A Phase 1/2 Study of the Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor NVL-655 in Patients with Advanced NSCLC and Other Solid Tumors (ALKOVE-1)

Published: 09-03-2023
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This study has been transitioned to CTIS with ID 2024-514266-39-00 check the CTIS register for the current data. Phase 1 Primary Objective(s):-to evaluate the overall safety and tolerability of NVL-655-to determine the RP2D and, if applicable, the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON56594

Source
ToetsingOnline

Brief title
ALKOVE-1

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Lung cancer, Non Small Cell Lung Cancer NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Nuvalent, Inc.,
Source(s) of monetary or material Support: Nuvalent Inc.

Intervention

Keyword: Advanced Non-small cell lung cancer, NVL-655 as aditional treatment, Selective Anaplastic Lymphoma Kinase (ALK) inhibitor

Outcome measures

Primary outcome

Phase I

Incidence and severity of TEAEs and changes in

clinically relevant laboratory parameters.

RP2D and, if applicable, the MTD as determined by

incidence of DLTs during Cycle 1, overall safety

profile, PK, pharmacodynamics, and preliminary

efficacy.

Phase II

ORR: Defined as the percent of patients with a CR or

PR according to RECIST 1.1 per BICR

Secondary outcome

Phase I

PK parameters of NVL-655: Cmax; Cmax - dose

normalized; Ctau; Cavg; Tmax; AUCtau; AUCtau - dose

normalized; AUC0-24; AUC0-24 - dose normalized;

AUCinf; AUCinf - dose normalized; CL/F; Vz/F; and t1/2 ORR: Defined as the percent of patients with a CR or PR according to RECIST 1.1 per Investigator assessment

DOR: In responders, defined as the time from first Investigator-assessed response per RECIST 1.1 to radiographic disease progression or death

IC-ORR: In patients with measurable metastatic CNS disease at baseline, defined as the proportion of patients with a confirmed intracranial response (IC-CR or IC-PR) per investigator, based on assessment of up to 5 intracranial target lesions according to RECIST 1.1 principles.

IC-DOR: In patients with intracranial response, defined as the time from first Investigator-assessed IC-response per RECIST 1.1 to radiographic IC-disease progression or death

CBR: Defined as the percent of patients with a confirmed CR or PR, or SD of at least 24 weeks duration according to RECIST 1.1 per Investigator assessment

Time to response: Defined as the time from first dose to first confirmed radiographic response according to RECIST 1.1 per Investigator assessment

PFS: Defined as the time from first dose to radiographic disease progression per RECIST 1.1 based on Investigator assessment or death

Phase II

DOR: In responders, defined as the time from first BICR-assessed response per RECIST 1.1 to radiographic disease progression or death

CBR: Defined as the percent of patients with a confirmed CR or PR, or SD of at least 24 weeks duration according to RECIST 1.1 per BICR

Time to response: Defined as the time from first dose to first confirmed radiographic response according to RECIST 1.1 per BICR assessment

PFS: Defined as the time from first dose to radiographic disease progression per RECIST 1.1 based on BICR assessment or death

OS: Defined as the time from first dose to death due to any cause

IC-ORR: In patients with measurable metastatic CNS disease at baseline, defined as the proportion of patients with a confirmed intracranial response (IC-CR or IC-PR) per BICR, based on assessment of up to 5

intracranial target lesions according to RECIST 1.1 principles.

IC-DOR: In patients with intracranial response, defined as the time from first BICR-assessed IC-response per RECIST 1.1 to radiographic IC-disease progression or death

Time to IC-response: In patients with measurable metastatic CNS disease, defined as the time from first dose to first confirmed radiographic IC-response according to RECIST 1.1 principles per BICR

The incidence of CNS as the first site of disease progression, alone or with concurrent extra-CNS progression

Incidence and severity of TEAEs and changes in clinically relevant laboratory parameters

PK parameters of NVL-655: Cmax, Cmax - dose normalized, Ctau, Cavg, Tmax, AUCtau, AUCtau - dose normalized, AUC0-24, AUC0-24 - dose normalized, AUCinf, AUCinf - dose normalized, CL/F, Vz/F, t1/2

Changes in PROs for all patients: Assessed by the European Organization for Research and Treatment of

Cancer QoL Questionnaire of Cancer Patients (EORTC

QLQ-C30) core questionnaire (for all patients)

Changes in PROs for patients with lung cancer:

Assessed by European Organization for Research and

Treatment of Cancer QoL Questionnaire Lung Cancer

(EORTC QLQ-LC29) module questionnaire (for patients

with lung cancer only)

Study description

Background summary

This clinical trial consists of two parts, Phase 1 and Phase 2. You could be enrolled in either Phase 1 or Phase 2, depending on the time of your enrollment.
• In Phase 1 of the clinical trial, the safety of NVL-655 will be tested at different dose levels, in about 54 patients. The first three patients to enroll in the trial will receive the lowest dose of NVL-655; and depending on how the drug is tolerated, subsequent patient groups will receive gradually increased doses until a dose that shows preliminary antitumor activity with tolerable side effects is found. A safety committee made up of medical doctors, including your own doctor and other scientists, will look at the data from each dose to check that it is safe to increase the dose or may recommend keeping the dose the same or lower it for subsequent patients. The goal is to find out what effects, good and/or bad, NVL-655 has on you and your disease.
• Once a dose level is selected for further study, then the study will proceed to Phase 2, which is planned to include approximately 160 patients. Several different groups (defined by prior treatments received and tumor type) will be treated with NVL-655 at the dose selected in the Phase 1 part of the study to further investigate how safe NVL-655 is for patients and how well it works.
If you are enrolled into the Phase 1 part of the study, neither you nor your doctor will be able to choose the dose group you will be assigned. Your study doctor will tell you which dose level of NVL-655 you have been assigned to. However, if you start treatment with a lower dose, you may be eligible to increase your dose once the higher dose level(s) are determined safe.
All patients will receive the same dose of study drug in the Phase 2 part of the study unless side effects require a reduction in dose for particular patients.
This is the first time NVL-655 will be tested in humans. Up to now, no patients

have received NVL-655.
The main purposes of the phase 1 portion of this study are to find out:
• What amount of NVL-655 study drug is safe and tolerable
• What side effects are associated with NVL-655
• How much of NVL-655 gets into your bloodstream and how long it takes for the body to get rid of it (through collection and analysis of pharmacokinetic (PK) blood samples)
• The effect of NVL-655 on your tumor (through imaging of your tumors)
The main purposes of the phase 2 portion of this study are to:
• Evaluate whether NVL-655 is effective at shrinking your tumors, and if so, how long the response to NVL-655 lasts
• Further understand the side effects associated with NVL-655
• Confirm how much of NVL-655 gets into your bloodstream and how long it takes for the body to get rid of it

Study objective

This study has been transitioned to CTIS with ID 2024-514266-39-00 check the CTIS register for the current data.

Phase 1 Primary Objective(s):
-to evaluate the overall safety and tolerability of NVL-655
-to determine the RP2D and, if applicable, the MTD of NVL-655 in patients with advanced ALK-positive solid tumors
Phase 2 Primary Objective(s):
- To evaluate the efficacy of NVL-655 at the RP2D in patients with advanced ALK-positive NSCLC, including those with ALK resistance mutations, and other solid tumors

Phase 1 Secondary Objective(s):
- To characterize the PK profile of NVL-655
- To evaluate preliminary antitumor activity of NVL-655 in patients with advanced ALK-positive solid tumors
Phase 2 Secondary Objective(s):
- To assess additional measures of clinical efficacy in patients with ALK-positive NSCLC, including those with ALK resistance mutations, and other solid tumors
- To evaluate the intracranial antitumor activity of NVL-655 at the RP2D in patients with advanced ALK-positive NSCLC and other solid tumors
- To characterize the safety and tolerability of NVL-655 at the RP2D
- To confirm the PK profile of NVL-655 at the RP2D
- To assess treatment-related symptoms and general health status using validated instruments of patient-reported outcomes (PROs) in patients treated with NVL-655

Study design

This is a first-in-human, Phase 1/2, multicenter, open-label, dose escalation and expansion study designed to evaluate the safety and tolerability of NVL-655, determine the RP2D and, if applicable, the MTD, and evaluate the antitumor activity in patients with advanced ALK-positive NSCLC and other advanced ALK-positive solid tumors. The study will be conducted in 2 phases.

