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Trastuzumab deruxtecan treatment for biomarker-selected (HER2 and ctDNA) patients with gastrooesophageal cancer

Submission date 05/05/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 09/10/2023	**Overall study status** Ongoing	
Last Edited 30/01/2025	**Condition category** Cancer	

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-%20trastuzumab-deruxtecan-for-oesophageal-stomach-gastro-oesophageal-junction-cancer-decipher

Background and study aims
Gastrooesophageal (GOA) cancer is a common, global cancer which often presents at an advanced stage. Those diagnosed early will generally have neoadjuvant treatment with FLOT chemotherapy followed by surgery followed by the same FLOT chemotherapy post-surgery. Treatment however is curative in less than 50%. Circulating tumour DNA (ctDNA) is found in the bloodstream. It refers to DNA that comes from cancerous cells and tumours. If ctDNA is positive it means that there are microscopic traces of tumour in the bloodstream (minimal residual disease). Patients who are ctDNA positive after chemotherapy and surgery are less likely to benefit from further FLOT chemotherapy and more likely to relapse. HER2 positive describes cells that have a protein called HER2 on their surface. In normal cells, HER2 helps control cell growth. Cancer cells that make too much HER2 may grow more quickly and are more likely to spread to other parts of the body. Trastuzumab deruxtecan (T-DXd) is an antibody that targets HER2 cells. It attaches to the HER2 cells on the tumour and destroys them. In the UK, trastuzumab deruxtecan (Enhertu) is currently offered to patients with advanced breast cancer who are HER2 positive. In the US, Israel and Japan it is licenced in patients with advanced HER2-positive GOA. DECIPHER aims to treat patients with GOA post-surgery who are both HER2 and ctDNA positive with trastuzumab deruxtecan (Enhertu) instead of standard-care FLOT chemotherapy. The aim of the trial is to treat the minimal residual disease reducing the chance of relapse. All trial patients will be followed for up to 2 years to record their response to treatment.

Who can participate?
Patients aged 18 years and over with biomarker-selected (HER2 and ctDNA) GOA cancer who have received chemotherapy and surgery.

What does the study involve?
When the patient provides consent for the trial and after chemotherapy and surgery, they will

have their ctDNA status confirmed using the Natera Signatera assay. Patients who are ctDNA positive will be treated with trastuzumab deruxtecan at a dose of 6.4 mg/kg intravenously every 21 days for a maximum of 8 cycles, or until disease recurrence. If required, patients may dose reduce to 5.4 mg/kg or 4.4 mg/kg.

During the treatment period of the trial, patients will visit the hospital every three weeks to undergo a physical examination and blood tests to ensure the patient is well enough to continue receiving the treatment. In addition to this, before the first dose of treatment, patients will be asked for an additional blood sample to be sent to a central laboratory. During treatment, patients will undergo a CT scan of their chest, abdomen and pelvis every 12 weeks from registration. Scans will continue for up to 24 months or until disease recurrence. During the study, participants will undergo other procedures and tests to ensure they are not experiencing any side effects from the drug. These procedures include eye tests, pulmonary function tests (or lung function tests), ECGs (electrocardiograms) and ECHO or MUGA scans.

Following treatment, patients will move to the follow-up period of the study, which will last for up to 2 years.

What are the possible benefits and risks of participating?
Participants may benefit from a longer period of disease remission by having the trastuzumab deruxtecan. However, this cannot be guaranteed and there may be no additional benefit in relation to how long the cancer is controlled. The information from this study may help to treat future patients with the same condition in a more effective way. Participants will be helping to further knowledge of how to treat cancer and this will also benefit society as a whole.
The main risks are the potential side effects from trastuzumab deruxtecan, however, the patient will be monitored regularly to assess any side effects of the treatment.
During the trial, additional blood will be collected from a vein, which may cause pain where the needle is inserted. There is a small risk of bruising or infection at the site of insertion. Some people may experience dizziness, an upset stomach or fainting when blood is taken, but every effort will be made by hospital staff to minimise this.
During the trial, participants will have high-resolution CT scans to assess their cancer. Some of these will be extra to those that would be completed as part of standard care. CT scans use ionising radiation to form images of the body. Ionising radiation may cause cancer many years or decades after exposure. In patients with the clinical condition under investigation in this trial, the chance of this happening is extremely small.

Patients may also have 2 MUGA scans, in centres where an ECHO is not performed, 1 of which will be extra to standard of care. The MUGA scan involves the injection of a radioactive marker into the bloodstream. The radiation dose from the procedure is equivalent to around 2 years' natural background radiation in the UK.

