A phase 3, multicenter, randomized, open-label, active-controlled study of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in subjects with high-risk HER2-positive primary breast cancer who have residual invasive disease in breast or axillary lymph nodes following neoadjuvant therapy

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This study has been transitioned to CTIS with ID 2023-507961-24-00 check the CTIS register for the current data. Primary objective:1. To evaluate IDFS with T-DXd treatment as compared to T-DM1Secundary objectives:1. To evaluate DFS with T-DXd...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON54210

Source
ToetsingOnline

Brief title
DESTINY-Breast05

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast Cancer, High-Risk HER2-Positive Primary Breast Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Sankyo Inc
Source(s) of monetary or material Support: Daiichi Sankyo Inc

Intervention

Keyword: High-risk HER2-positive breast cancer, Neoadjuvant therapy, Trastuzumab Deruxtecan (T-DXd), Trastuzumab Emtansine (T-DM1)

Outcome measures

Primary outcome

- IDFS is defined as the time from randomization to invasive local, axillary or distant recurrence, invasive contralateral breast cancer, or death from any cause.

- IDFS will be determined based on disease recurrence per Investigator assessment based on all available clinical assessments.

Secondary outcome

- DFS is defined as the time between randomization and the date of the first occurrence of an IDFS event including second primary non-breast cancer event or contralateral or ipsilateral DCIS. DFS will be determined based on disease recurrence per Investigator assessment.

- OS is defined as the time from randomization to death due to any cause.

- DRFI is defined as the time between randomization and the date of distant

breast cancer recurrence. DRFI will be determined based on disease recurrence per Investigator assessment.

- BMFI is defined as time from randomization to documentation of involvement of the CNS by metastatic cancer including parenchymal brain and spinal cord metastases as well as leptomeningeal carcinomatosis. BMFI will be determined based on disease recurrence per Investigator assessment.

- AEs including SAEs, TEAEs, and AESIs Physical examination findings, ECOG PS, vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and CT scans

- Serum concentrations of T-DXd, total anti HER2 antibody, and MAAA 1181a in the PK sampling cohort

- Percentage of subjects who are positive for ADAs at baseline, and postbaseline and treatment-emergent ADA positive. Titer and NAb will be determined for positive ADA samples.

Study description

Background summary

Breast cancer (BC) is the second most common cancer in the world and the most frequent cancer in women with an estimated 2 million new cases in 2018 globally (11.6% of all new cancers). In approximately 20% of BC cases, overexpression of human epidermal growth factor receptor 2 (HER2) occurs. HER2 overexpression in BC is associated with high risk of recurrence and metastasis.4 Several anti-HER2 targeted therapies such as HERCEPTIN® (trastuzumab), PERJETA® (pertuzumab) 5, KADCYLA® (trastuzumab emtansine [T-DM1]), and TYKERB® (lapatinib) have improved outcomes in BC patients who have HER2 overexpression, now known as HER2-positive tumors.

The use of adjuvant (postoperative) trastuzumab in HER2-positive early-stage BC improves patient outcomes as demonstrated in several large, randomized trials.

The 3-year disease-free survival (DFS) rate for patients receiving trastuzumab in these studies, all of whom had operable disease, was approximately 85% to 90%.

Although the KATHERINE study (T-DM1 vs. trastuzumab) was statistically significant, providing validation for ADC development in the post neoadjuvant setting, further unmet medical need exists in HER2-positive BC patients who do not achieve a pCR with increased risk of recurrence following neoadjuvant treatment.

It is recognized that patients who do not achieve pCR after appropriate neoadjuvant therapy are at higher risk of disease recurrence. This is a clinical setting where the application of more effective therapies would have a potentially large absolute impact on patient outcomes and can be considered an area of unmet medical need.

Based on the differentiating features of T-DXd and the anticancer activity in metastatic BC subjects after failure of T-DM1, the ADC T-DXd is anticipated to be effective even in the high-risk adjuvant subpopulation in which T-DM1 had not demonstrated compelling efficacy.

Study objective

This study has been transitioned to CTIS with ID 2023-507961-24-00 check the CTIS register for the current data.

Primary objective:
1. To evaluate IDFS with T-DXd treatment as compared to T-DM1

Secundary objectives:
1. To evaluate DFS with T-DXd treatment as compared to T-DM1
2. To evaluate OS with T-DXd treatment as compared to T-DM1
3. To evaluate DRFI with T-DXd treatment as compared to T-DM1
4. To evaluate BMFI with T-DXd treatment as compared to T-DM1
5. To evaluate safety of T-DXd
6. To evaluate pharmacokinetics (PK) of T-DXd
7. To evaluate immunogenicity of T-DXd

Study design

This is a global, multicenter, randomized, open-label, active-controlled, Phase 3 study of T-DXd versus T-DM1 in subjects with HER2-positive primary breast cancer (BC) who have residual invasive disease in breast or axillary lymph nodes with higher risk of recurrence, which includes subjects who were inoperable at disease presentation or had pathological node-positive status after neoadjuvant therapy. This study is designed to randomize at least 1600 subjects in a 1:1 ratio to receive T-DXd or T-DM1. Randomization will be stratified by

the following factors: • Operative status at disease presentation, prior to neoadjuvant therapy (operable [clinical stages T1-3, N0-1, M0] vs inoperable [clinical stages T4, N0-3, M0 or T1-3, N2-3, M0]) • Tumor hormone receptor (HR) status (positive vs negative) • Post-neoadjuvant therapy pathologic nodal status (positive [ypN1-3] vs negative [ypN0]) • HER2-targeted neoadjuvant therapy approach (single vs dual) The study will be divided into four periods: • The Tissue Screening Period will start on the day of obtaining a signed and dated written Tissue Screening informed consent form (ICF) from the subject prior to collecting tissue from the pre-neoadjuvant therapy biopsy or surgical specimen. Subjects may move into the main Screening Period before HER2 status results are available from central laboratory. • The Screening Period will start on the day of signing the main ICF and will have a maximum duration of 28 days. Rescreening is permitted once during this phase after consultation with the Sponsor if the subject fails initial screening. Eligible subjects will be randomized and enter the Treatment Period. • The Treatment Period starts at randomization and subjects will receive assigned study drug (T-DM1 or T-DXd) for a total of 14 cycles of treatment. First dose at Cycle 1 Day 1 should occur within 7 days after the date the subject is randomized (for subjects with concurrent radiotherapy [RT] or no RT) or within 21 d after last dose of RT (for subjects with sequential RT). For subjects that discontinue either T-DM1 or T-DXd prior to 14 cycles of treatment, subjects may receive additional HER2-targeted therapy as per standard of care (SOC) to complete up to 14 cycles of HER2-targeted treatment. • The Follow-up Period will start upon permanent discontinuation of T-DXd or T-DM1. Subjects will be followed for safety 40 d (+7 d) after the last study treatment administration or before starting new anticancer treatment, whichever comes first. If end of treatment (EOT) is >40 d after last treatment, then the EOT assessments do not need to be repeated at this visit. Disease follow-up to monitor for disease recurrence will be documented every 3 months during study treatment and up to 2 years, every 6 months from 3 to 5 years, and annually from 6 to 10 years until a confirmed IDFS event has occurred. Long-Term Follow-up (LTFU) contact (either visit or telephone call) will be performed every 6 months (±14 d), from the date of confirmed IDFS event, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first. The Primary Completion Date is the date when approximately 207 IDFS events have been recorded, if the study continues after interim analysis. This date is used as the cut-off date for the final analysis of IDFS. All subjects still on treatment or in follow-up at the primary completion date will continue to follow the study schedule of assessments until the overall End of Study (EOS) is reached. Overall EOS will occur when: • all subjects have discontinued treatment and maximum of 10 years follow-up (either disease follow-up or LTFU) from time that first patient has randomized; or • the study is discontinued by the Sponsor for other reasons (administrative, program-level or class-related) The subject*s EOS is the date of their last study visit/contact.

Intervention

Subjects will be randomly assigned to one of the following treatment groups:
1. Group 1: will receive a fixed dose of the study drug T-DXd (dose of 5.4 mg per kg body weight) every three weeks for 14 cycles
2. Group 2: will receive a fixed dose of the comparatory drug T-DM1 (dose of 3.6 mg per kg body weight) every three weeks for 14 cycles

The drugs will be given via an infusion once every three weeks.

Study burden and risks

The subject's participation in this study can last up to 10 years. The study is broken up into 4 main parts: a Tissue Collection Period, a Main Screening Period, a Treatment Period and a Follow-up Period.
In total, the subject will visit the hospital approximately 33 times during this study; each visit will take about 1 to 4 hours to complete.

Please refer to paragraph 1.3 of the protocol (schedule of events) for more information.

The following tests and procedures will take place during these visits:
- Questions are asked about the medical history, demographics and eligibility.
- Measurement of vital signs / physical examination (e.g. blood pressure, pulse and respiratory rate, temperature) and examination of breast area and lymph nodes, heart, lungs and other organ systems as needed), height, weight, check of oxygen saturation
- Eye test
- Blood and urine samples are taken
- Pregnancy test for woman of childbearing potential
- ECG
- ECHO/MUGA
- Chest CT scan
- Mammogram/breast MRI scan
- Tumor biopsy

