HERTHENA-Lung01: A Phase 2 Randomized Open-Label Study of Patritumab Deruxtecan (U3-1402) in Subjects with Previously Treated Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer (NSCLC)

Published: 06-10-2020
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This study has been transitioned to CTIS with ID 2024-512238-13-00 check the CTIS register for the current data. Primary objective: 1. To investigate the antitumor activity of patritumab deruxtecan in subjects with metastatic or locally advanced...

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

Summary

ID

NL-OMON52116

Source
ToetsingOnline

Brief title
U31402-A-U201

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lung Caner, Metastatic or Locally Advanced Non-Small Cell Lung Cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: EGFR mutaded NSCLC, Metastatic or Locally Advanced, Open-Label, Patritumab Deruxtecan (U3-1402)

Outcome measures

Primary outcome

1. ORR (objective response rate)

Description: ORR as assessed by blinded independent central review per response

Evaluation Criteria in Solid Tumors v1.1.

Time frame: Data are collected at baseline, then from the start of study

treatment until documented disease progression or other protocol defined

reason.

Secondary outcome

1. DoR (Duration of Response)

Description: DoR as assessed by blinded independent central review (BICR) and

Investigator per response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Time frame: Data are collected at baseline, then from the start of study

treatment until documented disease progression, death, lost to follow-up, or

withdrawal by subject.

2. PFS (Progression-free survival)

Description: PFS as assessed by BICR and Investigator per RECIST v1.1

Time frame: Data are collected at baseline, then from the start of study treatment until documented disease progression or other protocol defined reason. Death date is collected until the subject discontinues the study.

3. ORR (Objective Response Rate)

Description: ORR as assessed by Investigator per RECIST v1.11.

Time frame: Data are collected at baseline, then from the start of study treatment until documented disease progression or other protocol defined reason.

4. DCR (Disease control rates)

Description: DCR as assessed by BICR and Investigator per RECIST v1.1

Time frame: Data are collected at baseline, then from the start of study treatment until documented disease progression or other protocol defined reason.

5. TTR (Time to Response)

Description: as assessed by BICR and Investigator per RECIST v1.1 Time frame: Data are collected at baseline, then from the start of study treatment until documented disease progression or other protocol defined reason.

Time frame: Data are collected at baseline, then from the start of study treatment until documented disease progression or other protocol defined reason.

6. Best percentage change in the sum of diameters (SoD) of measurable tumors

Description: SoD as assessed by BICR and by Investigator per RECIST V1.1.

Time frame: Data are collected at baseline, then from the start of study treatment until documented disease progression or other protocol defined reason.

7. OS (Overall Survival)

Description: OS

Time frame: Death date is collected until the subject discontinues the study.

8., Safety parameters during the study*

Description: Descriptive statistics of safety endpoints

Time frame: From the time the subject signs the main study ICF and up to 40 (+ 7) days after the last dose of study drug (ie, 5 half-lives of the antibody drug conjugate/the follow-up period). *Although this is a secondary objective, this is a primary outcome measure.

9. Correlation between HER3 protein expression (as determined by HER3 IHC assay) and efficacy

Description: Descriptive summary of HER3 status, and a correlative analysis between HER3 protein expression level and efficacy

Time frame: Efficacy data are collected at baseline, then from the start of study treatment until documented disease progression or other protocol defined reason. HER3 data are collected at baseline (biopsy), at Cycle 2, and EOT (optional).

10. Immunogenicity

Description: anti-drug antibody status at baseline and post-baseline. Subjects who are negative for anti-drug antibody at all post-baseline time points are considered as post-baseline negative; subjects who are positive for anti-drug antibody at least once post-baseline are considered post-baseline positive.

Time frame: Data are collected from the start of study treatment until documented disease progression. Additional time-points are specified in the protocol, table 1.1 and table 1.2.

Study description

Background summary

In this study we are researching the possibility whether Patritumab Deruxtecan (U3-1402) has any effect on slowing tumor growth in lung cancer tumors. Research has shown that a specific type of protein called HER3 can be elevated in lung cancer cells. HER3 is thought to cause cancer cells to grow. Patritumab Deruxtecan (U3-1402) has been designed to bring chemotherapy inside HER3-positive cancer cells and destroy them. This could be a possible new option in the treatment of Previously Treated Metastatic or Locally Advanced EGFRmutated Non-Small Cell Lung Cancer.

Study objective

This study has been transitioned to CTIS with ID 2024-512238-13-00 check the CTIS register for the current data.

