HERTHENA-Lung02: A Phase 3, Randomized, Open-label Study of Patritumab Deruxtecan Versus Platinum-based Chemotherapy in Metastatic or Locally Advanced Epidermal Growth Factor Receptor-mutated (EGFRm) Non-small Cell Lung Cancer (NSCLC) After Failure of Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) Therapy

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This study has been transitioned to CTIS with ID 2023-507964-38-00 check the CTIS register for the current data. To compare the efficacy of patritumab deruxtecan versus platinumbased chemotherapy, as measured by progression-free survival (PFS),...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56070

Source
ToetsingOnline

Brief title
Phase 3 Study of Patritumab Deruxtecan Vs Chemotherapy in EGFRm NSCLC

Condition

- Other condition

Synonym
Lung cancer, Non-small cell lung cancer

Health condition

Non-squamous nonsmall cell lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Daiichi Sankyo, Inc., Patritumab Deruxtecan, U31402-A-U301

Outcome measures

Primary outcome

PFS as assessed by BICR based on RECIST v1.1

Secondary outcome

-Overall survival

-PFS as assessed by the Investigator per RECIST v1.1

-PFS2 as assessed by local standard clinical practice

-ORR as assessed by BICR and as assessed by the Investigator per RECIST v1.1

-DoR as assessed by BICR and as assessed by the Investigator per RECIST v1.1

-CBR as assessed by BICR and as assessed by the Investigator per RECIST v1.1

-DCR as assessed by BICR and as assessed by the Investigator per RECIST v1.1

-TTR as assessed by BICR and as assessed by the Investigator per RECIST v1.1

-Change from baseline for 5 symptoms assessed by NSCLC-SAQ, and 5 functioning

scales and global health status and

overall quality of life assessed by EORTC QLQC30

-Descriptive statistics of safety endpoints

-Descriptive summary of baseline tumor tissue HER3 status and a correlative

analysis between HER3 protein expression level and efficacy

-ADA prevalence and incidence. ADA is measured in the serum via a validated

assay.

-Intracranial PFS as assessed by BICR per CNS-RECIST

Study description

Background summary

Lung cancer is the second most common cancer and is the leading cause of cancer-related mortality worldwide, with an estimated 2.2 million new cases of lung cancer in 2020 (11.4% of all new cases) and 1.8 million deaths (18.0% of all cancer deaths) globally based on GLOBOCAN data. Low lung cancer survival rates reflect the large proportion of patients diagnosed with advanced disease (57%). Only 21.7% of all patients with lung cancer are alive 5 years or more after initial diagnosis.

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers. Multiple genomic alterations that guide therapeutic decision making have been identified in NSCLC. These genomic alterations include epidermal growth factor receptor (EGFR) gene mutations, among which a subset is associated with tumor sensitivity to EGFR tyrosine kinase inhibitors (TKIs), anaplastic lymphoma kinase (ALK) gene rearrangements associated with response to ALK TKIs, ROS proto-oncogene 1 (ROS1) gene rearrangements associated with responsiveness to ROS1 TKIs, neurotrophic tyrosine receptor kinase (NTRK) gene fusions associated with responsiveness to NTRK inhibitors, B-Raf proto-oncogene (BRAF) point mutations associated
with responsiveness to combined therapy with inhibitors of BRAF and mitogen-activated protein kinase (MEK), and other genomic alterations.5 Molecular testing is part of the standard of care in the evaluation of NSCLC during initial diagnosis and often when salvage therapies are being

considered.

Patritumab deruxtecan (U3-1402; HER3-DXd) is an antibody-drug conjugate (ADC) comprising a recombinant fully human antihuman epidermal growth factor receptor 3 (HER3) immunoglobulin G1 (IgG1) monoclonal antibody (mAb) (patritumab, U3-1287) covalently linked to MAAA-1162a (glycine-glycine-phenylalanine-glycine tetrapeptide linker containing a topoisomerase I inhibitor [MAAA-1181a]). MAAA-1181a, a derivative of exatecan (DX-8951f), is released after internalization and leads to apoptosis of the target tumor cells through the inhibition of topoisomerase I.
As supported by the clinical observations described below from the U31402-A-U102 study of subjects with EGFRm NSCLC after failure of EGFR TKI therapy, patritumab deruxtecan constitutes a promising investigational therapy for subjects with EGFRm NSCLC. Study U31402-A-U301 is designed to assess the efficacy and safety of patritumab deruxtecan in comparison to platinum-based chemotherapy in subjects with EGFRm NSCLC after failure of EGFR TKI therapy.

Study objective

This study has been transitioned to CTIS with ID 2023-507964-38-00 check the CTIS register for the current data.

To compare the efficacy of patritumab deruxtecan versus platinumbased chemotherapy, as measured by progression-free survival (PFS), in subjects with metastatic or locally advanced nonsquamous non-small cell lung cancer (NSCLC) with an EGFR-activating mutation (exon 19 deletion or L858R).

