A MULTICENTER, OPEN-LABEL PHASE 1 STUDY OF HE3-DXd IN SUBJECTS WITH METASTATIC OR UNRESECTABLE NON-SMALL CELL LUNG CANCER

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This study has been transitioned to CTIS with ID 2024-511205-33-00 check the CTIS register for the current data. Dose Expansion:Primary Objective-*To investigate the antitumor activity of HE3-DXdSecondary Objectives-*To assess the safety and...

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

Summary

ID

NL-OMON52400

Source
ToetsingOnline

Brief title
None

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lung Cancer, Non-Small Cell Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Pharmaceutical

Source(s) of monetary or material Support: Industry

Intervention

Keyword: Non-Small Cell Lung Cancer, Phase 1, Progression, U3-1402/HE3-DXd

Outcome measures

Primary outcome

Dose Expansion

Primary Endpoint (ie, Primary Outcome Measures)

*ORR as assessed by Independent Central Review Committee (Central Review) based on RECIST v1.1

Secondary outcome

Secondary Endpoints (ie, Secondary Outcome Measures)

*Investigator assessed ORR based on RECIST v1.1, DCR, DOR, TTR, PFS, and OS

*SAEs, TEAEs, physical examination findings (including ECOG PS), vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters (including *HR, *PR, *QTcF, and *QRS), and ECHO/MUGA findings

*Serum concentration of HE3-DXd, total anti-HER3 antibody, and free payload MAAA-1181a vs. time will be utilized. The serum PK parameters will include Cmax, Tmax, AUC8h, AUClast, and, if possible, Kel, t1/2, CL, Vz, and Vss ofHE3-DXd, anti-HER3 antibody, and MAAA 1181a. These PK parameters will be calculated both after the first dose and after multiple doses

Exploratory Endpoints (ie, Exploratory Outcome Measures)

*ADA measured in serum

*To determine biomarkers that correlate with response or toxicity to HE3-DXd, the endpoints will include measured markers in tumor specimens (eg, HER3 IHC) and markers measured in plasma (eg, cfDNA, cfRNA)

*Cohort 1 and 2 ONLY: Geometric mean ratios of AUClast and Cmax for HE3-DXd for Injection 50 mg/2.5 mL (frozen liquid) and HE3-DXd for Injection 100 mg (lyophilized powder) will be calculated after first dose (ie, Cycle 1)

*Relation between HE3-DXd, total anti-HER3 antibody, or MAAA-1181a serum concentration and *QTcF

Dose Expansion Cohort 4:

Primary Endpoint (ie, Primary Outcome Measures)

• Primary PK parameters: Cmax, area under the serum concentration-time curve from time 0 to infinite time (AUCinf), and AUClast for HE3-DXd, total anti HER3 antibody, and MAAA-1181a following the administration of the first dose of HE3-DXd drug product CTM-3.

Secondary Endpoints (ie, Secondary Outcome Measures)

• SAEs, TEAEs, adverse events of special interest (AESIs) (ie, ILD and elevation of aminotransferases and total bilirubin), physical examination findings (including ECOG PS), vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters (including ΔHR, ΔPR, ΔQTcF, and ΔQRS), and ECHO/ MUGA findings

• ORR, DCR, DOR, TTR, PFS as assessed by Investigator per RECIST v1.1, and OS

• Serum concentrations at each time point and PK parameters (through the first

4 treatment cycles) for:

* Cycle 1: U3-1402, total anti-HER3 antibody, and MAAA-1181a: Tmax, trough

concentration (Ctrough), AUC from time zero to Day 21 (AUC0-21d), and if data

permit, Kel, t1/2, CL, Vz, Vss

* Cycle 2 and beyond (through the first 4 treatment cycles):

* As applicable, all analytes: Cmax, Tmax, Ctrough, AUClast, AUC0-21d, and if

data permit, Kel, t1/2, CL, Vz, Vss

Exploratory Endpoint (ie, Exploratory Outcome Measures)