Where is the study run from?
Southampton Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
May 2023 to September 2028

Who is funding the study?
AstraZeneca (UK)

Who is the main contact?
DECIPHER Trial Team, decipher@soton.ac.uk

Contact information

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Public

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Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-003445-34

Integrated Research Application System (IRAS)
1006810

ClinicalTrials.gov (NCT)
NCT05965479

Protocol serial number
68838, IRAS 1006810, CPMS 55880

Study information

Scientific Title
DECIPHER: A single-arm phase II trial of trastuzumab deruxtecan in patients with gastrooesophageal adenocarcinoma cancer who are ctDNA and HER2 positive

Acronym
DECIPHER

Study objectives
Does T-DXd reduce micrometastatic disease burden in HER2-positive GOA patients who are ctDNA positive after chemotherapy and surgery?

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 18/09/2023, North East – Tyne & Wear South Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle Upon Tyne, NE2 4NQ, United Kingdom; +44 (0)207 104 8282; tyneandwearsouth.rec@hra.nhs.uk), ref: 23/NE/0104

Study design
Single-arm Phase II study

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Gastrooesophageal adenocarcinoma cancer

Interventions
Patients with pathologically documented adenocarcinoma of the stomach (the clinical stage before surgery of AJCC I-III), gastrooesophageal junction, or oesophagus, with HER2 overexpression (IHC 3+ or IHC2+/ISH+) based on local tissue testing results, will be recruited from a secondary care setting.
After chemotherapy and surgery, patients will have their ctDNA status confirmed using the Natera Signatera assay. Patients who are ctDNA positive will be treated with trastuzumab deruxtecan at a dose of 6.4 mg/kg intravenously every 21 days for a maximum of 8 cycles, or until disease recurrence. If required, patients may dose reduce to 5.4 mg/kg or 4.4 mg/kg. No dose re-escalation is permitted. During treatment, patients will be seen in the clinic every 3 weeks for monitoring. Patients will receive 12 weekly CT scans and ctDNA blood samples throughout the trial, which will be used to ascertain disease status.
Following treatment, patients will remain in follow-up for up to two years or until disease recurrence.

Intervention Type
Biological/Vaccine

Phase

Phase II

Drug/device/biological/vaccine name(s)
Trastuzumab deruxtecan

Primary outcome(s)
Percentage of people who are classed as ctDNA negative (ctDNA clearance yes/no) measured using the Signature ctDNA assay Signatera after 4 cycles of trastuzumab deruxtecan

Key secondary outcome(s))
1. ctDNA clearance measured using the Signature ctDNA assay Signatera after each cycle of trastuzumab deruxtecan
2. Disease-free survival. Time from surgery to recurrence of macroscopic disease on radiological imaging or death, expressed as Kaplan-Meier estimates of median DFS and percentage disease free at 12m and 24m
3. Overall survival after each cycle and follow-up visit. Time from surgery to death, expressed as Kaplan-Meier estimates of median OS and percentage alive at 12m, 18m and 24m
4. Symptoms and quality of life, as measured by the QLQ-C30, QLQ-OG25 and EQ-5D-5L questionnaires throughout the trial
5. Occurrence of adverse events (AEs), serious adverse events (SAEs), and changes from baseline in laboratory parameters, vital signs, and body weight throughout the trial

Completion date
30/09/2028

Eligibility

Key inclusion criteria
Current inclusion criteria as of 30/01/2025:
1. Pathologically documented adenocarcinoma of the stomach, gastrooesophageal junction, or lower oesophagus ypTanyNanyM0 with HER2 overexpression (IHC 3+ or IHC 2+/ISH+) based on local tissue testing results
2. ctDNA positive after surgery as per Signatera assay
3. Capable of giving signed informed consent prior to any mandatory study-specific procedures, sampling, or analyses and which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
4. Male and female participants must be at least 18 years of age at the time of signing the ICF
5. Treated with neoadjuvant chemotherapy before surgery for at least six weeks
6. Surgical resection with clear margins (R0)
7. Recovered from surgery in the opinion of the investigator
8. No previous treatment with trastuzumab or other HER2-directed therapy
9. No evidence of metastatic disease on post-surgical CT
10. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
11. Has LVEF ≥ 50% by either echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 28 days before treatment
12. Has adequate organ and bone marrow function within 14 days before treatment allocation as below:
12.1. Platelet count ≥ 100x109 (Platelet transfusion is not allowed within 1 week prior to screening assessment, use of thrombopoietin receptor agonists is not allowed within 2 weeks prior to screening assessment)
12.2. Hemoglobin ≥ 80 g/L. Participants requiring transfusions or growth factor support to

