A global, interventional, open-label trial of trastuzumab deruxtecan (T-DXd)–based therapy followed by palbociclib, endocrine therapy (ET), and dual HER2 blockade in first-line (1L) human epidermal growth factor receptor 2–positive (HER2+), hormone receptor–positive (HR+) advanced or metastatic breast cancer (mBC) and retreatment with T-DXd (DESTINY-Breast Guide)

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*At the time of the study.

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Plain Language Summary

Why are we performing this research?

This study is designed to evaluate a new treatment approach for adults with breast cancer (BC) that has spread to other parts of the body, called metastatic breast cancer (mBC), and who have cancers that are classified as human epidermal growth factor receptor 2–positive (HER2+) and hormone receptor–positive (HR+). HER2+ BC cells have higher levels of the HER2 protein, which helps cells grow quickly, and HR+ cells have estrogen receptor or progesterone receptor proteins.[1,2] Standard treatment for HER2+ mBC includes chemotherapy combined with HER2-targeting drugs such as trastuzumab and pertuzumab.[3] However, chemotherapy can cause troublesome side effects. Newer therapies like trastuzumab deruxtecan (T-DXd) have shown promising results in improving patient outcomes without the need for a separate chemotherapy medicine such as a taxane.[4] T-DXd is an antibody-drug conjugate that specifically binds to tumor cells that express HER2 to more directly deliver tumor-killing drugs into target cells.[5,6] T-DXd combined with pertuzumab is approved in some countries as a first-line (1L) therapy for patients with HER2+ mBC, and this treatment can help control the disease for longer than previous standard treatments; however, some patients may have difficulties tolerating T-DXd over a long period of time.[7,8] DB-Guide, a study sponsored by Daiichi Sankyo in collaboration with AstraZeneca, tests a sequential treatment that starts with T-DXd combined with pertuzumab for approximately 1 year to ensure that the tumor has shrunk sufficiently, followed by a maintenance phase that includes trastuzumab, pertuzumab, endocrine therapy (which blocks the hormone pathway), and palbociclib (a targeted therapy that has been shown to help control HER2+, HR+ mBC when included as part of maintenance treatment) in patients with HER2+, HR+ mBC. If the cancer progresses during maintenance, patients can be retreated with T-DXd alone. The study will evaluate whether this treatment plan can help control the cancer by targeting both the HER2 protein and the HR protein, can help people live longer, and can keep them feeling well. It also explores whether giving T-DXd again after maintenance can help control the cancer.

How are we performing this research?

DB-Guide is a global clinical trial, with sites in the United States, Canada, Europe, Asia, and Australia, and approximately 200 adult participants with previously untreated HER2+, HR+ advanced BC or mBC will be enrolled. The treatment has 3 parts. In the first treatment, participants will receive T-DXd plus pertuzumab for 18-24 cycles (about 12-17 months). This is to allow enough time for most patients to achieve the greatest possible tumor shrinkage. After the first treatment, if the cancer is under control and side effects are manageable, patients will then switch to maintenance treatment with trastuzumab, pertuzumab, palbociclib, and hormone therapy to keep the cancer from growing. If the cancer starts to grow again during maintenance treatment, eligible patients will receive T-DXd again as second-line treatment to try to control the cancer. The trial focuses on how well the treatment works and how safe it is. Key outcomes include how long patients live without their cancer worsening, how many patients are alive after 2 years, how well the cancer shrinks, the side effects experienced by patients, and the treatment's effects on patients' quality of life.

Who will participate in this study?

The study will include adults aged 18 years or older with HER2+, HR+ BC that cannot be removed by surgery or has spread to other parts of the body. Patients must not have previously received chemotherapy or HER2-targeted therapy for metastatic disease, including any cyclin-dependent kinase 4/6 inhibitors. Participants who previously received treatment for early BC or who have asymptomatic brain metastases may also be eligible if they meet the study requirements. Patients must meet specific health criteria and have measurable disease to track responses.

Where can I access more information?

More information about the DB-Guide study is available at https://clinicaltrials.gov/study/NCT07683754.