Intervention

Daily intake NVL-655 study medication - tablets, oral, with water prior any meail.
Time investment during hospital visits
Pregnancy prevention
Daily medication-intake diary
Biopsies and frequent scans (MRI and/orCT)
Frequent blood drawn

Study burden and risks

Vital sign measurements will be collected after the patient has been at rest (seated, supine, or semi-recumbent position) for at least 5 minutes. Vital signs will include sitting blood pressure, heart rate, respiratory rate, and temperature. Weight will be measured at each site visit. Height will be collected at Screening only.
A full physical examination will be conducted at Screening and EOT, which includes a neurological examination (see Section*11.5.2 for additional details). Symptom-directed physical examinations will be performed at other visits and as clinically indicated.
12-lead ECG will be obtained in triplicate after the patient has been at rest (seated, supine, or semi-recumbent position) for at least 5 minutes. QTc measurements will use the Fridericia*s correction method. ECGs will be read locally by the Investigator. ECGs are to be performed at Screening, on C1D1 pre-dose and post-dose at 2 hours (±15 minutes), 4 hours (±15 minutes), and 6 hours (±15 minutes) and on C1D15 pre-dose and post-dose at 4 hours (±15 minutes) and 6 hours (±15 minutes).
Ocular Examination (±7 days). See Section 11.5.5 and Section 9.7.
If applicable a screening serum pregnancy test must be performed within 7 days prior to the first NVL-655 dose to confirm eligibility, with a serum or urine test performed prior to first dose on C1D1. For WOCBP, serum or urine pregnancy tests will be done predose at the indicated study visits or more frequently, as required by local requirements.
Clinical laboratory assessments. C1D1 clinical laboratory tests may be performed within 7 days prior to the first NVL-655 dose (screening assessments may be used to fulfill the C1D1 requirements, if performed within this timeframe). Results from all clinical laboratory assessments (including blood chemistries, hematology, coagulation, and lipid profile) performed during screening or on C1D1 must be obtained and reviewed prior to first dose of

NVL-655. Lipid tests may be performed fasting or non-fasting. If results are abnormal, repeat testing must be performed fasting.
PK blood samples will be collected at the following time points on C1D1 and C1D15 (Phase 1): predose, and post-dose at 15 min (± 5 min), 30 min (± 10 min), 1 hr (± 10 min), 2 hr (± 10 min), 4 hr (± 15 min), 6 hr (± 15 min), and 24 hr (± 120 min; predose C1D2 and C1D16). C2D1 through C11D1 predose and post-dose at 1h (± 10 min) (Phase 1). During Phase 2, samples will be collected predose and post-dose at 2 hr (± 1 hr) on C1D1 through C11D1. During Phase 2 only, samples will be collected every other cycle from C13D1 through C21D1 predose (see Table*2). If a patient undergoes a lumbar puncture, a sample of CSF should be collected for exploratory analysis of NVL-655 concentration, if possible. If this CSF sample is collected, a blood sample for PK analysis should also be collected at approximately the same time as the CSF sample.
Pharmacodynamic blood samples will be collected at the following time points: C1D1 (predose), C1D15 (predose), C3D1 (predose), and EOT.
Tumor evaluation must occur within 4 weeks prior to first dose, at C3D1 (6 weeks), at C5D1 (12 weeks), every 8 weeks (±7 days) from C7D1 until C21D1, and every 12 weeks (±14 days) beginning with C24D1. In addition, Investigators are encouraged to a confirmatory tumor evaluation a minimum of 4 weeks (i.e., 28 days) after the first tumor evaluation that shows a CR or PR by RECIST 1.1, if consistent with local regulatory authority requirements. If a confirmatory scan is performed, the next scan should continue according to the schedule of assessments. Unscheduled imaging and additional studies are permitted if clinically indicated per the discretion of the Investigator. At Screening, imaging of brain (MRI), chest, abdomen, pelvis, as well as all other sites of disease with known (prior or current) or suspected involvement, is required. Recommended imaging includes CT with IV contrast for chest, CT or MRI with IV contrast for abdomen and pelvis, and MRI with and without IV contrast for brain. Similar imaging methodology should be used at Screening and all post-baseline tumor assessments. All scans will be collected and stored at a central facility to permit central reviewer assessment, if desired.
Additional imaging will not be required at the EOT visit if imaging was performed within 4 weeks prior to the EOT visit, unless new disease progression is suspected. Patients who discontinue treatment for reasons other than disease progression should continue to undergo tumor assessments every 8 weeks (if <=6 months from first dose) or 12 weeks (if >6 months from first dose) until radiologic disease progression, withdrawal of consent, or initiation of subsequent anticancer therapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age >=18 years
a. Phase 2 Cohort 2f only: Age >=12 years and weighing >40 kg. (Patients age 12 to 17 will only be enrolled in countries and at sites where regulations allow)
2. Disease criteria
a. Phase 1: Histologically or cytologically confirmed locally advanced or metastatic solid tumor with a documented ALK rearrangement or activating ALK mutation detected by certified assay (i.e. CLIA in the US). The report from this test is required to be submitted for eligibility.
b. Phase 2 Cohorts except 2f: Histologically or cytologically confirmed locally advanced or metastatic NSCLC (excluding patients with documented transformation to non-NSCLC histology) with a documented ALK rearrangement detected by certified assay (i.e. CLIA in the US). The report from this test is required to be submitted for eligibility.
c. Phase 2 Cohort 2f: Any other histologically or cytologically confirmed locally advanced or metastatic solid tumor with a documented ALK rearrangement or activating ALK mutation detected by certified assay,