• Immunogenicity - ADA prevalence and incidence

Study description

Background summary

This study proposes to evaluate HE3-DXd as an anticancer agent in NSCLC.
HE3-DXd is an antibody-drug conjugate ADC, comprised of a recombinant fully human antihuman epidermal growth factor receptor 3 (HER3) immunoglobulin G1 (IgG1) monoclonal antibody (patritumab) covalently conjugated to a drug-linker (MAAA-1162a) containing a drug component (MAAA-1181a), that targets HER3. The drug MAAA-1181a, a derivative of exatecan, is released after internalization and leads to apoptosis of the target tumor cells by the inhibition of topoisomerase I.
The ERBB3/HER3 oncogene is overexpressed in many cancers including breast, ovarian, prostate, head and neck, gastric, and lung. In NSCLC, HER3 overexpression has been demonstrated to be one of the mechanisms of acquired resistance to gefitinib treatment of EGFRm tumours and is an important mechanism of resistance in tumours such as those with amplification of c-MET.

Study objective

This study has been transitioned to CTIS with ID 2024-511205-33-00 check the CTIS register for the current data.

Dose Expansion:
Primary Objective
-*To investigate the antitumor activity of HE3-DXd

Secondary Objectives
-*To assess the safety and tolerability of HE3-DXd in metastatic or unresectable NSCLC subjects
-*To characterize the PK of HE3-DXd, total anti-HER3 antibody, and MAAA 1181a

Exploratory Objectives
-*To assess the incidence of ADAs against HE3-DXd
-*To identify biomarkers that correlate with HE3-DXd clinical activity
-*Cohort 1 and 2 ONLY: To assess PK similarities of frozen liquid and lyophilized powder dosage forms
-*To explore the concentration QTc relationships of HE3-DXd, total anti HER3 antibody, and MAAA 1181a

Study design

This is a Phase 1, multicenter, open-label, 2-part study of HE3-DXd in subjects with metastatic or unresectable NSCLC. This study has two parts: Dose Escalation and Dose Expansion.
HE3-DXd for Injection 50mg/2.5 mL (frozen liquid) will be supplied during Dose Escalation, with transition to HE3-DXd for Injection 100 mg (lyophilized powder) for the start of Dose Expansion.
CTM-1 will be used in Cohorts 1, 2, 3a, and 3b. CTM-3, a drug product manufactured by the commercial manufacturing sites, will be used in Cohort 4.

EU countries will only participate in Dose Expansion part of the study.

Dose Expansion
Upon completion of Dose Escalation and establishment of the RDE, Dose Expansion will begin, with the objectives of confirming the safety and tolerability of HE3-DXd at the RDE and evaluating preliminary efficacy. Beginning with Cycle 1, Day 1, HE3-DXd will be administered via IV infusion Q3W, in 21-day cycles. All subjects enrolled in Dose Expansion will receive HE3-DXd for Injection 100 mg (lyophilized powder). Available PK and safety data will be compared between approximately 12 initial subjects enrolled across Cohorts 1 and 2, and approximately 10 subjects enrolled in Dose Escalation who were administered HE3-DXd for Injection 50 mg/2.5 mL (frozen liquid) at the RDE. Enrollment of additional subjects in Dose Expansion will continue during this period of PK evaluation. Based upon evaluation of all available PK and safety data, the Sponsor will determine whether to continue enrolling subjects at the established RDE or to enroll subjects at an adjusted RDE (or, if applicable, adjusted RDE [aRDE]) for the lyophilized powder.

In addition, 90 subjects will be enrolled and randomized 1:1 into Cohort 3a

(RDE or, if applicable, aRDE) or Cohort 3b (Up-titration) to evaluate the efficacy and safety of an alternative dosing regimen.

All subjects enrolled in Dose Expansion Cohort 4 will receive HE3-DXd CTM-3 at 5.6 mg/kg Q3W.

Cohort 1
Up to 45 adenocarcinoma NSCLC subjects with EGFR mutation will be enrolled. Enrollment in Cohort 1 will be stopped once the first subject is randomized into Cohort 3a or 3b. Subjects receiving an EGFR TKI at the time of signing informed consent should continue to take the EGFR TKI until 5 days before their first dose of HE3-DXd

Cohort 2
Approximately 45 squamous or non-squamous NSCLC subjects (ie, without EGFR-activating mutations) will be enrolled.