maintain hemoglobin ≥ 80 g/L are not eligible. (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
12.3. Absolute neutrophil count ≥ 1.5 x 109 (granulocyte-colony stimulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment)
12.4. ALT/ AST ≤ 3 × ULN
12.5. Total bilirubin ≤ 1.5 × ULN or < 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia)
12.6. Serum albumin ≥ 2.5 g/dL
12.7. Creatinine clearance ≥ 50 mL/min as calculated using the Cockcroft-Gault equation
12.8. Adequate clotting function International normalized ratio (INR) or prothrombin time and either partial thromboplastin or activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN

Previous inclusion criteria:
1. Pathologically documented adenocarcinoma of the stomach (clinical stage before surgery of AJCC I-III), gastrooesophageal junction, or lower oesophagus (to include Type I Siewert only), with HER2 overexpression (IHC 3+ or IHC 2+/ISH+) based on local tissue testing results
All other inclusion criteria were the same

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase the risk of incurring AEs, or compromise the ability of the participant to give written informed consent.
2. Participants with a medical history of myocardial infarction within 6 months before treatment or symptomatic CHF (New York Heart Association Class II to IV), unstable angina pectoris, clinically important cardiac arrhythmias, or a recent (< 6 months) cardiovascular event, including myocardial infarction, unstable angina pectoris, and stroke. Participants with troponin levels above ULN at screening (as defined by the manufacturer), and without any myocardial-related symptoms, should have a cardiologic consultation before enrollment to rule out myocardial infarction.
3. Corrected QT interval (QTcF) prolongation to > 470 msec (females) or > 450 msec (males) based on an average of the screening triplicate 12-lead ECG.
4. History of (non-infectious) ILD/pneumonitis, current ILD/pneumonitis, or where suspected ILD /pneumonitis cannot be ruled out by imaging at screening.
5. Any of the following:
5.1. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any

underlying pulmonary disorder (eg, clinically significant pulmonary emboli within 3 months of treatment, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, clinically significant pleural effusion etc.)
5.2. Any autoimmune, connective tissue, or inflammatory disorders with pulmonary involvement (eg, rheumatoid arthritis, Sjogren's, sarcoidosis etc.), where there is documented, or suspicion of, pulmonary involvement at the time of Screening.
. 5.3. Prior pneumonectomy (complete)
6. Uncontrolled infection requiring intravenous (IV) antibiotics, antivirals, or antifungals.
7. Multiple primary malignancies within the prior 3 years, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumours curatively treated.
8. A pleural effusion, ascites or pericardial effusion that requires drainage, peritoneal shunt.
9. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. The following exemption will apply; stable chronic G2 toxicity which in the opinion of the investigator is not reasonably expected to be exacerbated by treatment with study drugs.
10. Known allergy or hypersensitivity to T-DXd or any of the study drug excipients.
11. History of severe hypersensitivity reactions to other monoclonal antibodies.
12. Pregnant or breastfeeding female participants, or participants who are planning to become pregnant.
13. Involvement in the planning and/or conduct of the study
14. Has substance abuse or any other medical 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.
15. Receipt of live, attenuated vaccine within 30 days prior to the first dose of trastuzumab deruxtecan. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of IMP
16. Active primary immunodeficiency, known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
17. Judgment by the Investigator that the participant should not participate in the study, if the participant is unlikely to comply with study procedures, restrictions, and requirements.

Date of first enrolment
10/04/2024

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Wales

Study participating centre
Southampton General Hospital
Tremona Road
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Study participating centre
St. James's University Hospital
Beckett Street
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Study participating centre
Churchill Hospital
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Study participating centre
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Clifford Bridge Road
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
University of Southampton

ROR
https://ror.org/01ryk1543

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Individual participant data will be made available, including data dictionaries, for approved data-sharing requests. Individual participant data will be shared that underlie the results reported in this article, after de-identification and normalisation of information (text, tables, figures, and appendices). The study protocol and statistical analysis plan will also be available. Anonymous data will be available for request from three months after publication of the article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate, signed a Data Sharing Agreement. Data will be shared once all parties have signed relevant data-sharing documentation, covering SCTU conditions for sharing and if required, an additional Data Sharing Agreement from Sponsor. Proposals should be directed to ctu@soton.ac.uk.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		28/11/2024	30/01/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes