An Open-label, Randomized, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Trastuzumab Deruxtecan as First-line Treatment of Unresectable, Locally Advanced, or Metastatic NSCLC Harboring HER2 Exon 19 or 20 Mutations (DESTINY-Lung04)

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This study has been transitioned to CTIS with ID 2023-503674-20-00 check the CTIS register for the current data. Primary objective: To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of PFS by BICR...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52083

Source
ToetsingOnline

Brief title
DESTINY-Lung04

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Locally advanced or metastatic NSCLC harboring HER2 exon 19 or 20 mutations, lungcancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: AstraZeneca

Intervention

Keyword: First line treatment, HER2, Non Small Cell Lung Cancer, Trastuzumab Deruxtecan

Outcome measures

Primary outcome

To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of PFS by BICR in participants with unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations.

PFS is defined as time from randomization until progression per RECIST 1.1 as assessed by BICR, or death due to any cause. The analysis will include all randomized participants, regardless of whether the participant withdraws from randomized therapy or receives another anticancer therapy.

The measure of interest is the HR of PFS.

Secondary outcome

- To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of OS.

- To further assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab in terms of PFS by investigator assessment, ORR, DoR, PFS2, and landmark analysis of PFS12 and OS24.

- To assess the efficacy of T-DXd relative to platinum with pemetrexed plus

pembrolizumab by assessment of CNS-PFS (per RECIST 1.1).

- To assess the safety and tolerability of T-DXd as compared to platinum with pemetrexed plus pembrolizumab.

- To assess the PK of T-DXd, total anti-HER2 antibody and DXd in serum.

- To investigate the immunogenicity of T-DXd.

- To assess the benefit of T-DXd relative to platinum with pemetrexed plus pembrolizumab with patientreported pulmonary symptoms associated with NSCLC.

- To describe patient-reported tolerability of T-DXd as compared to platinum with pemetrexed plus pembrolizumab.

Study description

Background summary

Lung cancer remains the leading cause of cancer-related mortality worldwide accounting for approximately 18% of all cancer deaths globally in 2018 (Bray et al 2018). The SoC treatment for patients with metastatic NSCLC is currently based on molecular characterization and matched targeted therapy for specific driver-mutated subsets (Heigener et al 2019). For metastatic NSCLC patients without EGFR or ALK genomic tumor aberrations, platinum-doublet chemotherapy with anti-PD-1/PD-L1 targeting immunotherapy (including pembrolizumab) is the current SoC based on results from KEYNOTE189 (Gandhi et al 2018).

There are several driver mutations for which targeted therapies have been approved, including EGFR, MET, ALK fusions, BRAF, MEK, ROS1, NTRK, RET fusions, EGFR exon 20 insertion, and KRAS G12C (Mazieres et al 2013, NCCN 2021). Although HER2 alterations have been widely studied as a predictive biomarker in breast cancer, with multiple therapeutic options, there have yet to be any approved therapies (targeted or not) for HER2 alterations in metastatic NSCLC. Available data suggest that therapies may result in poorer clinical outcomes in HER2-mutated NSCLC patients compared to NSCLC patients without driver mutations (Lai et al 2018; Mazieres et al 2019; Dziadziuszko et al 2019).

Study DS8201 A U204 (Smit et al 2020) provided encouraging preliminary clinical

efficacy data for T-DXd as monotherapy in the later-line setting for NSCLC harboring HER2 mutations. Given the efficacy observed in later-line settings and the current unmet for targeted therapies in treatment of metastatic NSCLC harboring HER2 mutations, it is of interest to evaluate the efficacy of T-DXd compared to currently available standard of care of platinum doublet chemotherapy with immunotherapy in the first-line setting. In this Phase 3 study, participants with unresectable, locally advanced, or metastatic NSCLC harboring a HER2 exon 19 or 20 mutation will be randomized to T-DXd or platinum with pemetrexed plus pembrolizumab Q3W to evaluate efficacy in treatment-naïve patients.

Study objective

This study has been transitioned to CTIS with ID 2023-503674-20-00 check the CTIS register for the current data.

Primary objective: To assess the efficacy of T-DXd relative to platinum with pemetrexed plus pembrolizumab by assessment of PFS by BICR in participants with unresectable, locally advanced, or metastatic NSCLC harboring HER2 exon 19 or 20 mutations.

Study design

This is a Phase 3, randomized, open-label, 2-arm, multicenter, international study assessing the efficacy and safety of T-DXd compared with SoC (platinum-based chemotherapy with pemetrexed in combination with pembrolizumab) in patients with NSCLC harboring HER2 exon 19 or 20 mutations.

Intervention

Participants will be randomized in a 1:1 ratio to one of the following interventions: T-DXd (Arm 1) or platinum (cisplatin or carboplatin; up to 4 cycles) with pemetrexed plus pembrolizumab Q3W (Arm 2). Randomization will be stratified by smoking history and presence of brain metastasis at baseline.

- Participants in Arm 1 (T-DXd) will receive 5.4 mg/kg of T-DXd as an IV infusion Q3W until RECIST 1.1-defined progression by investigator, until unacceptable toxicity, withdrawal of consent, or other discontinuation criteria. or other discontinuation criteria (with the exception of CNS-PD; see note below).
- Participants in Arm 2 (active comparator arm) will receive platinum chemotherapy (cisplatin or carboplatin) with pemetrexed and pembrolizumab Q3W. Note: Investigator choice of cisplatin or carboplatin (switch from cisplatin to carboplatin during the treatment period is permitted). Platinum chemotherapy will be administered for up to 4 cycles. Pembrolizumab and pemetrexed will be administered until RECIST 1.1-defined progression by investigator, until

unacceptable toxicity, withdrawal of consent, or other discontinuation criteria (with the exception of CNS-PD; see note below).

Note: In both arms, participants with objective radiological CNS-PD (based on RECIST 1.1), who in the investigator*s opinion, continue to receive benefit from their assigned treatment and meet the criteria for treatment in the setting of CNS-PD may continue to receive therapy on trial for as long as they are gaining clinical benefit and are without any discontinuation criteria, until one of the criteria Section 6.1.1.2 is met.

Study burden and risks

Patients need to come to the hospital more often and visits are longer.
Patients will undergo the following actions during the study:
- History (including medical history)
- Pulmonary function tests at screening and if ILD/pneumonitis is suspected
- ECHO/MUGA scan (LVEF assessment)
- Ophthalmologic assessments
- 12-Lead ECG
- Vital signs (blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation)
- Height and weight measurement
- ECOG performance status
- Physical examination
- Laboratory assessments (blood / urine / pregnancy test (if applicable))
- Questionnaires
- AE/SAE assessments
- CT/MRI of abdomen, chest and pelvis at screening, Q6W (± 1 week) for 54 weeks, and then Q9W (± 1 week), starting at Week 63, at end of treatment
- Brain metastasis assessments (CT/MRI) at screening, Required Q6W (± 1 week) for 54 weeks, and then Q9W (± 1 week), starting at Week 63 for participants with brain metastasis, or as needed based on neurological symptoms for all participants, at end of treatment
- HRCT of the chest at screening and if ILD/Pneumonitis is suspected
- Study intervention administration
- Biopsy at screening (if no tumor tissue is available or if it is insufficient)
- Biopsy at progression (optional)

The study drugs can also cause side effects. These side effects of T-DXd are very common (may affect more than 1 in 10 people):
• Nausea
• Feeling tired (Fatigue)
• Vomiting
• Hair loss (Alopecia)
• Constipation
• Feeling less hungry (Anorexia)
• Decrease in the number of red blood cells (Anemia). This may cause you to

feel tired or weak.
• Decrease in the number of white blood cells (includes decrease in neutrophils (neutropenia), leukocytes (Leukopenia) and lymphocytes (Lymphopenia). White blood cells help to fight infection.
• Diarrhea
• Decrease in the number of platelets (Thrombocytopenia). Platelets help the blood to clot
• Coughing
• Stomach (abdominal) pain
• Infections of the upper respiratory tract
• Headache
• Indigestion (Dyspepsia)
• Dry eye
• Dizziness
• Sores in or around your mouth (Stomatitis)
• Abnormal liver enzyme results (Increase in aspartate aminotransferase and increase in alanine aminotransferase). An enzyme is a type of protein in the blood. Abnormal levels are not normally associated with symptoms but may indicate a problem with your liver.
• Difficulty breathing (Dyspnea)
• Severe nose bleeds (Epistaxis)
• Lung problems (Interstitial Lung Disease)
• Low potassium in the blood (Hypokalemia). Potassium is a mineral which helps your nerves, muscles and heart function normally.
• Rash
• Fever (Pyrexia)
• Swelling of lower legs or hands (Edema peripheral)

These side effects of T-DXd are common (may affect up to 1 in 10 people):
• Reactions related to the infusion of the medicine (described below).
• Fever along with a decrease in the number of neutrophils (Febrile neutropenia)
• Abnormal liver function
• Abnormal liver enzyme results (Increase in blood alkaline phosphatase). An enzyme is a type of protein in the blood. Abnormal levels are not normally associated with symptoms but may indicate a problem with your liver.
• Blood bilirubin increased. Bilirubin is a yellow substance in the blood, produced by breakdown of red blood cells, which is normally removed by the liver. Increase may cause yellowing of the skin and might indicate a problem with your liver.
• Dehydration
• Itching (Pruritis)
• Pneumonia (An infection of the lungs).

The following serious side effect has been reported with the use of T-DXd
• Lung problems (pneumonitis/interstitial lung disease): trastuzumab deruxtecan may cause lung problems that may be life-threatening or fatal. Symptoms may be

similar to other lung or heart diseases. Contact your doctor right away if you have any new or worsening lung symptoms, including trouble breathing, shortness of breath, cough or fever.

The risks described below could possibly be observed with trastuzumab deruxtecan administration:
• Heart problems: shortness of breath, noticeably rapid, strong or irregular heartbeat or abnormally rapid heart rate.
• Trastuzumab deruxtecan Allergic reactions/Hypersensitivity: rash, joint pain, face, lip or tongue swelling, wheezing and difficulty breathing, and/or sudden drop in blood pressure. A severe allergic reaction could be life threatening.
• Infusion reaction: fever, chills, nausea, vomiting, headache, cough, dizziness, rash, and/or lower back pain usually of mild to moderate severity and may lead to shortness of breath and severe lowering of blood pressure.

Risks associated with chemotherapy (cisplatin, carboplatin and pemetrexed):
• Risk of Infection, bruising and bleeding
• Anemia (low number of red blood cells): This may make you feel tired and breathless.
• Feeling sick and being sick
• Loss of appetite
• Diarrhea or constipation
• Abdominal pain
• Tiredness
• Hair loss
• Changes in the way the liver works
• Changes in the way the kidneys work
• Decreases in the level of sodium, potassium, calcium and magnesium in your blood
• Numb or tingling hands or feet: due to the effect of carboplatin or cisplatin on nerves.
• Taste changes
• Changes in hearing: You may get ringing in your ears (tinnitus)
• Skin changes, including rash
• Pain in the joints and muscles
• Blood test abnormalities (low electrolytes)

Risks associated with pembrolizumab:

Most common adverse (reported in >=20% of patients):
• Fatigue
• Musculoskeletal Pain
• Decreased Appetite
• Pruritus
• Diarrhea
• Nausea
• Rash

• Pyrexia
• Cough
• Dyspnea
• Constipation
• Pain
• Abdominal Pain

Risks associated with Pembrolizumab in combination with chemotherapy
• Fatigue/asthenia
• Nausea
• Constipation
• Diarrhea
• Decreased appetite
• Rash
• Vomiting
• Cough
• Dyspnea
• Pyrexia
• Alopecia
• Peripheral neuropathy
• Mucosal Inflammation
• Stomatitis
• Headache

Contacts

Public
Astra Zeneca

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Male and female participants at least 18 years of age
- Locally advanced not amenable to curative therapy, or metastatic disease
- Histologically documented non-squamous NSCLC with HER2 mutation in exons 19 or 20 by tissue NGS or ctDNA
- Treatment-naïve for palliative intent systemic therapy for locally advanced or metastatic disease
- Left ventricular ejection fraction (LVEF) >= 50%
- Measurable disease assessed by Investigator based on RECIST v1.1
- Protocol-defined adequate organ function including cardiac, renal, hepatic function
- ECOG 0-1
- Having tumour tissue available for central testing

Exclusion criteria

- Tumors with targetable alterations to EGFR (or other targetable mutations including but not limited to ALK, if routinely tested as a targetable alteration with approved available therapy)
- Any clinically active brain metastases; previously treated brain metastases allowed
- Active autoimmune or inflammatory disorders
- Medical history of myocardial infarction within 6 months prior to randomization
- History of non-infectious pneumonitis/ILD, current or suspected ILD
- Lung-specific intercurrent clinical significant severe illness
- Contraindication to platinum-based doublet chemotherapy or pembrolizumab

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):	24-03-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta
Generic name:	pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatinum
Generic name:	carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Enhertu
Generic name:	Trastuzumab Deruxtecan (T-DXd)
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Keytruda

Generic name:	pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Platinol
Generic name:	cisplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-11-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-04-2022

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	CTIS2023-503674-20-00
EudraCT	EUCTR2021-000634-33-NL
ClinicalTrials.gov	NCT05048797
CCMO	NL78412.056.21