including but not limited to inflammatory myofibroblastic tumors, esophageal squamous cell carcinoma, renal medullary carcinoma, renal cell carcinoma, breast cancer, colorectal cancer, ovarian cancer, papillary thyroid carcinoma, cholangiocarcinoma, spitzoid tumors, neuroblastoma, and anaplastic thyroid cancer. The report from this test is required to be submitted for eligibility
3. Prior anticancer treatment:
a. Phase 1: Patients with ALK fusion-positive NSCLC must have previously received >=1 ALK TKI, one of which must be a 2nd or 3rd generation TKI (ceritinib, alectinib, brigatinib, or lorlatinib). Patients with other solid tumors must have previously received >=1 prior systemic anticancer therapy or be those for whom no satisfactory standard therapy exists.
b. Phase 2 Cohort 2a: 1 prior 2nd generation ALK TKI (ceritinib, alectinib, or brigatinib) as the only prior ALK TKI; no prior investigational agents targeting ALK; <= 2 prior lines of chemotherapy and/or immunotherapy.
c. Phase 2 Cohort 2b: 2-3 prior ALK TKIs (crizotinib, ceritinib, alectinib, brigatinib or lorlatinib; excluding patients who received lorlatinib as the 1st ALK TKI); no prior investigational agents targeting ALK; <= 2 prior lines of chemotherapy and/or immunotherapy.
d. Phase 2 Cohort 2c: Lorlatinib as the only prior ALK TKI; no prior investigational agents targeting ALK. Up to 1 prior line of chemotherapy and/or immunotherapy received prior to lorlatinib is allowed.
e. Phase 2 Cohort 2d: Treatment naïve to ALK TKI therapy. Up to 1 prior line of chemotherapy and/or immunotherapy is allowed.
f. Phase 2 Cohort 2e: Any number of prior ALK TKIs, chemotherapy and/or immunotherapy; not eligible for other Phase 2 cohorts.
g. Phase 2 Cohort 2f: >=1 prior systemic anticancer therapy, or for whom no satisfactory standard therapy exists
4. Phase 1: Must have evaluable disease (target or nontarget) according to RECIST 1.1. Phase 2: Must have measurable disease, defined as >=1 radiologically measurable target lesion according to RECIST 1.1. Note: Patients with CNS-only disease are eligible, provided that the disease is evaluable (Phase 1) or measurable (Phase 2) and does not meet Exclusion Criterion #11
5. Pre-treatment tumor tissue (archived, if available, or a fresh biopsy) submitted for central analysis. It is preferable that submitted tumor tissue be obtained during or after the most recent disease progression. If appropriate tissue is not available, and if biopsy is not considered safe and medically feasible by the Investigator, the patient may be approved for enrollment after consultation with the Sponsor's Medical Monitor
6. ECOG PS of 0 or 1
7. Adequate organ function and bone marrow reserve as indicated by the following laboratory values on last assessment prior to the first dose of study drug: a. Bone marrow function: ANC >=1500/µL; platelet count >75,000/µL;

hemoglobin >=8 g/dL (without transfusion)
b. Renal function: estimated creatinine clearance >=60 mL/min
c. Hepatic function: bilirubin <1.5×ULN, unless evidence of Gilbert Syndrome, in which the patient must have total bilirubin <3.0 mg/dL; AST and ALT <=3.0×ULN (<=5.0×ULN if liver metastases involvement)
8. All clinically relevant toxicities related to prior anticancer therapy must have recovered to Grade <=1 or baseline (except alopecia or ototoxicity)
9. WOCBP must be surgically sterile or be willing to abstain from sexual activity or use a highly effective contraceptive method (CTFG 2020) from the time of signing the ICF through at least 6 months after the last administration of study drug (or longer, if required by local or country-specific guidance). Male patients with pregnant or non-pregnant WOCBP partners must use male contraception (condom) from the time of signing the ICF through at least 4 months after the last administration of study drug (or longer, if required by local or country-specific guidance).
For criteria #10 please refer to protocol.