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Background

- In DESTINY-Breast09, T-DXd + pertuzumab significantly improved progression-free survival (PFS) and increased complete response (CR) rates versus taxane + trastuzumab + pertuzumab (THP) in patients with previously untreated HER2+ mBC (hazard ratio, 0.56 [95% CI, 0.44-0.71]), supporting its approval as a 1L treatment option in several countries[1,2]
- Despite the efficacy reported in DESTINY-Breast09, approximately 21% of patients receiving T-DXd + pertuzumab discontinued treatment because of treatment-emergent adverse events (TEAEs; versus 28.3% with THP), highlighting an opportunity to optimize patient management with T-DXd and to evaluate alternative treatment approaches in specific clinical situations[1]
- The traditional 1L standard-of-care treatment approach uses at least 6 cycles of THP induction, followed by chemotherapy-free trastuzumab + pertuzumab maintenance, to limit cumulative taxane toxicity, consistent with current ESMO guideline recommendations[3]
- More recently, phase 3 trials have further improved maintenance-based strategies to limit taxane toxicity after 4-8 cycles of THP induction:
  - In the PATINA trial, following THP induction and discontinuation of chemotherapy to limit cumulative toxicity, maintenance therapy with palbociclib + trastuzumab + pertuzumab + endocrine therapy (ET) improved PFS in patients with HER2+, HR+ mBC whose disease had not progressed (hazard ratio, 0.75 [95% CI, 0.59-0.96])[4]
  - Similarly, the HER2CLIMB-05 trial demonstrated that maintenance tucatinib + trastuzumab + pertuzumab improved PFS over trastuzumab + pertuzumab alone in patients with HER2+ 1L mBC without progressive disease (PD) after THP induction (hazard ratio, 0.64 [95% CI, 0.51-0.80])[5]
- In a post hoc analysis of DESTINY-Breast09, median time to maximum tumor reduction (tumor nadir) was approximately 11 months (≈16 cycles) in the overall population and 13 months (≈19 cycles) in patients with HER2+, HR+ mBC, with 80% of patients in the overall population reaching nadir by 24 months, suggesting that responses may continue to deepen after prolonged upfront therapy, without evidence of cumulative toxicity with extended T-DXd + pertuzumab treatment[6,7]
- On the basis of these results, DB-Guide will evaluate the efficacy and safety of a sequential treatment strategy of 18-24 cycles of upfront T-DXd + pertuzumab induction, followed by palbociclib-containing maintenance therapy and planned T-DXd retreatment after disease progression, to determine whether combining the proven efficacy of T-DXd with ET maintenance and second line (2L) T-DXd can improve outcomes while preserving quality of life in patients with HER2+, HR+ mBC

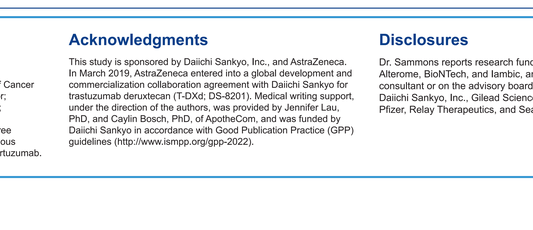
Study Design

- DB-Guide (NCT07683754) is a global, single-arm, open-label trial that aims to investigate the efficacy and safety of sequencing 1L T-DXd + pertuzumab followed by a palbociclib-containing maintenance regimen and T-DXd retreatment after disease progression in patients with HER2+, HR+ advanced or mBC
- In the upfront treatment phase, approximately 200 patients will receive 18-24 cycles (≈12-17 months) of T-DXd 5.4 mg/kg intravenously (IV) every 3 weeks (Q3W) + pertuzumab 840 mg IV loading dose, then 420 mg IV Q3W thereafter
  - Patients who achieve a confirmed CR per RECIST v1.1 can switch to maintenance therapy earlier after receiving at least 8 cycles of T-DXd + pertuzumab. Confirmation of CR should be obtained during the next protocol-defined scheduled tumor assessment.
- In the maintenance phase, patients with at least stable disease (SD) after upfront treatment will transition to trastuzumab 6 mg/kg IV Q3W + pertuzumab 420 mg IV Q3W + ET + palbociclib oral 125 mg daily (3 out of 4 weeks, every 4 weeks)
- In the retreatment phase, eligible patients with PD on maintenance therapy will receive 2L T-DXd 5.4 mg/kg IV Q3W