Study design

This is a global, multicenter, open-label, randomized, Phase 3 study designed to evaluate the efficacy and safety of patritumab deruxtecan versus platinum plus pemetrexed in subjects with metastatic or locally advanced nonsquamous NSCLC with an EGFR-activating mutation (exon 19 deletion or L858R) who have received 1 or 2 prior lines of EGFR TKI treatment (including a third-generation EGFR TKI [eg, osimertinib, lazertinib, aumolertinib, alflutinib) and have had disease progression on or following treatment with a third-generation EGFR TKI. Eligible subjects will be randomized in a 1:1 ratio to receive:

- Patritumab deruxtecan 5.6 mg/kg every 3 weeks (q3W), OR
- Platinum-based chemotherapy for 4 cycles: pemetrexed (500 mg/m2) plus either cisplatin (75mg/m2) or carboplatin (target area under the curve 5 [AUC5] by using the Calvert formula) q3W. Subjects without disease progression after 4 cycles of platinum plus pemetrexed therapy may continue treatment with maintenance pemetrexed (500 mg/m2 q3W) with no restriction on the number of

cycles.

Randomization will be stratified by the prior third-generation EGFR TKI used in the metastatic or locally advanced setting (osimertinib, other), line of prior third-generation EGFR TKI use in the metastatic or locally advanced setting (first-line, second-line), region (Asia, rest of world), and presence of brain metastases (present,absent).

Intervention

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Study burden and risks

-The study will take about 49 months in total for patients.
-Additional visits to the hospital, additional physical tests, including a test for HIV, hepatitis B and C and pregnancy.
-In total 150mL blood will be taken. This amount won't cause any problems (to compare: a blood donation involves 500ml of blood being taken each time). Possible side effects of blood tests are fainting, sore spot and sensitive area at the injection site and, in rare cases, an infection.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Sign and date the main ICF, prior to the start of any study-specific qualification procedures. Consent for the optional samples for EOT tumor biopsy and/or pharmacogenetic analysis will be covered in the main ICF.
A separate tissue screening consent will be obtained from all subjects to meet the baseline biopsy requirement.
2. Is a male or female subject aged >=18 years (follow local regulatory requirements if the legal age of consent for study participation is >18 years old).
3. Has histologically or cytologically documented metastatic or locally advanced nonsquamous NSCLC not amenable to curative surgery or radiation.
4. Has documentation of an EGFR-activating mutation detected from tumor tissue or from blood sample: exon 19 deletion or L858R at diagnosis or thereafter.
5. Received 1 or 2 prior line(s) of an approved EGFR TKI treatment in the metastatic or locally advanced setting, which must include a thirdgeneration EGFR TKI (ie, approved therapies designed with higher preferential activity for mutant vs. EGFRwt and that address acquired resistance to first- and second-generation EGFR TKI [eg, osimertinib, lazertinib, aumolertinib, alflutinib, and others in consultation with Medical Monitor]). If a subject has received 2 prior lines of EGFR TKI therapy, administration of the third-generation EGFR TKI must have been in the most recent line. Subject must have documentation of T790M mutation if subjects had treatment with a first- or second-generation EGFR TKI prior to treatment with a third-generation EGFR TKI. Enrollment of subjects receiving third-generation EGFR TKIs other than osimertinib will be a maximum of approximately 20% of the enrolled population in each treatment arm.
6. May have received either neoadjuvant and/or adjuvant treatment if progression to metastatic or locally advanced disease occurred at least 12 months after the last dose of such therapy and subsequently experienced disease progression on or after third-generation EGFR TKI treatment administered in the metastatic or locally advanced setting.
a. To provide an example, a patient who received osimertinib as adjuvant therapy after tumor resection, then progressed to having metastatic disease over a year following completion of adjuvant therapy must have also received a third-generation EGFR TKI as treatment for metastatic disease to be considered eligible for this study.
7. Has not received any other prior systemic therapies in the metastatic or

locally advanced setting (including chemotherapy, immunotherapy etc) (even if administered in combination with EGFR TKI).
8. Has documentation of radiographic disease progression while receiving or after a third-generation EGFR TKI for metastatic or locally advanced disease.
9. Has at least 1 measurable lesion as per RECIST v1.1 by Investigator assessment.
10. Is willing to provide sufficient quantity and quality of tumor tissue content.
11. Has an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 at Screening.
12. Has adequate bone marrow reserve and organ function based on local laboratory data within 14 days prior to randomization as described in the protocol.
13. If the subject is a female of childbearing potential, must have a negative serum pregnancy test at Screening and must be willing to use highly effective birth control upon randomization, during the Treatment Period, and for 7 months following the last dose of patritumab deruxtecan. A female is considered to be of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) or if permanently sterile (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) with surgery at least 1 month before randomization or confirmed by follicle stimulating hormone (FSH) test. For comparator drugs, the investigators should follow local practice guidelines and/or label approved in their country.
14. Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study Treatment Period and for at least 7 months after the final patritumab deruxtecan administration. For comparator drugs, the investigators should follow local practice guidelines and/or label approved in their country.
15. If male, must be surgically sterile or willing to use highly effective birth control upon randomization, during the Treatment Period, and for at least 4 months following the last dose of patritumab deruxtecan. For comparator drugs, the investigators should follow local practice guidelines and/or label approved in their country.
16. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period and at least 4 months after the final patritumab deruxtecan administration. For comparator drugs, the investigators should follow local practice guidelines and/or label approved in their country.
For the full list of criteria, please see section 5.1 in protocol