Primary objective:
1. To investigate the antitumor activity of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)

Secondary objectives:
1. To investigate the durability of patritumab deruxtecan antitumor activity in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)
2. To further investigate the antitumor activity of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)
3. To assess the safety and tolerability of patritumab deruxtecan in subjects with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R)
4. To evaluate HER3 protein expression in tumor tissue and its relationship with efficacy
5. To assess the immunogenicity incidence against patritumab deruxtecan

Study design

This is a global, multicenter, open-label, Phase 2 study of subjects with metastatic or locally advanced NSCLC with an EGFR-activating mutation (exon 19 deletion or L858R) who have received and progressed on or after at least 1 EGFR TKI and 1 platinum-based chemotherapy-containing regimen. This study will initially randomize subjects to one of 2 arms in a 1:1 ratio, for dose selection, to receive either a 5.6 mg/kg fixed dose regimen (Arm 1) or an

up-titration dose regimen (Cycle 1: 3.2 mg/kg; Cycle 2: 4.8 mg/kg; Cycle 3 and subsequent cycles: 6.4 mg/kg; Arm 2) of patritumab deruxtecan on Day 1 of each 21-day cycle. In the ongoing U31402-A-U102 trial, the same population is being studied in multiple expansion cohorts: Cohort 3a and 3b (with 45 subjects planned to be randomized to each dose regimen, 5.6 mg/kg every 3 weeks [Q3W] or up-titration) and Cohort 1 (45 subjects dosed with 5.6 mg/kg Q3W). If, during the conduct of the current trial (U31402-A-U201), analyses from the U31402-A-U102 study indicate that one dose regimen provides clear advantages over the other in terms of benefit/risk, further enrollment into one arm may be discontinued. Any such decision will be made with consideration of the ongoing review of the U31402-A-U201
safety data by the Data Monitoring Committee (DMC):
- If a single dose regimen (Arm 1 or Arm 2) is selected to continue enrollment, subjects enrolled after the decision point will be assigned to the selected dose regimen. Subjects enrolled before the decision point will continue their originally assigned dose regimen without crossover.
- If there is no significant difference in efficacy and/or safety from the U31402-A-U102 NSCLC study, both dose regimens/arms in this study (U31402-A-U201) will continue to enroll to study completion. The study will be divided into 3 periods: the Screening Period, Treatment Period, and Follow-up Period.
- The Screening Period will start on the day of signing the main informed consent form (ICF) and will have a maximum duration of 28 days. Rescreening is permitted one time for any subject who failed to meet reversible or transient eligibility criteria upon initial screening.
- Eligible subjects will be enrolled and enter the Treatment Period. The Treatment Period starts on the day of enrollment (ie, Cycle 1 Day 1) and continues until a subject permanently discontinues patritumab deruxtecan. To minimize the possibility of developing tumor flare with discontinuation of EGFR TKI, subjects who fulfill eligibility criteria and are receiving an EGFR TKI at the time of informed consent should be instructed to continue their current EGFR TKI until 5 days prior to Cycle 1 Day 1. Radiographic assessment of tumor response will be performed based on Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 24 weeks then every 12 weeks (±7 days), independent of treatment cycle, until documented disease progression (as assessed by the Investigator and confirmed by blinded independent central review [BICR]), initiation of new anticancer treatment, death, lost to follow-up, or withdrawal of consent. Subjects will continue to receive patritumab deruxtecan until documented disease progression (as assessed by the Investigator and confirmed by BICR), clinical progression, unacceptable toxicity, withdrawal of consent by the subject, physician*s decision, protocol deviation, pregnancy, lost to follow-up, study termination by the Sponsor, death, or other reasons.
- The Follow-up Period will start upon permanent discontinuation of patritumab deruxtecan. After completion of the 40-day (+7 days) safety Follow-up Visit, subjects will be followed every 3 months for survival.

The primary completion date will occur when all subjects have either a minimum of 9 months follow up or have discontinued from the study earlier. This date is used as the data cut-off (DCO) date for the primary analysis of the study. All subjects still on treatment and continuing to derive benefit from patritumab deruxtecan at the primary completion date will continue to follow the study Schedule of Events (SoE) (Protocol table 1.2) until the overall End of Study (EOS) is reached. The overall EOS will occur after the last subject last visit has occurred, when all subjects have discontinued treatment and discontinued long-term survival follow-up or have died, an alternative study becomes available for subjects continuing to derive benefit from treatment with patritumab deruxtecan where the study drug is offered to these subjects, or the study is discontinued by the Sponsor for other reasons (administrative, program-level or class-related).
See Figure 1.1 for the study flow diagram.

Intervention

Subjects will be randomly assigned to one of the following treatment groups:
- Group 1: will receive a fixed dose of the study drug (dose of 5.6 mg per kg body weight) every three weeks
- Group 2: will go from a lower to a higher dose of the study drug for the first three cycles every three weeks
• Cycle 1: dose of- 3.2 mg per kg body weight
• Cycle 2: dose of 4.8 mg per kg body weight
• Cycle 3 & additional cycles: dose of 6.4 mg per kg body weight

The study drug will be given via an infusion once every 3 weeks.