Study start: September 4, 2026; recruiting patients

Key Eligibility Criteria

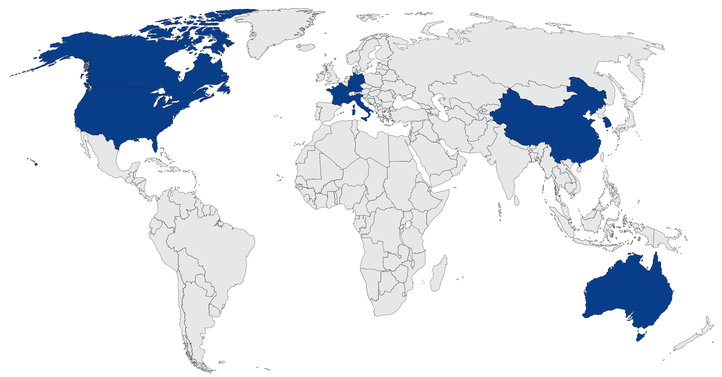
- Patients aged ≥18 years
- HER2+ (IHC 3+ or IHC 2+/ISH+)[a]/HR+, de novo or recurrent mBC
- No prior chemotherapy or HER2-targeted therapy for advanced or mBC[b]
- ECOG PS 0 or 1
- DFI >6 months[c]
- Asymptomatic brain metastases allowed



[a]As classified by 2020 ASCO-CAP guidelines.
[b]1 prior line of ET is allowed for mBC.
[c]Patients who have received systemic therapy in the neoadjuvant or adjuvant setting are eligible, with a DFI >6 months from completion of systemic chemotherapy or HER2-targeted therapy (except T-DXd) to advanced or metastatic diagnosis of >6 months and at least >12 months since completion of prior T-DXd treatment in the neoadjuvant or post-neoadjuvant setting.
[d]Patients who experience protocol-defined unacceptable toxicity during upfront therapy can transition to maintenance at any time.
[e]Aromatase inhibitor or fulvestrant.

Countries with participating study sites

Australia, Canada, China, France, Germany, Italy, Republic of Korea, and US



Key Inclusion Criteria

- 18 years or older

For the upfront treatment phase

- Has pathologically documented BC that is:
  - Locally advanced and unresectable or metastatic (participants who can be treated with curative intent are not eligible)
  - Histologically confirmed HER2+ mBC
  - Locally tested as HR+ (estrogen receptor–positive [ER+] and/or progesterone receptor–positive [PgR+] [ER or PgR ≥1%]) per ASCO-CAP guidelines in the metastatic setting or from the primary tumor with the latest sample available
- Is treatment naive to chemotherapy or HER2-targeted therapy in the metastatic setting
  - Participants who have received chemotherapy or HER2-targeted therapy, radiotherapy, or surgery in the neoadjuvant or adjuvant setting are eligible with DFI >6 months from completion of therapy to diagnosis of advanced or metastatic disease
  - 1 prior line of ET monotherapy in the metastatic setting is allowed
- ECOG PS 0 or 1
- Has at least 1 measurable lesion, not previously irradiated, that can be measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI), or non-measurable, bone-only disease that can be assessed by CT, MRI, or X-ray
- Brain metastasis allowed if asymptomatic and does not require immediate local intervention

For transition into the maintenance treatment phase

- Has no evidence of disease progression on T-DXd + pertuzumab by local assessment per RECIST v1.1
- Is willing to switch therapy
- Has completed ≥8 cycles of T-DXd + pertuzumab with a confirmed CR, or
- Has completed 18 cycles of T-DXd with SD or partial response, and the last 2 scans showed no further tumor shrinkage (from 2 subsequent scans ≥6 weeks apart) or has an unconfirmed CR
- Participants who developed grade 1 or 2 interstitial lung disease (ILD) in the upfront treatment phase must have fully recovered and be asymptomatic. Participants experiencing non-ILD toxicities are eligible if toxicities have resolved to grade 0 or baseline and are based on the investigators' best judgment
- Has received no more than 24 cycles of therapy with T-DXd + pertuzumab

For the T-DXd retreatment phase

- Has received ≥1 dose of maintenance treatment
- Has documented disease progression per RECIST v1.1 per investigator assessment during maintenance treatment
- Participants who experienced grade 1 ILD during maintenance treatment must have fully resolved before starting retreatment with T-DXd