Possible side effects that are already known are described in the Investigator's Brochure and the subject informed consent form.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Sign and date the tissue screening and main ICFs, prior to the start of any study-specific qualification procedures. 2. Adults >=18 y old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 y old). 3. HER2-positive breast cancer, meeting all of the criteria listed in the protocol (see protocol for full details). 4. Histologically confirmed invasive breast carcinoma at time of disease presentation. Subjects with inflammatory breast cancer are allowed provided all eligibility criteria are met. 5. Clinical stage at disease presentation of T1-4, N0-3, M0 prior to neoadjuvant therapy (Note: patients presenting with T1N0 tumors will not be eligible). 6. Pathologic evidence of residual invasive carcinoma in the breast and/or axillary lymph nodes following completion of neoadjuvant therapy meeting one of the high-risk criteria described in detail in the protocol. 7. Completion of neoadjuvant systemic therapy, including taxane- based chemotherapy and HER2-directed treatment. 8. Adequate excision as confirmed per medical records: surgical removal of all clinically evident disease in the breast and axillary lymph nodes (see Section 8.1.2). 9. An interval of no more than 12 weeks between the date of last surgery and the date of randomization. 10. Known hormone receptor status, per local laboratory assessment, as defined by ASCO-CAP guidelines (>=1%): HR-positive status defined by either positive estrogen receptor (ER) or positive progesterone receptor (PR) status. HR-negative status defined by both known negative ER and known negative PR. 11. Left ventricular ejection fraction (LVEF) >= 50% within 28 days prior to randomization. 12. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 13. Has adequate organ function within 14 days before randomization as defined in the protocol. 14. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 4 months for males and 7 months for females after the last dose of study drug. See protocol for full details 15. Male subjects must not freeze or donate sperm starting at randomization and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm should be considered prior to enrolment in this study. 16. Female

subjects must not donate, or retrieve for their own use, ova from the time of randomization and throughout the study treatment period, and for at least 7 months after the final study drug administration. They should refrain from breastfeeding throughout this time. Preservation of ova may be considered prior to randomization in this study.

Exclusion criteria

1. Stage IV (metastatic) breast cancer. 2. History of any prior (ipsi- or contralateral) breast cancer except lobular carcinoma in situ (LCIS). 3. Evidence of clinically evident gross residual or recurrent disease following neoadjuvant therapy and surgery (see Section 8.1.2.1). 4. An overall response of progressive disease according to the investigator at the conclusion of preoperative systemic therapy 5. Prior treatment with T-DXd, T-DM1 or other anti-HER2 ADC or prior enrollment in any clinical trial with T-DXd (regardless of treatment arm). 6. History of exposure to the following cumulative doses of anthracyclines (see protocol for full details). 7. History of other malignancy within the last 5 years except for appropriately treated carcinoma in situ (CIS) of the cervix, nonmelanoma skin carcinoma, Stage I melanoma skin carcinoma, Stage I uterine cancer, or other appropriately treated non-breast malignancies with an outcome similar to those mentioned above. 8. History of (noninfectious) ILD/pneumonitis that required steroids or has ILD/pneumonitis noted on computed tomography (CT) scan of the chest at Screening (asymptomatic interstitial changes confined to recent radiation therapy fields are not excluded). 9. Known pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (eg, pulmonary emboli within three months prior to randomization, severe asthma, severe chronic obstructive pulmonary disease (COPD), restrictive lung disease, etc.). 10. Any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (eg, Rheumatoid arthritis, Sjogren's, sarcoidosis, etc.), where there is documented, or a suspicion of pulmonary involvement, or pneumonectomy at the time of screening. 11. Uncontrolled or significant cardiovascular disease, including: Medical history of myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV), troponin levels consistent with myocardial infarction as defined according to the manufacturer 28 days prior to randomization. 12. Has a corrected QT interval per Fridericia's formula (QTcF) prolongation to > 470 msec (females) or > 450 msec (males) based on screening 12-lead electrocardiogram (ECG). 13. History of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product. 14. History of severe hypersensitivity reactions to other monoclonal antibodies (MAb). 15. Inadequate washout period before Randomization/Cycle 1 Day 1, as defined in the protocol. 16. Substance abuse or medical conditions such as clinically significant cardiac or psychological conditions, that may, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results. 17. Social, familial, or geographical factors that would interfere with study participation or follow-up. 18. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals. 19. Active primary immunodeficiency, known uncontrolled active (HIV) infection or active hepatitis B or C infection. 20. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade <= 1 or baseline. 21. Is pregnant or breastfeeding or planning to become

pregnant. 22. Has history of receiving live, attenuated vaccine (mRNA and replication-deficient adenoviral vaccines are not considered attenuated live vaccines) within 30 days prior to the first exposure to study intervention.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-03-2022
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Enhertu
Generic name:	Trastuzumab deruxtecan
Product type:	Medicine
Brand name:	Kadcyla
Generic name:	Trastuzumab emtansine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	20-09-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-507961-24-00
EudraCT	EUCTR2020-003982-20-NL
ClinicalTrials.gov	NCT04622319
CCMO	NL75585.029.20