Exclusion criteria

1. Patient's cancer has a known oncogenic driver alteration other than ALK. Investigators should discuss enrollment with the Sponsor regarding co-mutations.
2. Known allergy/hypersensitivity to excipients of NVL-655.
3. Major surgery within 4 weeks of the first dose of study drug. Minor surgical procedures (e.g., port insertion) are permitted, but with sufficient time for wound healing as deemed clinically appropriate.
4. Ongoing or recent anticancer therapy within the following timeframe prior to first dose of study drug (NVL-655 may be started within limits for prior TKI or chemotherapy if considered by the Investigator to be safe and within the best interest of the patient, with prior approval from the Sponsor):
a. TKI or other non-chemotherapy/non-immunotherapy anticancer agents therapy not listed in exclusion criteria 4b or 4c below: <5 half-lives or <7 days, whichever is longer.
b. Chemotherapy, ADCs, or other antibodies <21 days
c. Immunotherapy or cellular therapy <28 days
5. Ongoing or recent radiation therapy within the following timeframe prior to first dose of study drug:
a. Radiation therapy (except palliative radiation to relieve bone pain) <14 days
b. Palliative radiation to relieve bone pain <48 hours
c. Stereotactic or small field brain irradiation <7 days
d. Whole brain radiation <14 days
6. Prior high-dose chemotherapy requiring stem cell rescue.

7. Uncontrolled clinically relevant bacterial or fungal infection requiring systemic therapy.
8. Has known active tuberculosis or active Hepatitis B or C. Active Hepatitis B is defined as a known quantitative HBV DNA results greater than the lower limits of detection of the assay. Active Hepatitis C is defined by a known quantitative HCV RNA results greater than the lower limits of detection of the assay.
9. Patient has a QTcF >450 msec (repeated demonstration on more than one assessment). Patient has a history of prolonged QT syndrome or Torsades de pointes.
10. Patients with clinically significant cardiovascular disease as follows:
a. Within 3 months of enrollment: cerebral vascular accident/stroke; myocardial infarction; unstable angina; Grade >= 3 atrial fibrillation.
b. History of congestive heart failure (New York Heart Association Classification Class >=II); second-degree or third-degree atrioventricular block (unless paced) or any atrioventricular block with PR consistently >220 msec; or ongoing cardiac dysrhythmias of NCI-CTCAE Grade >=2 (excluding atrial fibrillation).
11. Patient has CNS metastases or a primary CNS tumor that is associated with progressive neurological symptoms or requires increasing doses of corticosteroids to control the CNS disease. If a patient requires corticosteroids for management of CNS disease, the dose must have been stable for the 2 weeks preceding C1D1. Asymptomatic leptomeningeal carcinomatosis is allowed.
12. Symptomatic spinal cord compression.
13. Patients with moderate to severe cognitive impairment or psychiatric disturbances that would compromise the patient's ability to comply with study requirements, in the Investigator's opinion.
14. Evidence of active malignancy (other than current ALK-positive solid malignancy) requiring systemic therapy within the prior 2 years. Exceptions: nonmelanoma skin cancer, in situ melanoma, in situ cervical cancer, papillary thyroid cancer, or localized and presumed cured breast or prostate cancer. Patients on long-term anti-hormonal therapy for a prior malignancy are allowed if the malignancy has not been active within the prior 2 years.
15. Concomitant use (within 12 days of first dose of study drug) of strong CYP3A4 inducers or strong CYP3A4 inhibitors.
16. Manifestation of malabsorption due to prior gastrointestinal surgery, disease, or other illness that could affect oral absorption, distribution, metabolism, or excretion of the study drug.
17. Patient is pregnant or breastfeeding. WOCBP must have a negative serum pregnancy test at Screening and negative serum or urine test prior to first dose of study drug.
18. Patient is actively receiving systemic treatment or direct medical intervention on another therapeutic clinical study.
19. Any evidence of current ILD or pneumonitis or a prior history of ILD or non-infectious pneumonitis.

20. Any medical condition or laboratory abnormality that in the opinion of the Investigator or Sponsor would pose a risk to study patient or confound the ability to interpret study results.

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):	07-06-2024
Enrollment:	18
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	NVL-655-01
Generic name:	NVL-655-01

Ethics review

Approved WMO

Date:	09-03-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	21-12-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	CTIS2024-514266-39-00
EudraCT	EUCTR2022-000122-21-NL

Register	ID
ClinicalTrials.gov	NCT05384626
CCMO	NL83206.042.23