Exclusion criteria

1. Has any previous histologic or cytologic evidence of small cell OR combined small cell/non-small cell disease in the archival tumor tissue or pretreatment tumor biopsy, or squamous NSCLC histology.

2. Has any history of ILD (including pulmonary fibrosis or radiation pneumonitis), has current ILD, or is suspected to have such disease by imaging during Screening.
3. Has clinically severe respiratory compromise (based on the Investigator's assessment) resulting from intercurrent pulmonary illnesses as described in the protocol.
4. Is receiving chronic systemic corticosteroids dosed at >10 mg prednisone or equivalent anti-inflammatory activity or any form of immunosuppressive therapy prior to randomization. Subjects who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.
5. Has any history of or evidence of current leptomeningeal disease.
6. Has evidence of clinically active spinal cord compression or brain metastases, defined as being symptomatic and untreated, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive or treated brain metastases who are asymptomatic (i.e., without neurologic signs or symptoms and not requiring treatment with corticosteroids or anticonvulsants) may be included in the study but must have a stable neurologic status for at least 2 weeks prior to randomization. Subjects with asymptomatic brain metastases and treated with anticonvulsants as prophylaxis are able to enrol.
7. Has had inadequate washout period prior to randomization defined as follows:
a. Whole brain radiation therapy <28 days or stereotactic brain radiation therapy <7 days.
b. Major surgery (excluding placement of vascular access) <28 days.
c. Radiotherapy treatment to >30% of the bone marrow or with a wide field of radiation <28 days or palliative radiation therapy <7 days.
d. Chloroquine or hydroxychloroquine <=14 days.
e. Live virus vaccination <=28 days.
8. Has had prior treatment with the following:
a. Any agent including an ADC containing a chemotherapeutic agent targeting topoisomerase I.
b. HER3 antibody.
c. Any systemic therapies (other than EGFR TKIs) in the metastatic or locally advanced setting, including chemotherapy or any other systemic therapy in combination with an EGFR TKI.
9. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved by the National Cancer Institute - Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0), Grade <=1 or baseline. Subjects with chronic Grade 2 toxicities [defined as no worsening to Grade >2 for at least 3 months prior to randomization and managed with SoC treatment]) that the Investigator deems related to previous anticancer therapy may be randomized.
10. Has history of other active malignancy within 3 years prior to randomization, except the following:
a. Adequately resected nonmelanoma skin cancer.
b. Adequately treated intraepithelial carcinoma of the cervix.

c. Any other curatively treated in situ disease.
11. Has uncontrolled or significant cardiovascular disease prior to randomization as described in the protocol.
12. Has active hepatitis B and/or hepatitis C infection, such as those with serologic evidence of active viral infection within 28 days of randomization.
13. Has a known HIV infection that is not well controlled. All the following criteria are required to define an HIV infection that is well controlled: undetectable viral ribonucleic acid (RNA) load, CD4+ counts/levels of >350 cells/µL, no history of AIDS-defining opportunistic infection within the past 12 months, and stable for at least 3 weeks on same anti-HIV retroviral medications. If an HIV infection meets the above criteria, the subject's viral RNA load and CD4+ cell count should be monitored per local SoC (e.g., every 3 months).
14. Has any evidence of severe or uncontrolled diseases (eg, active bleeding diatheses, active infection) psychiatric illness/social situations, geographical factors, substance abuse, or other factors that, in the Investigator's opinion, make it undesirable for the subject to participate in the study or that would jeopardize compliance with the protocol. Screening for chronic conditions is not required for eligibility.
15. Has known hypersensitivity to either the drug substance or inactive ingredients in any of the drug products.
16. Is a female who is pregnant or breastfeeding or intends to become pregnant during the study.
For full list of exclusion criteria, refer to section 5.2 of the protocol.

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: Pending

Start date (anticipated):	01-02-2023
Enrollment:	18
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Patritumab Deruxtecan
Generic name:	Patritumab Deruxtecan
Product type:	Medicine
Brand name:	Pemetrexed
Generic name:	Pemetrexed
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-08-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-01-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-01-2023

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	10-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-03-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2024
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	CTIS2023-507964-38-00
EudraCT	EUCTR2021-005879-40-NL
ClinicalTrials.gov	NCT05338970
CCMO	NL81196.056.22