for the treatment of breast cancer

Key Exclusion Criteria
- Prior treatment with T-DXd or T-DXd + THP
- Patients with a history of moderate/severe interstitial lung disease
- Organ or brain dysfunction
- Recent (within 6 months) treatment with a targeted antibody or any investigational drug or agent
- Other serious disease, condition, or illness that, in the investigator’s opinion, may be placed at risk by the study therapy

Enrollment Start: 25 October 2021 | Currently Recruiting Patients

Countries with participating study sites
- Austria, Brazil, Bulgaria, Canada, China, Germany, India, Italy, Japan, Peru, Philippines, Poland, Russia, Saudi Arabia, South Korea, Spain, Taiwan, Thailand, United States

Key Study Endpoints
- ORR by RECIST v1.1
- 3-year DFS
- 3-year IDFS
- Overall survival
- Patient-reported tolerability
- Physical functioning
- Immuno-Pharmacokinetics
- Safety and tolerability

References

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Abbreviations
- AJCC, American Joint Committee on Cancer; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; EFS, event-free survival; EHR, electronic health record; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease-free survival; ISH, in situ hybridization; LVEF, left ventricular ejection fraction; NMIBC, nonmuscle invasive bladder cancer; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; QoL, quality of life; TCGA, The Cancer Genome Atlas; THP, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; T, tumor; Visible, a new tool for the comprehensive evaluation of imaging data and its potential utility in assessing therapy response in breast cancer.