Cohorts 3a and 3b
Approximately 90 NSCLC (including any histology other than combined small cell and non-small cell) subjects with EGFR mutation will be enrolled and randomized 1:1 to RDE (or, if applicable, an aRDE) (Cohort 3a) or an uptitration regimen (Cohort 3b). The up-titration regimen consists of HE3-DXd dosed on Day 1 of the first 3 cycles as described below:
*Cycle 1, Day 1: 57% of RDE (or, if applicable, aRDE)
*Cycle 2, Day 1: 86% of RDE (or, if applicable, aRDE)
*Cycle 3 and subsequent cycles, Day 1: 114% of RDE (or, if applicable, aRDE)

Cohort 4
Approximately 45 subjects with NSCLC (including any histology other than small-cell or combined small-cell and non-small cell) with an EGFR-activating mutation will be enrolled.

Subjects receiving an EGFR TKI at the time of signing informed consent should continue to take the EGFR TKI until 5 days before their first dose of HE3-DXd
The number of treatment cycles is not pre-determined in this study. Subjects will continue study treatment until withdrawal of consent, progressive disease (PD), or unacceptable toxicity for all subjects in Dose Escalation and Dose Expansion.

Intervention

All subjects (except cohort 3b) enrolled in Dose Expansion will receive HE3-DXd for Injection 100 mg (lyophilized powder).
All subjects enrolled in Dose Expansion Cohort 4 will receive HE3-DXd CTM-3 at 5.6 mg/kg Q3W.

See Study Design above.

Study burden and risks

Lung Cancer is the leading cause in cancer-related deaths worldwide in both men and women. In this study we are looking to see whether HE3-DXd has any effect on slowing tumor growth in NSCLC tumors. Many of the tests and procedures are also done as standard of care.

Contacts

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US
Scientific
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MT. AIRY RD 211
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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

Inclusion Criteria for Dose Escalation 1. Male or female subjects aged 18 years

and older. 2. Has histologically or cytologically documented adenocarcinoma NSCLC. 3.Has locally advanced or metastatic NSCLC, not amenable to curative surgery or radiation 4. Has acquired resistance to EGFR TKI according to the Jackman criteria (PMID: 19949011): a. Historical confirmation that the tumor harbors an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q), OR b. Has experienced clinical benefit from an EGFR TKI, followed by systemic progression of disease (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 or World Health Organization [WHO]) while on continuous treatment with an EGFR TKI. 5. Is currently receiving and able to discontinue erlotinib, gefitinib, afatinib, or osimertinib. 6. Has been receiving erlotinib, gefitinib, afatinib, or osimertinib for least 6 weeks with well-controlled related toxicities less than Grade 3 in severity at the time of Screening. 7. Has radiological documentation of disease progression while receiving continuous treatment with erlotinib, gefitinib, afatinib, or osimertinib. 8.Has at least one measurable lesion per RECIST version 1.1 9. Is willing to provide archival tumor tissue from a biopsy performed within 6 months of progression during treatment with erlotinib, gefitinib, afatinib, or osimertinib OR has at least 1 lesion, not previously irradiated, amenable to core biopsy and is willing to undergo Screening tumor biopsy. 10. Demonstrates absence of EGFR T790M mutation if treated with erlotinib, gefitinib, or afatinib. No EGFR mutation testing is required if treated with osimertinib. 11.Has Eastern Cooperative Oncology Group performance status of 0 or 1, with no deterioration over the previous 2 weeks For additional Inclusion criteria please refer to protocol Inclusion Criteria for Dose Expansion only: 1. Male of female subjects aged >=18 years (follow local regulatory requirements if the legal age of consent for study participation is >18 years old). 2. Has locally advanced or metastatic NSCLC not amenable to curative surgery or radiation. 3.Has received systemic therapy for locally advanced or metastatic disease including at least 1 platinum-based chemotherapy regimen 4.Has documented radiological disease progression during/after most recent treatment regimen for locally-advanced or metastatic disease 5. Has at least 1 measurable lesion per RECIST v1.1. 6.Is willing to provide archival tumor tissue from a biopsy performed within 6 months of consent and performed after progression during/after treatment with most recent cancer therapy regimen OR has at least 1 lesion, not previously irradiated, amenable to core biopsy and is willing to undergo tumor biopsy For additional inclusion criteria please refer to protocol Additional Inclusion Criteria Specific to Cohorts 1, 3a, and 3b and 4 please refer to protocol Additional Inclusion Criteria Specific to Cohort 2 please refer to protocol Additional Inclusion criteria specific to Cohort 5 please refer to the protocol