Study burden and risks

The subject's participation in this study will last about 14 months. The total duration of the subjects participation will also depend on how their cancer responds to the study drug and the ability to be safely treated without significant side effects.

This study is divided into 4 periods: a pre-screening phase, screening phase, treatment phase and a follow-up phase (which also includes a long term survival fullow-up). In total the subject will visit the hospital approximately 20 times during this study. Each visit will take about 4 to 8 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 questions..
- Measurement of vital signs / physical examination (e.g. blood pressure, heart

rate, temperature, and respiratory rate), height, weight, check of your oxygen levels)
- Eye test
- Blood and urine samples are taken.
- Pregnancy test for woman of childbearing potential.
- ECG
- ECHO/MUGA
- CT/MRI
- Bone 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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US
Scientific
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US

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 tissue ICF and the main ICF, prior to the start of any study-specific
qualification procedures.
2. Male or female subjects aged >=18 years (follow local regulatory requirements if the legal age of consent for study participation is >18 years old).
3. Histologically or cytologically documented locally advanced or metastatic NSCLC not amenable to curative surgery or radiation.
4. Documentation of radiological disease progression while on/after receiving most recent treatment regimen for locally advanced or metastatic disease. Subjects must have received both of the following:
a. Prior treatment with osimertinib. Subjects receiving an EGFR TKI at the time of signing informed consent should continue to take the EGFR TKI until 5 days prior to Cycle 1 Day 1.
b. Systemic therapy with at least 1 platinum-based chemotherapy regimen.
5. Documentation of an EGFR-activating mutation detected from tumor tissue or blood sample: exon 19 deletion or L858R.
6. At least 1 measurable lesion confirmed by BICR as per RECIST v1.1 (please refer to section 10.4 of the protocol)
7. Consented and willing to provide required tumor tissue of sufficient quantity (as defined in the Laboratory Manual) and of adequate tumor tissue content (as confirmed by hematoxylin and eosin [H&E] staining at the central laboratory).Required tumor tissue can be provided as either:
a. Pretreatment tumor biopsy from at least 1 lesion not previously irradiated and amenable to core biopsy
OR
b. Archival tumor tissue collected from a biopsy performed within 3 months prior to signing of the tissue consent and since progression while on or after treatment with the most recent cancer therapy regimen.
AND consent to provide a required on-study tumor biopsy. After approximately 15 on-study tumor biopsies in each arm have been collected, the Sponsor will notify the Investigator of a change to the requirement.
8. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 at Screening (see Section 10.3.3 of the protocol)
9. Has adequate bone marrow reserve and organ function based on local laboratory data within 14 days prior to Cycle 1 Day 1 (please refer to schedule in protocol, paragraph 5.1).
10. If the subject is a female of childbearing potential, she must have a negative serum
pregnancy test at Screening and must be willing to use highly effective birth control, as
detailed in Section 10.3.4 of the protocol, upon enrollment, during the Treatment Period, and for 7 months following the last dose of study drug. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless

permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) with surgery at least 1 month before the first dose or confirmed by follicle stimulating hormone (FSH) test. Please refer to section 8.4.2 of the protocol.
Pregnancy Test for further details regarding confirmation of post-menopausal status.
11. 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 study drug administration.
12. If male, the subject must be surgically sterile or willing to use highly effective birth
control (Please refer to section 10.3.4) upon enrollment, during the treatment period, and for at least 4 months following the last dose of study drug.
13. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration.
14. Is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.

Exclusion criteria

1. Any previous or current histologic or cytologic evidence of small cell OR combined small cell/non-small cell disease in the archival tumor tissue or pretreatment tumor biopsy.
2. Any history of interstitial lung disease (including pulmonary fibrosis or radiation pneumonitis), has current interstitial lung disease (ILD), or is suspected to have such disease by imaging during screening.
3. Clinically severe respiratory compromise (based on Investigator*s assessment) resulting from intercurrent pulmonary illnesses including, but not limited to:
a. Any underlying pulmonary disorder (eg, pulmonary emboli within 3 months prior to of the study enrollment, severe asthma, severe chronic obstructive pulmonary disease [COPD]), restrictive lung disease, pleural effusion);
b. Any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (eg, rheumatoid arthritis, Sjogren's syndrome, sarcoidosis);
OR prior complete pneumonectomy.
4. Is receiving chronic systemic corticosteroids dosed at >10 mg prednisone or equivalent anti-inflammatory or any form of immunosuppressive therapy prior to enrollment. Subjects who require use of bronchodilators, inhaled or topical steroids, or local steroid injections may be included in the study.
5. Evidence of any leptomeningeal disease.
6. Evidence of clinically active spinal cord compression or brain metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids

or anticonvulsants to control associated symptoms. Subjects with clinically inactive or treated brain metastases who are asymptomatic (ie, without neurologic signs or symptoms and not requiring treatment with corticosteroids or anticonvulsants) may be included in the study. Subjects must have a stable neurologic status for at least 2 weeks prior to Cycle 1 Day 1.
7. Inadequate washout period prior to Cycle 1 Day 1, defined as:
a. Whole brain radiation therapy <14 days or stereotactic brain radiation therapy <7 days;
b. Any cytotoxic chemotherapy, investigational agent or other anticancer drug(s) from a previous cancer treatment regimen or clinical study (other than EGFR TKI), <14 days or 5 half-lives, whichever is longer;
c. Immune checkpoint inhibitor therapy <21 days;
d. Major surgery (excluding placement of vascular access) <28 days;
e. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation <28 days or palliative radiation therapy <14 days; or
f. Chloroquine or hydroxychloroquine <14 days.
8. Prior treatment with an anti-human epidermal growth factor receptor 3 (HER3) antibody or single-agent topoisomerase I inhibitor.
9. Prior treatment with an antibody drug conjugate (ADC) that consists of any topoisomerase I inhibitor
10. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, Grade <=1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible at the discretion of the Investigator after consultation with the Sponsor Medical Monitor or designee.
11. Has history of other active malignancy within 3 years prior to enrollment, except:
a. Adequately treated non-melanoma skin cancer;
b. Superficial bladder tumors (Ta, Tis, T1);
c. Adequately treated intraepithelial carcinoma of the cervix uteri;
d. Low risk non-metastatic prostate cancer (with Gleason score <7, and following local treatment or ongoing active surveillance);
e. Any other curatively treated in situ disease.
12. Uncontrolled or significant cardiovascular disease prior to Cycle 1 Day 1, including:
a. QT interval corrected with Fridericia*s formula (QTcF) prolongation interval of >470 ms for females and >450 ms for males;
b. Left ventricular ejection fraction (LVEF) <50% by either echocardiogram (ECHO) or multigated acquisition (MUGA) scan;
c. Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg);
d. Myocardial infarction within 6 months;
e. New York Heart Association (NYHA) Classes 2 to 4 congestive heart failure (See protocol section 10.3.2) within 28 days;
f. Uncontrolled angina pectoris within 6 months;
g. Cardiac arrhythmia requiring antiarrhythmic treatment.

13. Active hepatitis B and/or hepatitis C infection, such as those with serologic evidence of viral infection within 28 days of Cycle 1 Day 1.
a. Subjects with past or resolved hepatitis B virus (HBV) infection are eligible if:
i Hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody [anti-HBc] positive; OR
ii HBsAg positive and HBV deoxyribonucleic acid (DNA) viral load is documented to be <=2000 IU/mL in the absence of anti-viral therapy and during the previous 12 weeks prior to the viral load evaluation with normal transaminases values (in the absence of liver metastasis); OR
iii HBsAg positive and HBV DNA viral load is documented to be <=2000 IU/mL, in the absence of anti-viral therapy and during the previous 12 weeks prior to the viral load evaluation for subjects with liver metastasis and abnormal transaminases with a result of AST/ALT <3 × ULN.
b. Subjects with a history of hepatitis C infection will be eligible for enrollment only if the viral load according to local standards of detection is documented to be below the level of detection in the absence of anti-viral therapy during the previous 12 weeks (ie, sustained viral response according to the local product label but no less than 12 weeks, whichever is longer).
14. Subject with any human immunodeficiency virus (HIV) infection.
15. Any evidence of severe or uncontrolled diseases including active bleeding diatheses, active infection, psychiatric illness/social situations, geographical factors, substance abuse, or other factors which in the Investigator*s opinion makes it undesirable for the subject to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required.
16. History of hypersensitivity to either the drug substance or any excipients in patritumab deruxtecan.
17. Female who is pregnant or breast-feeding or intends to become pregnant during the study.
18. Prior or ongoing clinically relevant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the Investigator*s opinion, could affect the safety of the subject; alter the absorption, distribution, metabolism or excretion of the study drug; or confound the assessment of study results.
19. Has clinically significant corneal disease.

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-06-2021
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Patritumab Deruxtecan
Generic name:	Patritumab Deruxtecan

Ethics review

Approved WMO Date:	06-10-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-04-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	26-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	12-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2023
Application type:	Amendment
Review commission:	METC NedMec

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	CTIS2024-512238-13-00
EudraCT	EUCTR2020-000730-17-NL
CCMO	NL75165.031.20