Key Exclusion Criteria

For the upfront treatment phase

- Has prior therapy with any cyclin-dependent kinase (CDK) 4/6 inhibitor
- Has received prior therapy with T-DXd for early BC with event-free survival or DFI <12 months from completion of T-DXd in the neoadjuvant or post-neoadjuvant setting
- Has a history of ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening

For transition into the maintenance treatment phase

- Is receiving concurrent therapy with other trial interventions (except pertuzumab)
- Has any unresolved serious adverse event (SAE) related to prior T-DXd + pertuzumab treatment in the upfront treatment phase, defined as an event that has not resolved to baseline at the time of eligibility assessment for maintenance treatment
- Has experienced grade 3 or 4 ILD/pneumonitis during the upfront treatment phase
- Has spinal cord compression of clinically active central nervous system metastases, defined as untreated or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control symptoms

For the T-DXd retreatment phase

- Has developed grade ≥2 ILD/pneumonitis during the upfront or maintenance treatment phase
- Has any unresolved SAE related to prior maintenance treatment therapies, defined as an event that has not resolved to baseline at the time of eligibility assessment for the T-DXd retreatment phase
- Has developed non-ILD toxicities related to T-DXd in the upfront treatment phase that required T-DXd discontinuation

Key Study Endpoints

1° Primary endpoint

- PFS rate at 24 months (analysis conducted 24 months after the last patient has received their first dose of study drug) by investigator per RECIST v1.1

2° Secondary endpoints

Efficacy

- PFS rate at 12 months
- Objective response rate (ORR) during upfront and retreatment phases
- PFS rate from the start of maintenance treatment at 12 months
- Overall survival at 24 months

Safety

- TEAEs (including TEAEs associated with trial intervention discontinuation, delay, interruption, and dose reduction), SAEs, adverse events of special interest (AESIs), and death
- Time to first AESI and TEAE

Quality of life

- Change in quality of life and patient-reported outcomes (EORTC-QLQ-C30, EQ-5D-5L, EQ-VAS)
- Time to deterioration/improvement after transition to maintenance treatment (EORTC-QLQ-C30, EQ-5D-5L, EQ-VAS)

Exploratory endpoints

- PFS2 (defined as the time from initiation of T-DXd + pertuzumab until PD after any 2L therapy or death, whichever comes first)
- Impact of objective response level achieved prior to transition to maintenance treatment on PFS
- ORR during maintenance phase
- Association between circulating tumor DNA levels and response categories
- Change in treatment-specific side effects

Poster

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Abbreviations

1L, first line; **2L,** second line; **AESI,** adverse event of special interest; **ASCO-CAP,** American Society of Clinical Oncology-College of American Pathologists; **BC,** breast cancer; **CDK,** cyclin-dependent kinase; **CR,** complete response; **CT,** computed tomography; **DFI,** disease-free interval; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **EORTC-QLQ-C30,** European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; **EQ-5D-5L,** EuroQol 5-Dimension 5-Level; **EQ-VAS,** EuroQol Visual Analogue Scale; **ER,** estrogen receptor; **ESMO**, European Society of Medical Oncology; **ET,** endocrine therapy; **HER2,** human epidermal growth factor receptor 2; **HR,** hormone receptor; **IHC,** immunohistochemistry; **ILD,** interstitial lung disease; **ISH,** in situ hybridization; **IV,** intravenous; **mBC,** metastatic breast cancer; **MRI,** magnetic resonance imaging; **ORR,** objective response rate; **PD,** progressive disease; **PFS,** progression-free survival; **PFS2,** progression-free survival 2; **PgR,** progesterone receptor; **Q3W,** every 3 weeks; **RECIST v1.1,** Response Evaluation Criteria in Solid Tumors version 1.1; **SAE,** serious adverse event; **SD**, stable disease; **T-DXd,** trastuzumab deruxtecan; **TEAE,** treatment-emergent adverse event; **THP**, taxane + trastuzumab + pertuzumab.

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Disclosures

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DESTINY Breast-Guide

Poster presented at the European Society for Medical Oncology (ESMO) 2026 Congress; October 23-27, 2026; Madrid, Spain.