Exclusion criteria

Exclusion Criteria for Dose Expansion: 1. Has any evidence of small cell histology, or combined small cell and non-small cell histology, in original

tumor biopsy or in Screening biopsy performed after progression 2. Has previously documented evidence of anaplastic lymphoma kinase (ALK) fusion, ROS1 fusion, BRAF V600E mutation, RET rearrangement, HER2 mutation, MET amplification, or MET exon 14 skipping mutation. No new testing for these genomic alterations is required for Screening. 3.Treatment with any of the following: a. Any cytotoxic chemotherapy, investigational agent or other anticancer drug(s) from a previous cancer treatment regimen or clinical study (other than EGFR TKI in Cohort 1 only), within 14 days prior to first dose of HE3-DXd b. Immune checkpoint inhibitor therapy within 21 days prior to dose of HE3-DXd c. Prior treatment with an anti-HER3 antibody d. Prior treatment with a topoisomerase I inhibitor e. Prior treatment with an antibody-drug conjugate (ADC) that consists of an exatecan derivative that is a topoisomerase I inhibitor (eg, DS-8201a) f. Major surgery (excluding placement of vascular access) within 4 weeks prior to first dose of HE3-DXd g. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks prior to first dose of HE3-DXd 4. Has history of other active malignancy within 3 years prior to first dose of HE3-DXd, except: a. Adequately treated non-melanoma skin cancer OR b. Superficial bladder tumors (Ta, Tis, T1) OR c. Curatively treated in situ disease 5. Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Participants with clinically inactive brain metastases may be included in the study. Participants with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment (1 week for stereotactic radiotherapy) 6. Has history of myocardial infarction within the past 6 months 7. Has symptomatic congestive heart failure[New York Heart Association (NYHA) Classes III-IV], unstable angina, or cardiac arrhythmia requiring antiarrhythmic treatment 8. Has left ventricular ejection fraction (LVEF) < 45% by either echocardiogram (ECHO) or multigated acquisition scan (MUGA) 9. Has any clinically important abnormalities in rhythm, conduction or morphology of resting electrocardiogram (ECG), eg, complete left bundle branch block, third-degree heart block, second-degree heart block, or PR interval > 250 milliseconds (ms) 10. Has a mean corrected QT interval using Fridericia's Correction Formula (QTcF) prolongation to > 470 ms for females and > 450 ms for males in three successive Screening measurements 11. Unable or unwilling to discontinue concomitant drugs that are known to prolong the QT interval 12. Has any factors that increase the risk of corrected QT (QTc) interval prolongation or risk of arrhythmic events, such as congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives. 13. Has any history of interstitial lung disease (pulmonary fibrosis or severe radiation pneumonitis)has current ILD/pneumonitis, or is suspected to have such disease by imaging during Screening. 14. Has any evidence of severe or uncontrolled systemic diseases (including uncontrolled hypertension, and active bleeding diatheses or active

infection, including hepatitis B, hepatitis C, and human immunodeficiency virus [HIV]), psychiatric illness/social situations,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. 15. Is pregnant or breastfeeding, or is planning to become pregnant. 16. Has clinically significant corneal disease. For Common Exclusion Criteria for Dose Expansion please refer to protocol

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-07-2020
Enrollment:	8
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	U3-1402 / HE3-DXd
Generic name:	NA

Ethics review

Approved WMO

Date:	10-09-2019
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	13-02-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-08-2021
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	23-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-03-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-04-2024
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	CTIS2024-511205-33-00
EudraCT	EUCTR2017-000543-41-NL
CCMO	NL70299.031.19