Trastuzumab deruxtecan (T-DXd), a HER2-directed antibody-drug conjugate, has emerged as a transformative therapy for patients with HER2-positive and HER2-negative breast cancer. Recent clinical trials have expanded its potential indications and demonstrated robust efficacy across disease settings. DB06 extends the evidence base to patients with HR-positive, HER2-low/ultralow metastatic breast cancer pretreated with endocrine therapy. In this population, T-DXd significantly prolongs PFS versus investigator-choice chemotherapy, marking a pivotal advance for patients with limited options. The efficacy of T-DXd in HER2-negative tumors reinforces its unique mechanism of action and positions it as a preferred therapy beyond traditional HER2-positive cohorts.

The DB09 phase III trial evaluates T-DXd in combination with pertuzumab and trastuzumab as a first-line treatment for HER2-positive metastatic breast cancer. Early findings suggest that the T-DXd regimen achieves improved progression-free survival (PFS) relative to standard-of-care HER2-targeted therapies, including trastuzumab, pertuzumab, and chemotherapy. The trial further explores safety and tolerability, which remain

consistent with previous studies, confirming the manageable toxicity profile of T-DXd in this setting.

DB05 demonstrated a highly statistically significant and clinically meaningful improvement in Invasive Disease-Free Survival (IDFS) compared to the current standard of care, trastuzumab emtansine (T-DM1). This trial involved high-risk patients who had residual invasive disease after receiving neoadjuvant (pre-operative) treatment. As the first head-to-head comparison of Enhertu and T-DM1 in this setting, the results suggest Enhertu may be a superior post-neoadjuvant treatment option.

DB11 expands this transformative potential by targeting patients with HER2-positive early metastatic breast cancer. In this study, T-DXd demonstrated compelling anti-tumor activity and meaningful clinical benefit, further redefining how clinicians assess and treat HER2 expression in early breast cancer. The study showed improved outcomes compared to conventional chemotherapy, establishing T-DXd as a promising option for tumors previously classified outside the reach of HER2-directed therapies.

Across the DESTINY-Breast clinical program, T-DXd has demonstrated substantial efficacy in HER2-positive and HER2-negative breast cancer, including in first-line, recurrent/metastatic, and CNS-involved settings. These results support continued investigation of T-DXd in early-stage breast cancer and rare/unmet populations, with the potential to further reshape the treatment landscape and improve outcomes across the disease continuum.

Reference: Enhertu improved IDFS in early BC in DB-05